Basile DP et al reviewed the role of T helper 17 (Th17) cells on the development of interstitial fibrosis and the development of hypertension. Recruited Th17 cells and released interleukin 17 enhance the production of extracellular matrix, cytokines, and reactive oxygen species in the macrophage and pericytes.
Aims and Scope

Kidney Research and Clinical Practice (KRCP; formerly The Korean Journal of Nephrology; ISSN 1975-9460, launched in 1982), the official journal of the Korean Society of Nephrology, is an international, peer-reviewed journal published in English. Its ISO abbreviation is Kidney Res Clin Pract.

The journal considers articles on all aspects of nephrology and hypertension as well as molecular genetics, anatomy, pathology, physiology, pharmacology, and immunology related to kidney disease. In particular, the journal focuses on translational renal research that helps bridging laboratory discovery with the diagnosis and treatment of human kidney disease. The journal publishes the topics covered basic science with possible clinical applicability and the papers on the pathophysiological basis of the kidney disease. Original studies from areas of diagnostic and interventional nephrology or dialysis access are also welcomed. Major article types considered for publication include original research and reviews on current topics of interest.

To provide an efficient venue for dissemination of knowledge and discussion of topics related to basic research, translational study and clinical practice in nephrology, the journal offers online only open access, in which all published articles are free for everyone to read and download.

The journal is currently indexed in Science Citation Index Expanded (SCIE), Scopus, ScienceDirect, PubMed, PubMed Central (PMC), Directory of Open Access Journals (DOAJ), DOl/Crossref, Google Scholar, KoMCI, KoreaMed, ScienceCentral, CAS, Current Content Clinical Medicine and Essential Science Indicators.

Open Access

Every peer-reviewed research article in this journal is freely available via our website (https://www.krcp-ksn.org). Articles published in KRCP are distributed under the terms of the Creative Commons Attribution Non-Commercial and No Derivatives License (https://creativecommons.org/licenses/by-nc-nd/4.0/), which permits unrestricted non-commercial use, distribution of the material without any modifications, and reproduction in any medium, provided the original works properly cited. ANY USE of the open access version of this Journal in whole or in part must include the customary bibliographic citation, including author and publisher attribution, date, article title, Kidney Research and Clinical Practice (Kidney Res Clin Pract), and the URL https://www.krcp-ksn.org and MUST include a copy of the copyright notice. If an original work is subsequently reproduced or disseminated not in its entirety but only in part or as a derivative work this must be clearly indicated. For any commercial use of material from the open access version of the journal, permission MUST be obtained from KRCP. If necessary, please contact the Editorial Board through our editorial office (registry@ksn.or.kr). Proprietary rights notice for KRCP online were available at: https://www.krcp-ksn.org/authors/permission.php.

Publisher The Korean Society of Nephrology
Editor-in-chief Tae-Hyun Yoo, MD, PhD

Editorial office
The Korean Society of Nephrology
1401 (Hyundai Kirim Bldg.), 42 Seocho-daero 78-gil, Seocho-gu, Seoul 06626, Korea
Tel: +82-2-3486-8736  Fax: +82-2-3486-8737  E-mail: registry@ksn.or.kr

Publishing office
M2PI
8th FL, DreamTower, 66 Seongsui-ro, Seongdong-gu, Seoul 04784, Korea
Tel: +82-2-6966-4930  Fax: +82-2-6966-4945  E-mail: support@m2-pi.com

Published on March 31, 2021

Editor-in-chief
Tae-Hyun Yoo
Seoul, Korea

Deputy Editors
Sungjin Chung
Seoul, Korea
Jeonghwan Lee
Seoul, Korea

Associate Editors
Eun Hui Bae
Gwangju, Korea
Kent Doi
Tokyo, Japan
Seung-Yeup Han
Daegu, Korea
Hee Gyung Kang
Seoul, Korea
Chan-Duck Kim
Daegu, Korea
Soo Wan Kim
Gwangju, Korea
Tae-Hwan Kwon
Daegu, Korea
Young-Ki Lee
Seoul, Korea
Beom Jin Lim
Seoul, Korea
Ming-Zhi Zhang
Nashville, USA

Statistical Editors
Hakmook Kang
Nashville, USA
Sangin Lee
Daejeon, Korea
Hyunsun Lim
Ilsan, Korea
Eunwoo Nam
Seoul, Korea

Emeritus Editor
Gheun-Ho Kim
Seoul, Korea

Editorial Board Members
Varun Agrawal
Burlington, USA
Mustafa Arici
Ankara, Turkey
Seon Ha Baek
Hwaseong, Korea
Patrick Biggar
Coburg, Germany
Jin Joo Cha
Ansan, Korea
Christopher T. Chan
Toronto, Canada
Heegeun Cho
Seoul, Korea
Bum Soon Choi
Seoul, Korea
Mary E. Choi
New York, USA
Byung Ha Chung
Seoul, Korea
Jørgen Frøkjær
Aarhus, Denmark
Hyo Wook Gil
Cheonan, Korea
Reiko Imag
Tokyo, Japan
Faïcal Jarraya
Sfax, Tunisia
Jong Hyun Jhee
Seoul, Korea
Kamyar Kalantar-Zadeh
Torrance, USA
Sejoong Kim
Seongnam, Korea
Mori Kiyoshi
Kyoto, Japan

Manuscript Editor
Yun Joo Seo
Infolumi, Korea

Managing Editor
Jin Soo Kang
The Korean Society of Nephrology, Korea
## Table of Contents

### Editorials
1. A new opportunity for *Kidney Research and Clinical Practice* to make a great leap forward as a Science Citation Index Expanded journal
   *Jeonghwan Lee, Sungjin Chung, Tae-Hyun Yoo*

6. Effect of volume indices of bioimpedance analysis on clinical outcomes, including left ventricular hypertrophy, in patients undergoing peritoneal dialysis
   *Jun Young Do*

9. Does Th1/Th2 cell imbalance affect immunoglobulin A nephropathy?
   *Tae Ryom Oh, Eun Hui Bae*

### Review Articles
12. T helper 17 cells in the pathophysiology of acute and chronic kidney disease
   *David P. Basile, Md Mahbub Ullah, Jason A. Collet, Purvi Mehrotra*

29. A Korean perspective on the 2019 Kidney Disease Outcomes Quality Initiative guidelines for vascular access: what has changed and what should be changed in practice?
   *Hyung Seok Lee, Sung Gyun Kim*

40. Pediatric acute kidney injury: new advances in the last decade
   *Sidharth K. Sethi, Timothy Bunchman, Ronith Chakraborty, Rupesh Raina*

### Special Article
52. Trends in epidemiologic characteristics of end-stage renal disease from 2019 Korean Renal Data System (KORDS)
   *Yu Ah Hong, Tae Hyun Ban, Chae-Yeong Kang, Sun Deuk Hwang, Sun Ryoung Choi, Hajeong Lee, Hee-Yeon Jung, Kyeongmin Kim, Young Eun Kwon, Su Hyun Kim, Tae Hee Kim, Ho-Seok Koo, Chang-Yun Yoon, Kiwon Kim, Jongha Park, Yang Kyun Kim*

### Original Articles
62. Comparison of chronic kidney disease trial designs and analysis strategies
   *John Lawrence*
Serum interferon-γ and urinary monocyte chemoattractant peptide-1 are important factors in the pathogenesis of IgA nephropathy

Sang Youb Han, Kyung Hwan Jeong, Chun-Gyoo Ihm, Young Sun Kang, Dae Ryong Cha

Histopathologic and clinicopathologic classifications of antineutrophil cytoplasmic antibody-associated glomerulonephritis: a validation study in a Korean cohort

Jeong-Hoon Lim, Man-Hoon Han, Yong-Jin Kim, Yena Jeon, Hee-Yeon Jung, Ji-Young Choi, Jang-Hee Cho, Chan-Duck Kim, Yong-Lim Kim, Hajeong Lee, Dong Ki Kim, Kyung Chul Moon, Sun-Hee Park

The comparative effects of intravenous iron on oxidative stress and inflammation in patients with chronic kidney disease and iron deficiency: a randomized controlled pilot study

Xenophon Kassianides, Andrew Gordon, Roger Sturmey, Sunil Bhandari

Clinical outcomes among hemodialysis patients with atrial fibrillation: a Korean nationwide population–based study

Yeunmi Kang, Hyung Yun Choi, Young Eun Kwon, Ji Hye Shin, Eun Mi Won, Ki Hwa Yang, Hyung Jung Oh, Dong-Ryeol Ryu

Elevated levels of soluble ST2 but not galectin-3 are associated with increased risk of mortality in hemodialysis patients

Ae Jin Kim, Han Ro, Hyunsook Kim, Kwang-Pil Ko, Jae Hyun Chang, Hyun Hee Lee, Wookyung Chung, Ji Yong Jung

Changes in plasma sclerostin level associated with use of a medium cut–off dialyzer in end-stage renal disease

Seon-Ho Ahn, Mi Mi Ko, Ju Hung Song, Jong Hwan Jung

Changes in extracellular water and left ventricular mass in peritoneal dialysis patients

Theerasak Tangwonglert, Andrew Davenport

Are there any further modalities for prediction of subclinical volume overload in advanced stages of chronic kidney disease?

Aber Halim Baki, Cherry Kamel, Hazem Mansour

Peripherally inserted central catheter procedure at the bedside by a nephrologist is safe and successful

Seong Cho

Impact of acute kidney injury in deceased donors with high Kidney Donor Profile Index on posttransplant clinical outcomes: a multicenter cohort study

Woo Yeong Park, Yoon Kyung Chang, Young Soo Kim, Kyubak Jin, Chul Woo Yang, Seungyeup Han, Byung Ha Chung

Correspondence

Initiating telenephrology in the coronavirus disease (COVID) era: a tertiary care experience in India

Abhilash Chandra, Namrata Rao, Divya Srivastava
A new opportunity for Kidney Research and Clinical Practice to make a great leap forward as a Science Citation Index Expanded journal

Jeonghwan Lee1,2, Sungjin Chung1,3, Tae-Hyun Yoo1,4

1Editorial Board of Kidney Research and Clinical Practice, Official Journal of the Korean Society of Nephrology, Seoul, Republic of Korea
2Department of Internal Medicine, Boramae Medical Center, Seoul National University College of Medicine, Seoul, Republic of Korea
3Department of Internal Medicine, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea
4Department of Internal Medicine, Yonsei University College of Medicine, Seoul, Republic of Korea

Accepted: March 14, 2021
Correspondence: Tae-Hyun Yoo
Department of Internal Medicine, Yonsei University College of Medicine, 50-1 Yonsei-ro, Seodaemun-gu, Seoul 03722, Republic of Korea. E-mail: yosy0316@yuhs.ac
ORCID: https://orcid.org/0000-0002-9183-4507

Copyright © 2021 by The Korean Society of Nephrology
This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial and No Derivatives License (http://creativecommons.org/licenses/by-nc-nd/4.0/) which permits unrestricted non-commercial use, distribution of the material without any modifications, and reproduction in any medium, provided the original works properly cited.

Introduction

Kidney Research and Clinical Practice (KRCP, ISSN 1975-9460), the official journal of the Korean Society of Nephrology (KSN), has recently been indexed in the Science Citation Index Expanded (SCIE) in the field of Urology & Nephrology by the editorial board of the Web of Science, Clarivate Analytics (Philadelphia, PA, USA) for issues published after January 2018. Registration of KRCP in the SCIE-indexed journal list had been a long-cherished ambition of the KSN, and it has taken 8 years since KRCP was first published in English. In this article, we summarize the history and progress of KRCP to present and suggest upcoming goals to overcome competition with both classical and emerging journals. We hope that this article will be helpful to other academic journals seeking SCIE registration and to be established as an international journal.

Genesis of Kidney Research and Clinical Practice

The official journal of the KSN, “Taehan Sinjang Hakhoe chi (The Korean Journal of Nephrology),” was first published in Korea on a biannual schedule in 1982. Initially, the main title of the journal was presented in Korean, and it translated to “Magazine of the KSN” (Fig. 1A). In 1989, the journal’s Korean name was changed to “Journal of the Korean Society of Nephrology”, and the frequency of publication was increased to quarterly (Fig. 1B). From 1998, it was published six times a year on a bi-monthly schedule. Until 2006, the journal’s main title and all other contents were presented in Korean. In 2007, the name of the journal was officially changed to an English title, The Korean Journal of Nephrology, and manuscripts included a title, author name and affiliation, abstract, keywords, and bibliographic information in English, but the main text was in Korean (Fig. 1C). From 2008, the official logo of the KSN was established as the shape of both kidneys in orange and yellow color, as it is now, and the cover design of the journal was changed (Fig. 1D).

Since the 2000s, publication of academic research work in SCIE-indexed journals has been considered important in the evaluation of investigators and institutions. In addition, other academic journals in other domestic societies have
been registered in the SCIE one by one. The necessity of achieving SCIE registration was raised by many members in the KSN for continued publication of high-level research and survival and progress of KRCP in academia.

A new beginning for *Kidney Research and Clinical Practice* in English

In 2010, the KSN began to plan an upgrade of the journal with the aim of future registration in the SCIE. At that time, there were many opinions within the KSN that the publication of the journal in English was essential for SCIE registration. However, there was also considerable concern that when manuscripts were published in English, many studies submitted by members in the KSN might not be accepted. The executive board, under the leadership of the president of the KSN, promoted a new project for the journal’s complete conversion into English, and formed a new Editorial Board (publication director, professor Gheun-Ho Kim) in May 2010.

While some sought to maintain the existing English journal name (*The Korean Journal of Nephrology*), it was decided to choose a new English name that would represent its future success on the global academic stage. After discussion in the Editorial Board, several candidate English journal names were proposed, and the new name “*Kidney Research and Clinical Practice*” (abbreviated as *Kidney Res Clin Pract*) was finally selected through public voting among the members of the KSN during the 31st Spring Meeting of the KSN in May 2011.

In line with confirmation of the English journal name, overall work related to preparation of the English journal began. The instructions to authors were reorganized in English, the role of the Editorial Board was redefined, a pool of reviewers from among KSN members was secured, and foreign members of Editorial Board (two in the United States, two in Denmark, one in Thailand, and one in China) were newly recruited before conversion of the journal into English. A statistical editor was selected to improve the quality of accepted manuscripts. Five types of papers would be accepted in the new English journal: editorials, review articles, original articles, case reports, and letters. After July 1, 2011, only manuscripts written in English were accepted, and the publication of Korean literature was stopped in December 2011. The general information, cover design, manuscript layout, and front and back content of the journal were confirmed. Elsevier was selected as the new publisher, and, in March 2012, the first KRCP, an open-access and peer-reviewed international journal, was published in English as a whole, distributing a total of 1,500 copies (Fig. 1E).

Growth and advancement of *Kidney Research and Clinical Practice*

Since the first publication of the KRCP, various activities have been carried out to improve the quality of the journal. The Editorial Board selected a high-quality English editing service and encouraged authors to submit their articles for professional English editing before final acceptance. The submission system has been improved so that all co-authors

---

can be notified of the submission by e-mail at the time of initial submission. The review system has been reorganized so that statistical editors can be selected as reviewers in order to facilitate statistical consultation. Based on these efforts, in March 2013, KRCP was listed on Elsevier’s Scopus journal list. Scopus is an accredited tool for evaluating the research power of authors, journals, and affiliations, and it was an opportunity for KRCP to grow in quality. The Editorial Board held a workshop for KRCP Editorial Board members and discussed various agenda matters including maintenance of a consistent style of literature, streamlining the review process, recruitment of excellent reviewers, improvement of different levels of review, and invitation of the highest-level thesis. In May 2014, the Editorial Board organized the KRCP special session program during the 34th Spring Meeting of the KSN and dealt with publication ethics focused on thesis plagiarism, dual publication, and thesis similarity check systems. We discussed together with Elsevier ways to correct editorial errors and long-term plans to improve editing quality.

Receiving many excellent papers was identified as an important prerequisite for improving the quality of KRCP. The principles and rules of the KSN’s research funds were revised to increase the submission of excellent academic papers in KRCP. The publication of at least one research article in KRCP was set as a requirement when applying for KSN’s research funds. The results of research funded by the KSN could be preferentially submitted to KRCP. To expand the scope of review papers and improve their level, the Editorial Board invited outstanding domestic and foreign speakers to KSN conferences to increase the contribution of review papers to KRCP. In particular, we focused on topics that were of high interest among the speakers invited to the KSN annual academic conference. In order to attract excellent papers, members of KSN who had recently attended overseas training were asked to submit manuscripts based on their new knowledge and research experience. A series of review articles have been published on research methodology and controversy in clinical practice, which is of high interest to many researchers and physicians. Skilled foreign researchers were continuously recommended and selected as new editorial board members. A newsletter that introduced studies in KRCP and noteworthy studies citing KRCP was produced and released to the public. This allowed more excellent studies listed in the KRCP to be referenced and cited in subsequent studies.

Based on these efforts to improve the level of submitted manuscripts, KRCP was approved for PubMed scientific evaluation on August 7, 2015 and listed in PubMed Central on October 22, 2015. Due to these achievements, an initial application letter of journal evaluation for SCIE registration was sent to Thomson Reuters (Web of Science) but was not successful. However, KRCP was listed in the Emerging Sources Citation Index (ESCI) in August 2016. Additional efforts and activities were carried out to progress toward KRCP’s SCIE registration. Submission and contribution rules have been continuously improved for the publication of high-quality studies. Instructions for authors and reviewers were revised to facilitate the submission of excellent original and review papers, and to allow more foreign researchers to participate in the peer-review process. Reviewer evaluation was strengthened to enable high-quality reviews. The layout and design of the homepage were improved to increase the accessibility of KRCP papers. The Editorial Board also developed a public relations and publicity program to promote citations of published papers.

In 2017, the publisher was switched from Elsevier to Inforang/Medrang, and the journal’s design was improved once again to simplify the submission and review process. Case report articles were eliminated from consideration to create more space for influential original articles. Submission ethics and regulations were reinforced. The role of each author was designated by the Editorial Manager, and the approval code/number of each institution, such as the Institutional Review Board or Institutional Animal Care and Use Committee number, was required for submission. In addition, notation of all authors’ ORCID identifiers was set as mandatory. The Editorial Board also reviewed the Principles of Transparency and Best Practice guidelines.

Kidney Research and Clinical Practice prepares for a new leap forward

In May 2020, professor Gheun-Ho Kim, who had been the Editor-in-Chief of KRCP for approximately 10 years, resigned, and professor Tae-Hyun Yoo took office as the new Editor-in-Chief in June 2020. With the aim of SCIE registration, priority tasks were the submission of many high-quality papers, reorganizing the website, strengthening ethical regulations, and improving the proofing and editing.
Along with the growth of KRCP, the number of manuscripts had increased, so a higher level of peer-review had become necessary. The new Editorial Board established new awards for excellent reviewers. In addition, plans were made to increase the journal's reputation and recognition, including public relations activities for KRCP at overseas academic conferences. Based on the overall growth of KRCP, the number of citations of KRCP increased to more than 300 per year. It was rated as within the top 25% of urology journals with 0.91 points in the 2019 Scimago Journal Ranking (SJR 2019). In July 2020, a letter was sent to Clarivate Analytics to inquire about the evaluation of KRCP for SCIE listing. On October 31, 2020, we received a recommendation from Clarivate Analytics with regard to changes that could be made to the submission regulations and homepage contents, raising expectations for SCIE registration in the near future. Finally, on November 4, 2020, we received a confirmation letter for KRCP’s SCIE listing from Clarivate Analytics, Web of Science. The timeline of the official journal of KSN from first publication to recent SCIE registration is summarized in Table 1.

The reasons for the success of KRCP’s SCIE listing were as follows. First, there was full support from the KSN for KRCP’s growth and development. The Editor-in-Chief, with the 5-year term, was able to maintain a consistent and stable editorial direction. Next, the great interest and commitment of the members of the KSN to KRCP has contributed to the submission of high-quality papers, active citation, and promotion of academic research. Through the dedication of many editors, various problems were discovered and improved. KRCP published timely topics such as coronavirus disease 2019 (COVID-19) Korean clinical practices guidelines in hemodialysis facilities and disaster preparedness for earthquakes in hemodialysis units, and played a leading role in academic society [1,2]. In addition, by strengthening cooperation with other international academic societies and organizations, the publication of papers in KRCP on important topics worldwide is increasing. A special article on nomenclature for kidney function and disease, an executive summary and glossary discussed at the Kidney Disease: Improving Global Outcomes (KDIGO) Consensus Conference, was published in conjunction with the International Society of Nephrology [3,4].

In January 2021, the Editorial Board selected M2PI Publishing Inc. as KRCP’s new publishing company, improved the design of the homepage, improved mobile accessibility, and changed the system to full online publishing. Although KRCP succeeded in SCIE listing, there are many challenges to be addressed in order to continue to move forward. The intense competition among various classical and new journals must be overcome. Recently, a number of research papers have been preoccupied with competitively establishing open-access sister journals in renowned journals. In order to increase the competitiveness of KRCP, efforts should be made to publish leading research papers or review articles on topics of interest in nephrology. Inviting guest editors for special editions on specific topics could also attract new readers and citations. The publication of clinically controversial contents in a series within a single volume can also raise readers’ interest. Based on its growth so far and the dedication of its many researchers and reviewers, KRCP will continue to develop into an even more highly-ranked international journal.

**Conflicts of interest**

All authors are Editorial Board members of the Korean Society of Nephrology, serving as editor-in-chief and deputy editors of its official journal, *Kidney Research and Clinical Practice*. No other competing interests are declared.
Authors’ contributions

Conceptualization: SC, THY
Visualization: All authors
Writing–original draft: JL
Writing–review & editing: SC, THY

ORCID

Jeonghwan Lee, https://orcid.org/0000-0003-3199-635X
Sungjin Chung, https://orcid.org/0000-0002-9886-8339
Tae-Hyun Yoo, https://orcid.org/0000-0002-9183-4507

References

Effect of volume indices of bioimpedance analysis on clinical outcomes, including left ventricular hypertrophy, in patients undergoing peritoneal dialysis

Jun Young Do

Division of Nephrology, Department of Internal Medicine, Yeungnam University Hospital, Daegu, Republic of Korea

Volume status is an important risk factor that affects morbidity and mortality in patients undergoing peritoneal dialysis (PD). Volume overload may lead to major cardiovascular complications, such as left ventricular hypertrophy (LVH). Proper monitoring and intervention in cases of volume overload are important for improving survival in patients that are undergoing PD. Multifrequency bioimpedance analysis (BIA) is a simple and accurate method of body composition analysis.

In the current issue of *Kidney Research and Clinical Practice*, Tangwonglert and Davenport [1] reported an analysis of the impact of fluid status on left ventricular mass (LVM) in patients undergoing PD. This study reinforces the importance of extracellular water (ECW) expansion rather than systolic or mean arterial blood pressure and the detrimental effect of the same on LVH. An equal regression in LVH along with a reduction in ECW volume has also been discussed. I want to discuss the effects of BIA volume indices on clinical outcomes, including LVH, in patients undergoing PD.

Hypoalbuminemia is an important determinant of tissue overhydration (OH) and can be linked to inflammation or peritoneal protein loss in patients undergoing PD. The presence of excess fluid is not equivalent to expanded plasma volume; rather, it is associated with increased extravascular ECW accumulation in patients with hypoalbuminemia. Several factors, such as diabetes, sex, age, residual renal function (RRF), and modality of PD should be considered when interpreting the volume status in patients undergoing PD. Van Biesen et al. [2] observed a substantial volume overload in a cohort that was comprised of incident patients on PD, with patients with diabetes and males being affected more severely. Volume overload has been associated with mortality. In patients with diabetes undergoing PD, an increase in ECW volume was found to be secondary to increased vascular permeability and albumin transfer to interstitial tissues. Because RRF is an important determinant for PD success, there is a tendency in clinical practice to allow an increase in ECW volume in patients undergoing PD. The relationship between ECW/total body water (TBW) and RRF preservation remains in debate. McCafferty et al. [3] reported that the increments and decrements in ECW/TBW were not associated with changes in RRF.
However, Kang et al. [4] reported that RRF at 1 year after PD initiation was higher in the initial low edema index (ECW/TBW) group than in the initial high edema index group, and that a baseline high edema index was associated with higher mortality among patients undergoing PD. With defining the time-averaged RRF (TA-RRF) as the mean RRF values at PD initiation and 1 year after PD initiation, the authors also reported that a high TA-RRF tertile was associated with a lower edema index at 1 year in patients undergoing PD [5].

Tangwonglert and Davenport [1] reported that in the group with LVM index (LVMI) reductions, none of the patients were initially treated with automated PD (APD). Rather, a greater number of patients with increased LVMI were initially treated with APD cycler. This might be attributable to the differences in peritoneal sodium removal processes in different PD modalities and the types of peritoneal dialysates that were used. Adequate removal of water and sodium via dialysate might be important for preventing hypervolemia, especially in patients undergoing APD. The use of a low-sodium dialysate, icodextrin dialysate, and long-term exposure of dialysate could be helpful to mitigate sodium retention in patients undergoing APD. In most cases in this study, relatively sufficient sodium and fluid removal was facilitated by using icodextrin (80%) and a suitable long-term PD modality (both continuous ambulatory PD [CAPD] and continuous cycler PC [CCPD], 90%).

For more accurate measurement of BIA, patients are recommended to maintain an empty abdomen during the evaluation of body composition. The presence of peritoneal dialysates has been observed to lead to an increase in not only intracellular water, ECW, and TBW volume but also the edema index (ECW/TBW), leading to an underestimation of body fat mass [6]. The ECW/TBW ratio may increase in confounding conditions, such as muscle loss, diabetes, and hypoalbuminemia, and this ratio has been validated as a predictor of survival. The ECW/TBW ratio should be normalized based on sex and age. An ECW/TBW ratio of ≥0.4 was used to define OH, as suggested by the manufacturer (Biospace, Seoul, Korea). In this study, the mean ECW/TBW values during the first and second rounds of echocardiography were less than 0.4. Several studies have reported a negative correlation between ECW/TBW and clinical outcomes, including cardiovascular mortality. Shu et al. [7] reported that bioimpedance-assessed OH (ECW/TBW) is a predictor of mortality and technique failure in patients undergoing PD. However, the correlation between volume control and RRF preservation in patients undergoing PD must be observed closely. Strict volume control for normalizing the ECW/TBW ratio in comorbid patients undergoing PD may lead to hypovolemia and RRF loss. Although the ECW/TBW ratio is most widely accepted as an index of hydration in patients undergoing PD, it does not indicate the degree of OH. The OH status is commonly defined by OH/ECW > 15%, as described by Wizemann et al. [8] in a body composition monitor. Another recent study showed that chronic fluid overload strongly predicted the risk of death and transfer to hemodialysis in patients undergoing PD. The IPOD-PD (Initiative of Patient Outcomes in Dialysis-Peritoneal Dialysis) Study Group reported that a volume overload of >17.3% was independently associated with a higher death risk than in cases with relative volume overload of ≤17.3% [2].

Tangwonglert and Davenport [1] reported on the relationship between ECW and LVM in patients undergoing PD. Regardless of whether the expansion in extracellular volume was suitable for RRF preservation, the hypervolemic effect on LVH might be an important determinant of clinical outcomes in patients undergoing PD. In this study, only the ECW/height ratio was independently associated with the percentage change in LVMI in a multivariable model; however, it was not associated with ECW/TBW or changes in systolic or mean arterial pressure, urine output, 24-hour PD ultrafiltration, or net sodium balance. A limited number of studies have reported on serial echocardiograms in PD patients. In a large-scale Korean study, Hong et al. [9] showed that strict volume control based on repeated measurements using bioimpedance spectroscopy was an independent predictor of left ventricular (LV) systolic function in non-anuric patients undergoing PD. However, they were not able to assess whether changes in LVM were related to changes in ECW. The Korean COMPASS (Control of Fluid Balance Guided by Body Composition Monitoring in Patients on Peritoneal Dialysis) study also did not reveal differences in clinical outcomes, including echocardiographic parameters, between the BIS-guided and control groups [10].

Patients with chronic kidney disease (CKD) exhibit several potential risk factors for LVH, as they are more likely to have hypertension, ECW volume expansion, and anemia. Nevertheless, owing to renin-angiotensin system activation and other disruptions in circulation, certain patients...
remain hypertensive even though their ECW volume status is carefully monitored. Sustained volume overload or longstanding hypertension could be directly associated with eccentric or concentric LVH, respectively. Antihypertensive medications that are used, such as angiotensin II receptor blockers, could exert beneficial effects on LVH regression. In this study, less than 20% of patients undergoing PD were treated with renin-angiotensin blockers/receptors, and unexpectedly, the majority of patients showed concentric LVH. Ejection fraction (EF), which is measured using conventional echocardiography, is an insensitive parameter due to both intra- and interobserver variability. Furthermore, LVH and changes in LV structure in patients with CKD could lead to LV systolic dysfunction despite a normal EF. The prevalence of impaired LV global longitudinal strain (GLS) despite preserved left ventricular EF in predialysis patients and those undergoing dialysis is relatively high (32%). In this respect, LV GLS is effective for early detection of LV systolic dysfunction in patients with CKD with preserved EF. Although there is currently no consensus on hydration measurements using BIA, several cohort studies have shown that OH, as measured using the ECW/TBW or OH/ECW ratio, is strongly associated with a poor survival outcome in patients undergoing PD. However, the impact of ECW/height on LVH should be tested in carefully designed clinical trials.

Conflicts of interest

The author has no conflicts of interest to declare.

ORCID

Jun Young Do, https://orcid.org/0000-0002-6360-9310

References

Immunoglobulin A (IgA) nephropathy is the most common form of glomerulonephritis both in Korea and worldwide. Clinical manifestations of IgA nephropathy vary among patients ranging from asymptomatic hematuria to nephrotic syndrome. The renal survival rate of IgA nephropathy is poor. IgA nephropathy is characterized by mesangial deposition of immune complexes, including under-glycosylated IgA, with or without IgG and complement [1]. Despite many previous studies conducted to determine the pathogenesis of IgA nephropathy, its pathogenesis has not yet been clearly identified. Previous studies have demonstrated that IgA nephropathy is a systemic disease that is not kidney-specific [2,3]. Recently, functional abnormalities in T lymphocytes was suggested to be a cause of mesangial deposition of IgA with altered glycosylation, and several studies have shown that T lymphocytes play a major role in the pathogenesis of IgA nephropathy.

CD4+ T cells are classified by transcription factor expression; T-bet in Th1 cells, GATA3 in Th2 cells, RORyt in Th17, Foxp3 in Treg, and Bcl6 in follicular helper T cells. Each T cell subtype expresses a cell-specific cytokine and plays a unique immunological role. Th1 lymphocytes contribute to cellular immunity via secretion of interleukin (IL)-2, interferon gamma (IFN-γ), and tumor necrosis factor alpha. Th2 lymphocytes induce humoral immunity by secreting IL-4, IL-5, and IL-13 [4]. Th1 and Th2 lymphocytes modulate systemic immune system function through mutual regulation (Fig. 1). Several studies have shown a role for Th1/Th2 lymphocyte polarization and associated cytokine production in the pathogenesis of IgA nephropathy. Th1 polarization was demonstrated in the early stages of IgA nephropathy in a ddY murine model of IgA nephropathy [5]. In addition, administration of Th1 cytokines can result in crescentic lesions of glomeruli in hyper-IgA mice [6]. By contrast, another study showed polarization toward the Th2 response in tonsil mononuclear cells displaying IgA nephropathy [7]. To date, the pathogenic role of Th1/Th2 polarization remains unclear.

Han et al. [8] reported elevated serum IFN-γ, a Th1 cytokine, and urinary monocyte chemoattractant peptide (MCP)-1 in IgA nephropathy in comparison to healthy controls. IFN-γ acts as a major pathogenic cytokine in IgA nephropathy, and increased IFN-γ promotes urinary MCP1 production. Notably, this study simultaneously obtained cytokine profiles from various sources, including serum, urine, kidney, peripheral blood mononuclear cells, and
evaluated the response of mesangial cells to Th1/Th2 cytokines. IgA nephropathy-specific Th1/Th2 polarization was also assessed. This study has important clinical significance in that they present the results of comprehensive analyses of human and in vitro experimental data, but it also has some limitations. First, similar to most studies in this field, the sample size was small. Second, temporal changes in Th1/Th2 lymphocytes and relevant cytokines were neither considered nor analyzed. Third, the study design cannot infer causal relationships. The correlation analyses provide interesting results, but they do not prove causality. Further research is needed to determine causality. These studies present clinically important results despite these limitations.

Previous studies have investigated the influence of T lymphocytes on the pathogenesis of IgA nephropathy. The most influential limitations of the previous studies are the small numbers of subjects and their methodology that cannot infer a causal relationship. Studies aimed at identifying specific T lymphocytes and relevant cytokines as therapeutic targets, or as surrogate markers for evaluating therapeutic response, have recently been highlighted, but in these studies, specific T lymphocytes and related cytokines were not clearly identified. Potential therapeutic strategies for treating early-stage IgA nephropathy using immunity-related T lymphocytes have provided accumulating evidence in support of clinical application. Much research in numerous fields must be completed to allow clinical application of new treatments utilizing T cell immunity. For disease monitoring and risk stratification in IgA nephropathy, further studies are required to clarify the association between renal function deterioration, histological damage, and T lymphocytes and their secreted cytokines. In addition, to date, no temporal analyses of T cell immunity over the course of disease progression have been conducted, thus studies of the efficacy of serial T cell monitoring are needed.

Well-designed large-scale future studies should elucidate the influence of Th1/Th2 polarization and related cytokines on IgA nephropathy, and these studies should facilitate the development of new therapeutic strategies that involve the regulation of related pathways. It may also be possible to control disease progression through the regulation of immunity.

**Conflicts of interest**

Eun Hui Bae is an Associate Editor of *Kidney Research and Clinical Practice*. All authors have no other conflicts of interest to declare.

**Funding**

This research was supported by Chonnam National University Hospital Biomedical Research Institute Grant (BCRI 20076). The sponsor had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

**Authors’ contributions**

Conceptualization: TRO, EHB
Data curation: TRO, EHB
Formal analysis: TRO, EHB
Funding acquisition: EHB
Investigation: TRO, EHB
Methodology: TRO
Project administration: EHB
Visualization: TRO
Writing–original draft: TRO
Writing–review & editing: EHB
All authors read and approved the final manuscript.

**ORCID**

Tae Ryom Oh, https://orcid.org/0000-0002-3713-0939
Eun Hui Bae, https://orcid.org/0000-0003-1727-2822

References

Both acute and chronic kidney disease have a strong underlying inflammatory component. This review focuses primarily on T helper 17 (Th17) cells as mediators of inflammation and their potential to modulate acute and chronic kidney disease. We provide updated information on factors and signaling pathways that promote Th17 cell differentiation with specific reference to kidney disease. We highlight numerous clinical studies that have investigated Th17 cells in the setting of human kidney disease and provide updated summaries from various experimental animal models of kidney disease indicating an important role for Th17 cells in renal fibrosis and hypertension. We focus on the pleiotropic effects of Th17 cells in different renal cell types as potentially relevant to the pathogenesis of kidney disease. Finally, we highlight studies that present contrasting roles for Th17 cells in kidney disease progression.

Keywords: Acute kidney injury, Fibrosis, Hypertension, Inflammation

Background

As of 2017, the global burden of chronic kidney disease (CKD) was estimated to be approximately 9.1%, indicating that CKD is a significant healthcare concern worldwide. Global age-adjusted mortality rates for patients with CKD have declined in the last 30 years, and quality of life metrics decrease as glomerular filtration rate declines [1]. In the period between 1990 and 2017, there was an approximate 41% increase in the number of patients with end-stage renal disease (ESRD). Despite this, CKD patients are more likely to die due to complications such as hypertension, cardiovascular disease, anemia, and bone and mineral disorders, and these patients also have an increased cancer incidence [8].

Acute kidney injury (AKI), generally defined as a rapid loss of kidney function, results in renal damage caused by factors such as nephrotoxins, radiocontrast agents, hypoperfusion, surgery, sepsis, and antibiotics [2]. AKI occurs in up to 7% of hospital admissions per year in the United States [2–4], while a recent study based on KDIGO (Kidney Disease: Improving Global Outcomes) guidelines suggested that up to 1 in 5 adult hospitalized patients worldwide have some form of AKI [5]. AKI is associated with significant morbidity and mortality [4,6,7], and surviving patients are at increased risk of developing CKD and ESRD [8].

Copyright © 2021 by The Korean Society of Nephrology
Both acute and CKD have a strong underlying inflammatory component. The purpose of this review is to focus primarily on T helper 17 (Th17) cells as mediators of inflammation and present evidence that these cells modulate both acute and CKD and that the primary cytokine produced by these cells, interleukin (IL) 17A, is a potential therapeutic target in kidney disease.

**T helper 17 definition and roles**

CD4+ T cells have pleiotropic potential and are thought to assist in the humoral immune response indirectly by affecting innate immune cells such as neutrophils and macrophages. T-cell activation occurs when T-cell receptors (TCRs) recognize specific peptides on MHCII+ antigen presenting cells (APCs). Coupled with co-stimulatory signals derived from APCs, as well as cytokines and other signals from innate immune cells, these combined inputs drive T-cell differentiation and expansion. In 1986, Mosmann et al. [9] defined two distinct sets of T-helper cells based on their lymphokine profiles; Th1 and Th2 cells. The transcription factors T-bet and STAT-1 are essential for the differentiation of Th1 cells, characterized by the secretion of interferon (IFN)-γ, IL-2, IL-12, and tumor necrosis factor (TNF)-α. The primary function of Th1 cells is to assist in the macrophage response against intracellular pathogens such as viruses or bacteria [9]. In contrast, STAT-6 and GATA3 drive differentiation of Th2 cells, characterized by the secretion of IL-4 as well as IL-10, IL-13, and IL-25 [11]. A primary function of Th2 cells in immune responses is to fight extracellular parasites by regulating mucous production in the gastrointestinal tract and stimulating antibody production to facilitate destruction of invading parasites by eosinophils or mast cells [10].

In 2005, two groups described a population of T-helper cells referred to as Th17 cells based on the expression of the signature cytokine IL-17A. These cells also secrete other factors such as IL-17F, IL-21, IL-22, IL-23, and TNF-α [12-14]. Th17 cells play a critical role in host protection against certain types of pathogens such as extracellular bacteria, which are not traditional targets of Th1 or Th2 cells [10]. Under the influence of IL-17A, Th17 cells are strongly proinflammatory, resulting in an influx of neutrophils to fight infections [14].

Like Th1 and Th2 cells, Th17 cells differentiate from naïve Th0 cells following engagement of TCRs and the influence of local cytokines (reviewed in [15,16]). This response is dependent on the expression of RAR-related orphan receptor gamma T (RORγt), the key transcriptional regulator of Th17 cell differentiation. This process is dependent on the proinflammatory cytokine IL-6 and the activation of STAT3. Other proinflammatory cytokines, such as IL-21, can also activate STAT3 to induce expression of RORγt (Fig. 1). In addition, transcription factors such as basic leucine zipper ATF-like transcription factor or interferon regulatory factor 4 can modulate the chromatin accessibility of Th17 specific genes and act cooperatively with RORγt to modulate Th17 differentiation [17]. Th17 differentiation is also thought to be dependent on the activity of transforming growth factor (TGF)-β, since TGFβ null mice, or mice that express a dominant negative form of TGFRII on CD4+ cells, lack the ability to produce mature Th17 cells, while mice overexpressing TGF-β display enhanced Th17 activation [16].

Calcium signaling is induced following TCR stimulation, which is critical in driving the differentiation response. Several studies have indicated an important role for the store-operated calcium release activated calcium channel (CRAC) Oria1 in Th17 differentiation. Activation of this channel is dependent on depletion of endoplasmic reticulum stores of Ca2+ secondary to TCR activation, which is sensed by the endoplasmic reticulum transmembrane protein Stim1 and its subsequent interaction with plasma membrane Orai1 to mediate enhanced Ca2+ influx (Fig. 1) [18,19]. Mutations in either Orai1 or Stim1 result in a severe combined immunodeficiency phenotype [20]. Kim et al. [21] identified putative Orai1 inhibitors that showed greater selectivity in abrogating Th17 differentiation vs. Th1 or Th2 differentiation by screening a chemical library. Orai1 inhibition also reduced the nuclear accumulation of nuclear factor of activated T cells and RORγT. We suggested a requirement for Orai1 in Th17 differentiation in our recent study of a rat model of kidney injury; IL-17 expression by CD4+ cells was exclusive to those cells that expressed Orai1 and was not detected in CD4+ cells that lacked expression of this channel [22].

The IL-17 receptor family comprises five members; IL-17RA, IL-17RB, IL-17RC, IL-1-7RD, and IL-17RE. The primary ligands secreted by Th17 cells, IL-17A and IL-17F, form homodimers or IL-17A/F heterodimers and engage primarily with IL-17RA, but likely require complex formation with IL-17RC for efficient binding or signal transduction (for a detailed
A complex pattern of differing affinities of IL-17A, IL-17F, and IL-17A/F for different receptors, as well as different ratios of IL-17RA and IL-17RC present in different cell types have been proposed to account for tissue-specific responses [24]. Importantly, Kuestner et al. [25] demonstrated that a soluble IL17RC-Fc fusion protein was able to bind to both IL-17A and IL-17F, an approach that was shown to inhibit the activity of both of these ligands in vivo.

Role of interleukin 17 in kidney pathophysiology

IL-17 receptors are expressed in many different cell types but are prominent in cells of hematopoietic origin [24]. Because the kidney is vulnerable to infection, Th17 cells are thought to serve a critical role in antimicrobial host defense [26,27]. IL-17 is among a number of factors that are elevated in patients with acute urinary tract infections (UTIs) [28]. Increased expression of IL-17A was observed in the bladders of mice infected with uropathogenic Escherichia coli. Furthermore, IL17A−/− mice have reduced macrophage and neutrophil influx, resulting in impaired clearance of bacterial load [29]. Interestingly, Olson et al. [30] demonstrated increased UTI severity in male mice vs. female mice and suggested that sex differences in UTI...
outcomes were due to a greater IL-17 response in females than males [31]. In a model of systemic Candida albicans infection, infected mice were shown to have increased IL-17 expression while null IL17RA-/- mice showed increased renal fungal colonization, reduced neutrophil infiltration, and decreased survival [32]. An interesting study by Ramani et al. [33] demonstrated that tubular specific deletion of IL17RA was essential for activation of host defenses in response to C. albicans infection, suggesting that IL-17 expressed by renal parenchymal cells plays a role in fighting infections.

Autoimmune and inflammatory diseases

While the Th17 system plays an important role in host-defense, unrestrained or inappropriate IL-17 signaling may exacerbate tissue damage due to its strong proinflammatory properties. Accumulating evidence suggests that Th17 cells or increased IL-17 expression is a common feature of many kidney diseases (Table 1 [22,28,34–59]). For example in the setting of autoimmune disease, although initially considered the result of Th1-mediated effects, hyper-activation of Th17 cells (or potentially other IL-17-secreting cells) has been suggested to exacerbate conditions such as psoriasis, inflammatory bowel disease, and autoimmune encephalitis [60].

Systemic lupus erythematosus (SLE) is an autoimmune disorder characterized by the production of auto-antibodies. Th17 cells have been proposed to mediate the interaction between immune complexes and alterations in kidney structure and function [61]. Lupus patients have been shown to have more circulating CD4+IL-17+ cells than control patients [34], and circulating IL-17 levels were shown to be higher in patients with active rejection than those in a non-rejection state and were undetectable in healthy control patients [35]. Another study reported that baseline levels of IL-17 and IL-23 in SLE patients predicted a poor response to treatment [36].

Similarly, Krebs et al. [38] demonstrated higher levels of kidney RORγ+ T cells in patients with antineutrophil cytoplasmic antibody (ANCA)-associated glomerular nephritis. Patients with acute ANCA vasculitis had higher circulating IL-17 and IL-23 than healthy controls, and these levels remained persistently elevated above those in control patients even after inflammation resolved [40]. IL-17 immunostaining was identified in renal biopsies from patients with ANCA nephritis, although positively-stained cells were initially identified as polymorphonuclear granulocytes with lower frequencies of IL-17+ T cells [39]. Both serum and urinary levels of IL-17 have been shown to be elevated in patients with immunoglobulin A (IgA)-nephropathy (IgAN) [41], another immune complex-mediated disease triggered by mesangial deposition of IgA leading to CKD.

Data from multiple mouse models support the hypothesis that Th17 cells contribute to inflammatory disease progression. These mouse models include crescentic glomerular nephritis following myeloperoxidase injection [62,63]; exposure to the Goodpasture antigen, α3IV-NC1 [64]; lupus nephritis induced by pristane injection [65]; and injection of anti-glomerular basement membrane antibody [38]. Th17 cell accumulation in the inflamed kidneys was reported for all these models. Furthermore, reduced prevalence of kidney disease was observed in studies that used IL17A-/- mice or rorγ-/- mice [66] relative to wild-type mice. The protection was associated with reduced infiltration of other cells such as neutrophils and macrophages and the expression of cytokines such as C-C motif chemokine ligand (CCL) 5.

Paust et al. [67] examined the dynamics of both Th1 and Th17 cells following injection of sheep serum into mice to induce glomerular inflammation. Th17 cells peaked in the earlier phase of the disease (i.e., 10 days following injection), while Th1 cells peaked during the later phase of the disease (>20 days). Null mutations or immunoneutralization of either IL-17 or IFNγ reduced the degree of renal dysfunction and tissue injury, while adoptive transfer of wild-type splenocytes, but not IL17A-/- or IFNγ-/- derived splenocytes, sustained the degree of renal damage in T-cell-deficient Rag1-/- mice. Interestingly, adoptive transfer of Th17 cells primed by glomerular antigens into Rag1-/- mice was sufficient to drive the formation of glomerular crescents [68].

Infiltration of Th17 cells into the kidney is due in part to local expression of cytokines. Using the MRL/lpr model of lupus nephritis, Steinmetz et al. [69] reported an influx of both Th1 and Th17 cells that appeared to be dependent on the activity of CXCR3 on CD4 cells, as mutation of this receptor reduced infiltration of both Th1 and Th17 cells. CXCR3 interacts with at least three ligands, Mig/CXCL9, IP-10/CXCL10, and ITAC/CXCL11, suggesting that these may play a role in Th17 infiltration. Lu et al. [70] demonstrated that incubation of human mesangial cells with serum from IgAN patients stimulated the production of CCL20.
### Table 1. Interleukin (IL) 17 expression in kidney diseases and hypertension

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Study</th>
<th>Observation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>UTI</strong></td>
<td>Sundac et al. [28]</td>
<td>Proteomics identified IL-17 as a highly expressed cytokines in the urine of patients with UTI.</td>
</tr>
<tr>
<td></td>
<td>Shah et al. [34]</td>
<td>Increased circulating Th17 cells in patients with lupus.</td>
</tr>
<tr>
<td><strong>Autoimmune/antibody-based</strong></td>
<td>Jakiela et al. [35]</td>
<td>IL-17 identified in serum of lupus patients; higher levels in patients with active rejection.</td>
</tr>
<tr>
<td><strong>diseases</strong></td>
<td>Zickert et al. [36]</td>
<td>Increased baseline levels of IL-6, IL-10, IL-17, IL-23, and IL-17 staining in biopsies from lupus patients vs. controls. Baseline IL-17 and IL-23 levels predicted poor responses to treatment.</td>
</tr>
<tr>
<td><strong>Autoimmune/antibody-based</strong></td>
<td>Crispín et al. [37]</td>
<td>DN T cells from patients with SLE produced significant amounts of IL-17 and IFN-gamma; IL-17(+) and DN T cells were present in kidney biopsies of patients with lupus nephritis.</td>
</tr>
<tr>
<td><strong>diseases</strong></td>
<td>Krebs et al. [38]</td>
<td>RORγt+ T cells were identified in biopsies of patients with ANCA glomerular nephritis.</td>
</tr>
<tr>
<td></td>
<td>Velden et al. [39]</td>
<td>Immunostaining of biopsies of ANCA patients revealed the presence of IL-17.</td>
</tr>
<tr>
<td></td>
<td>Nogueria et al. [40]</td>
<td>Serum levels of IL-17 and IL-23 were elevated in ANCA patients vs. healthy controls; persistent elevation was associated with resolution of inflammation.</td>
</tr>
<tr>
<td></td>
<td>Wątorek et al. [41]</td>
<td>Elevated IL-17 levels were found in patients with immunoglobulin A nephropathy.</td>
</tr>
<tr>
<td></td>
<td>Jen et al. [42]</td>
<td>Children with acute Henoch-Schönlein purpura showed higher serum IL-17 and IL-6 levels, increased numbers of Th17 cells, and higher IL-17 production from peripheral blood mononuclear cells.</td>
</tr>
<tr>
<td><strong>NS</strong></td>
<td>Wang et al. [43]</td>
<td>Pediatric patients with NS had an increased frequency of IL-17+ cells and RORγt.</td>
</tr>
<tr>
<td></td>
<td>Liu et al. [44]</td>
<td>Increased Th17/T_reg ratio was found in adult patients with minimal change NS.</td>
</tr>
<tr>
<td><strong>Acute and chronic rejection in</strong></td>
<td>Loverre et al. [45]</td>
<td>Increased numbers of CD4+/IL-17+ cells and tubular expression of IL-17 were observed in biopsies of T-cell mediated rejection.</td>
</tr>
<tr>
<td><strong>renal transplant</strong></td>
<td>Hesiah et al. [46]</td>
<td>IL-17 staining was positive in biopsies of renal allografts with evidence of rejection; IL-17 mRNA was detected in the urinary sediment of patients with borderline subclinical rejection.</td>
</tr>
<tr>
<td></td>
<td>de Menezes Neves et al. [47]</td>
<td>Increased IL-17 and tumor necrosis factor-α expression was detected by immunohistochemistry in biopsies of patients with acute rejection compared with control patients.</td>
</tr>
<tr>
<td></td>
<td>Millián et al. [48]</td>
<td>Increased soluble IL-17 in plasma was considered predictive of acute liver and kidney rejection.</td>
</tr>
<tr>
<td></td>
<td>Matignon et al. [49]</td>
<td>IL-17 mRNA levels were elevated in renal biopsies of transplant recipients with non-successful reversal of acute rejection.</td>
</tr>
<tr>
<td></td>
<td>Chung et al. [50]</td>
<td>Increased prevalence of Th17 cells was found in patients with chronic allograft nephropathy.</td>
</tr>
<tr>
<td><strong>AKI</strong></td>
<td>Mehrrota et al. [22]</td>
<td>Increased Th17 cells and IL-17+ and Orai+ PBMCs were detected in ICU patients with AKI vs. non-AKI patients.</td>
</tr>
<tr>
<td><strong>CKD/fibrosis</strong></td>
<td>Maravitsa et al. [51]</td>
<td>IL-17 levels were higher in septic patients that developed AKI than those that did not.</td>
</tr>
<tr>
<td></td>
<td>Coppock et al. [52]</td>
<td>Elevated IL-17 expression in biopsies of CKD patients with interstitial fibrosis.</td>
</tr>
<tr>
<td></td>
<td>Chung et al. [53]</td>
<td>End-stage renal disease was associated with IL-17-producing memory T cells.</td>
</tr>
<tr>
<td><strong>DN</strong></td>
<td>Zhang et al. [54]</td>
<td>Increased percentage of Th1 and Th17 cells and increased IL-6 expression was observed in patients with T2 DN.</td>
</tr>
<tr>
<td></td>
<td>Niewczas et al. [55]</td>
<td>IL-17A levels in plasma predicted progressive nephropathy in T1 and T2 DN patients.</td>
</tr>
<tr>
<td><strong>Hypertension</strong></td>
<td>Madhur et al. [56]</td>
<td>IL-17 levels were elevated in the serum of hypertensive diabetic patients vs. normotensive diabetic patients.</td>
</tr>
<tr>
<td></td>
<td>Yao et al. [57]</td>
<td>Serum IL-17 level was elevated in prehypertension (defined as BP of 120 to 139 mmHg) and in those patients with a diastolic BP of 80 to 89 mmHg vs. the optimal BP group.</td>
</tr>
<tr>
<td></td>
<td>Simundic et al. [58]</td>
<td>A correlation was observed between IL-17A level and the duration of hypertension in patients without BP control.</td>
</tr>
<tr>
<td></td>
<td>Hosseini et al. [59]</td>
<td>Serum IL-17 levels were increased in patients with pre-eclampsia.</td>
</tr>
</tbody>
</table>

AKI, acute kidney injury; ANCA, antineutrophil cytoplasmic antibody; BP, blood pressure; CKD, chronic kidney disease; DN, diabetic nephropathy; ICU, intensive care unit; mRNA, messenger RNA; NS, nephrotic syndrome; PBMC, peripheral blood mononuclear cell; RORγt, RAR-related orphan receptor gamma T; SLE, systemic lupus erythematosus; Th, T-helper cell; T_reg, T-regulatory; UTI, urinary tract infection.
Through interaction with its cognate receptor chemokine receptor 6 (CCR6), CCL20 was shown to be chemo-attractant to IL-17+CD3+ T cells in transwell experiments. These IL-17+ T cells showed enhanced expression of CCR6, and immunofluorescence staining identified a population of CD3+IL-17+CCR6+ cells in kidneys of IgAN patients but not in control kidney samples [70]. In the study of Paust et al. [67], infiltration of Th17 cells was attributed to an early increase in the expression of CCL20. Using a method dependent on a photo-convertible fluorescent protein in Kaede mice, Th17 cells were shown to traffic from the gut to the kidney in response to ANCA exposure. The migration of Th17 cells was dependent on the activity of the CCL20/CCR6 axis, and the severity of the disease and infiltration of Th17 cells could be up- or down-modulated by treatments that affected resident gut T cells [38].

Complications in renal transplantation

The Th17 system has also been suggested to contribute to rejection of solid organ transplants. Acute allograft rejection is initiated by alloreactive T cells primed in secondary lymphoid organs and recruited to the graft. There is increasing evidence that IL-17 expression in local tissue is associated with allograft rejection [71,72]. In the setting of kidney transplantation, IL-17 was identified by immunohistochemistry in biopsies of patients with acute rejection compared with control patients, while levels of Foxp3, a marker of T-regulatory (T$_{\text{reg}}$) cells that inhibits Th17 cells via the activity of IL-10, were reduced [46,47]. Chronic IL-17 expression in tubular epithelial cells was also shown to be associated with acute antibody-mediated rejection [45]. Some studies have suggested that outcomes in acute rejection are dependent on the degree of Th17 activation. For example, Millán et al. [48] showed that circulating IL-17 levels and the percentage of IFN-γ’CD4’CD69’ and IFN-γ’CD8’CD69’ cells could identify patients at high risk of acute rejection following either liver or kidney transplantation. Matignon et al. [49] demonstrated that elevated IL-17 messenger RNA (mRNA) in renal biopsies of elderly transplant recipients was associated with non-successful reversal of acute rejection. Recently, Nova-Lamperti et al. [73] demonstrated that tolerant recipients had fewer Th17 cells than patients with chronic rejection, while isolated peripheral blood mononuclear cells (PBMCs) from tolerant transplant recipients manifested reduced TCR signaling and Th17 differentiation compared to PBMCs from patients developing chronic rejection.

Evidence from animal models further supports a role for IL-17 in transplant chronic rejection [46]. In models of cardiac or liver allograft rejection, increased expression of IL-17 by both CD4 and CD8 cells was observed, and an imbalance in Th17/T$_{\text{reg}}$ cells was shown to be associated with allograft rejection [74–76]. In a liver model of allograft transplantation, immunoneutralization of IL-17 improved expression of T$_{\text{reg}}$ cells and liver survival [75], while IL17$^{-/-}$ mice exhibited increased T$_{\text{reg}}$ expression and survival following cardiac allograft transplant surgery [76].

Patients with chronic allograft nephropathy showed an increase in prevalence of Th17 cells following renal transplantation [50]. Mortazavi et al. [77] demonstrated that immunosuppressive therapy was associated with an improved Th17/T$_{\text{reg}}$ balance. Abadja et al. [78] demonstrated that mycophenolate has a stronger Th17 inhibitory effect than tacrolimus in in vitro activated human CD4 cells. In addition, these investigators showed that patients treated with both mycophenolate and low doses of tacrolimus had lower circulating levels of IL-17 than patients treated with tacrolimus alone. Low vitamin D levels have been shown to inversely correlate with Th17 cells in transplant recipients, and calcitriol supplementation was shown to suppress Th17 cells relative to treatment with tacrolimus alone [79]. These data suggest a role for Th17 cell responses in graft outcomes.

Responses in acute injury

As described above, T-lymphocytes as well as other immune cells are known to play roles in autoimmune and immune-mediated diseases as well as complications from renal transplant. However, other kidney disorders, such as acute injury, hypertensive and diabetic nephropathy, and the development of interstitial fibrosis, have a complicated pathophysiology that entails cellular responses to injury secondary to hypoxia, toxins, or elevated pressures, alterations in hemodynamics, activation of fibrogenic factors, and interstitial remodeling. Studies over the past few years have shown that the immune system plays a previously unappreciated role as a modulator of primary pathophysiological processes in these different types of kidney disease.

For example, AKI is a significant clinical disorder resulting
from renal ischemia or nephrotoxic injury. While damage to the renal microvasculature or tubular epithelium is the primary component in the pathogenesis of AKI [2], the potential role of inflammation as a modulator of renal injury has received significant attention over the last 15 years [80]. Yokota et al. [81] published several seminal studies describing the importance of lymphocytes as mediators of renal injury. Studies from this group using STAT4-/- mice suggested a potential role for Th1 in the pathogenesis of AKI, while studies using STAT6-/- mice suggested a potential role for Th2-derived IL-4 in protection from renal injury [82].

Recently, the potential contribution of Th17 cells to AKI has been examined. Our group demonstrated an increase in circulating IL-17+ PBMC and Th17 (CD4+IL-17+) cells in patients of intensive care unit after diagnosis of AKI vs. critically ill patients without AKI [22], while Maravitsa et al. [51] reported that IL-17 levels were increased in septic patients that developed AKI. Using a rat model of renal ischemia/reperfusion (I/R) injury, our research group demonstrated that Th17 cells were the predominant T-helper subtype present in the kidney following acute injury, peaking between 1 to 3 days post I/R but remaining persistently elevated for several weeks following recovery from I/R. Worsening AKI in rats that were placed on a vitamin D-deficient diet was associated with an increased number of Th17 cells and a decreased number of Treg cells compared to rats on a standard diet [83]. Treatment with sIL17RC or the store-operated Ca2+ entry channel (SOCC) inhibitor YM58483 blocked Th17 induction and significantly attenuated the development of renal injury [22,84]. Similar increases in Th17 cells in response to I/R injury have been reported in mice, while T-cell specific STAT3 deletion attenuated Th17 activation and resulted in protection against I/R [85]. In addition, rats with a mutation of the gene encoding RORyt showed impaired Th17 responses but not Th1 or Th2 responses, and were protected from renal injury by I/R [86]. In other models of AKI, such as the cecal-ligation puncture model of sepsis, IL17-/- mice showed reduced renal cytokine expression, neutrophil infiltration, and tubular injury relative to wild-type mice [87]. Chan et al. [88] demonstrated reduced injury in response to cisplatin treatment in IL17-/- mice and Roryt-/- mice, while our group demonstrated that Th17 blockade protected against AKI in glycerol-induced rhabdomyolysis [22]. The influx of Th17 cells in the setting of AKI may be due in part to the activation of CCL20 [88]. In addition, a recent study suggests that damaged renal tubules produce IL-17C, which may recruit Th17 cells to promote inflammation via binding to the receptor IL-17RE [89]. The precise mechanisms by which Th17 cells contribute to renal injury are not clear, but are likely related to an overall inflammatory response leading to recruitment of effector cells or contributions to vascular congestion and hypoxia.

Effective recovery from AKI is a result of a tissue repair response. However, incomplete or ineffective repair may predispose to the secondary development of CKD. The AKI-to-CKD transition may result from persistent alterations in vascular, tubular, and/or interstitial compartments [90]. Our group recently proposed a central role for persistent Th17 activity in this process. An AKI-to-CKD transition model was established by exposing rats to a high-salt diet after 5 weeks of recovery from I/R injury. This procedure, which hastened the development of inflammation, fibrosis, and hypertension, also potently stimulated the re-expression of Th17 cells [91]. CKD progression and hypertension in response to high-salt treatment was attenuated by mycophenolate, which also blocks induction of Th17 cells [84,92]. Th17 activation and CKD progression were also blocked by treatment with losartan or the SOCC inhibitor YM58483 [22,84]. Interestingly, the AKI-to-CKD transition in athymic nude rats, which lack conventional Th17-cells but display a compensatory increase in IL-17 production by natural killer cells (NK cells; CD3-/-CD161+), was also blocked by sIL17RC [84].

**Chronic kidney disease, fibrosis, and hypertension**

Biopsies of patients with renal fibrosis showed elevated renal IL-17 expression [52], while other studies have identified polymorphisms within the IL17E and IL17RA genes associated with ESRD [93]. CKD models associated with interstitial fibrosis, such as the unilateral ureteral obstruction (UUO) model [52,94-97] or adriamycin-induced nephropathy, are characterized by elevations in renal Th17 cells [98]. In all of these studies, strategies to neutralize IL-17 activity, either with antibodies or by using IL17-/- mice, mitigated the degree of renal fibrosis in these models. The fibrotic effect of IL-17 may be modulated by other cytokines. For example, the activity of the IL-17/IL-23 axis in inducing renal fibrosis was diminished in animals that lacked IL-36...
receptors [94], while IL27− mice showed increased Th17-induced fibrosis in response to UUO [99].

Diabetic nephropathy is known to have a strong inflammatory component and the role of Th17 cells in this setting has received significant attention in recent years [100]. Patients with type II diabetic nephropathy show a skew toward circulating Th1 and Th17 cells and have increased serum levels of IL-6 and IL-17, correlated with renal albumin excretion [54]. A recent study of both type 1 and 2 diabetes patients demonstrated that IL-17A and IL-17F were among a panel of proinflammatory cytokines that could predict CKD progression [55]. In addition to other studies that have demonstrated that Th17 cells may contribute to pancreatic beta cell destruction [101], these observations suggest an important role for Th17 cells in diabetic nephropathy.

In streptozotocin–induced diabetes, mycophenolate treatment reduced Th17 cell infiltration into the kidney and alleviated the development of albuminuria and renal fibrosis without effects on glycemic control [102], while IL17− mice, or mice treated with anti-IL-17 antibody were protected from the development of proteinuria and renal scarring [103]. Recently, Lavoz et al. [104] reported similar results; IL-17A immunoneutralization attenuated renal dysfunction and disease progression in BTBR ob/ob mice.

Renal inflammation also plays an important role in the development of hypertension [105,106]. Recent studies identified elevated levels of circulating IL-17 in patients with prehypertension, defined as a systolic BP of 120-139 [57]. In diabetic patients, IL-17 was elevated in those with hypertension vs. those without hypertension [56]. In another study of patients without blood pressure control, a correlation was observed between IL-17A level and the duration of hypertension [58].

Multiple animal models support the hypothesis that lymphocytes contribute to the development of hypertension. Genetic deletion of the Rag1 gene in Dahl salt-sensitive (S) rats resulted in depletion of mature T and B cells and a reduction in salt-sensitive hypertension [107]. In models of chronic angiotensin II (Ang II)-induced hypertension, the initial increase in blood pressure in response to Ang II infusion appeared largely independent of inflammation. However, sustained infusion of Ang II for up to 3 weeks in rats on a high-salt diet or in Dahl S rats resulted in increased renal lymphocyte accumulation, while mycophenolate treatment significantly abrogated the development of hypertension and renal fibrosis [108].

In C57BL/6j mice, Ang II infusion increased the percentage of circulating Th17 cells and IL-17A. IL17A− mice showed similar elevations in blood pressure in the first 2 weeks of Ang II infusion as wild-type mice, but developed less severe hypertension (~30 mmHg) and reduced inflammation during the subsequent 2 weeks of infusion [56]. Similarly, Wade et al. [109] reported that treatment with sIL17RC attenuated the degree of hypertension in Ang II-infused Dahl S rats. These data suggest that Th17 activation contributes to the full development of hypertension in Ang II-dependent models.

In other models, Amador et al. [110] demonstrated that mineralocorticoid-dependent hypertension was associated with activation of Th17 cells and the down-regulation of Foxp3 expression, while immuno-neutralization of IL-17 significantly attenuated the degree of hypertension and renal damage. Chiasson et al. demonstrated that the calcineurin inhibitor cyclosporine A increased expression of IL17A and IL-17 in diabetic nephropathy [59]. In a pregnant reduced uterine perfusion pressure (RUPP) rat model of pre-eclampsia, infusion of sIL17RC significantly attenuated the development of hypertension [112].

It has been suggested that renal injury and antigen presentation promote activation of adaptive immune responses in the setting of hypertension or following acute injury (reviewed in [105,106,113]). Other physiological factors may influence the degree of lymphocyte activation and modulate Th17 responses. For example, increased dietary salt intake has been shown to increase Th17 expression not only in models of kidney injury, but also other models of Th17-dependent inflammation [114–117], suggesting that the effect of dietary salt is not dependent exclusively on kidney damage. In vitro studies demonstrated that elevated extracellular sodium concentration can hasten differentiation of naïve Th0 cells to a Th17 phenotype in vitro [118]. It has been suggested that a high-salt diet can increase Na+ deposition in extracellular glycosaminoglycans in the skin, which has been postulated to increase local Na concentration relative to extracellular fluid [119].
Our group demonstrated that Ang II in combination with elevated extracellular sodium (170 mM) synergistically enhanced IL-17 production in CD4+ lymphocytes isolated from post-ischemic kidneys [91]. In addition, losartan dramatically attenuated Th17 cell accumulation in response to a high-salt diet following ischemic AKI, suggesting that the Ang II pathway contributes directly to activation of these cells [91]. Recent studies have shown that patients with salt-losing tubulopathies have reduced skin sodium content associated with reduced Th17 activation and impaired immune responses. It was suggested that an altered ionic environment resulted in reduced Th17 cells activity as lymphocytes from these patients were able to activate the Th17 pathway in vitro in response to extracellular sodium [120]. These studies further indicate that sodium status has a direct impact on the activation of Th17 cells.

**Effects of interleukin 17 effects on different renal cell types promote alterations in renal function and the development of fibrosis**

The role of Th17 cells likely varies in different types of kidney disease due to underlying differences in the etiology of various kidney diseases and the highly pleiotropic nature of IL-17A. As described above, IL-17 receptors are localized in neutrophils, which contribute to the strong proinflammatory effect of Th17 cells in inflammatory conditions. However, the precise roles of Th17 cells in different kidney diseases remain to be fully elucidated. As part of this process, an appreciation of the different cell types with the potential to be influenced by IL-17A is required.

To date, few studies have directly evaluated the presence of IL-17 receptors in the various cell types of the kidney. However, gene profiling studies are providing insight into the dynamics of IL-17-IL-17R expression. For example, Liu et al. [121] utilized a transgenic RNA-translating ribosome affinity purification (TRAP) approach to profile genes in a cell-type specific fashion in response to I/R injury. By incorporating Cre-specific promoters to drive tagged ribosomal protein expression, RNA isolated from tagged ribosomes was used for cell specific gene profiling. A search of the Gene Expression Omnibus (GEO) public data set utilized in this study [121] indicated that the highest baseline (i.e., non-injury) expression of IL-17RA mRNA was in the epithelial compartment. However, following renal I/R injury, relative IL-17RA mRNA expression was significantly induced by ~2.5, ~4, and ~6-fold in interstitial, endothelial, and myeloid-derived cells, respectively. Therefore, in addition to its effects on neutrophils, the expression of IL-17 receptors on multiple cell types points to a complex role for IL-17 in renal pathophysiology (Fig. 2).

**Effects on epithelial cells**

IL-17 likely mediates blood pressure responses in part by regulating renal sodium transporters in the epithelium. Norlander et al. [122] demonstrated that IL-17A upregulation secondary to angiotensin infusion increased the expression of the sodium hydrogen exchanger-3 (NHE 3) and the sodium chloride cotransporter (NCC). IL-17A treatment of mouse distal convoluted tubules or human proximal tubule cells in vitro also increased expression of these sodium transporters, which was dependent on the phosphorylation of serine/threonine-protein kinase (SGK)-1 [122]. In vivo, mice exhibited impaired diuresis and natriuresis responses to acute saline loads following chronic Ang II infusion, and this was significantly attenuated in IL17A−/− mice [123]. Damaged tubules also play an important role in the activation of inflammatory pathways leading to renal fibrosis [124,125], and IL-17 activity may contribute to this effect. In vitro studies of proximal tubule cells demonstrated that IL-17 stimulation increased the expression of profibrotic molecules and the production of IL-6 and IL-8, in part via activation of extracellular signal-regulated kinase 1/2 phosphorylation [50,126]. It is unclear if elevated IL-17 is sufficient to induce elevated blood pressure responses or if it serves to modulate other sodium-retaining factors to effect hypertension.

**Effects on endothelial cells and vascular smooth muscle cells**

Immune cells in the kidney may represent a source of oxidant stress. IL-17 has been shown to impair endothelial nitric oxide synthase activity, suggesting that altered vascular activity may also contribute to the development of hypertension [114,127]. A recent study by Orejudo et al. [128] suggested that vascular remodeling of small arteries is influenced by IL-17A. In this study, IL-17 induced hypertrophy of vascular smooth muscle cells in vitro, while IL-17 administration in mice increased blood pressure and
induced inward remodeling of small mesenteric vessels. Hydralazine normalized blood pressure but had no effect on the inward remodeling induced by IL-17 [128]. IL-17 also stimulates endothelial cells to promote neutrophil recruitment by activation of p38MAPK and STAT3 [129,130]. In brain-derived endothelial cells, TNF-α and IL-17 increased the production of CCL2 and CXCL1; other cytokines including CCL20 and IL-17 facilitated the migration of Th17 cells through the endothelial monolayer [131].

Activation of smooth muscle-like pericytes is considered to play a central role in the development of interstitial fibrosis [132]. No studies have directly evaluated the effects of IL-17 on renal pericytes or myofibroblasts in the setting of kidney disease. However, Th17 cells play a key role in asthma, and IL-17 has been shown to direct remodeling of airway smooth muscle [133]. Studies of pericytes and smooth muscle cells from other organs suggest that these cells are highly responsive to IL-17. Gene array analysis of human aortic smooth muscle cells found that over 30 genes, including inflammatory cytokines and chemokines, were stimulated by incubation with IL-17 [56]. Cultured dermal or placental microvascular pericytes stimulated with IL-17 produced soluble factors that enhanced neutrophil migration and stabilized pericyte/neutrophil interactions [134,135].

**Effects on macrophages**

In a model of wound healing, IL-17 administration increased
inflammation, aggravated fibrogenic scar formation, and delayed wound healing. Blockade of macrophages with clodronate reduced the inflammatory response to IL-17 and improved wound healing [136]. Ge et al. [137] investigated the effects of macrophage-specific deletion of IL-17RA in a model of UUO and demonstrated reduced accumulation of monocytes and renal fibrosis. It is unclear whether IL-17 influences macrophage polarization. One study reported that IL-17 stimulation of human monocytes did not alter M1/M2 markers but rather increased the expression of co-stimulatory molecules and proinflammatory cytokines in response to stimulation with oxidized low-density lipoprotein [138]. However, other studies suggested that IL-17 may mediate M2 polarization, consistent with an anti-inflammatory/pro-repair or fibrotic phenotype [139,140].

**Beneficial effects of interleukin 17 on outcomes in kidney disease models**

While the majority of evidence suggests that inappropriate activation of Th17 cells enhances inflammation and contributes to acute and CKD, these data should be viewed with caution, since several studies have reported that IL-17 may be protective in renal disease. Inhibition of IL-17 was reported to aggravate renal injury and fibrosis in a UUO model [141] and response to DOCA-salt/Ang II-induced hypertension [142]. An in vitro study demonstrated that IL-17 inhibited TGF-β stimulation of renal fibroblasts from IL17−/− mice following UUO [143]. Overexpression of IL-17 by adenovirus reduced inflammation and renal fibrosis, which was suggested to be the result of the local kallikrein-kinin system altering the balance of extracellular matrix-degrading enzymes [96]. In C57BL6/Ipr mice, a model of SLE, mutation of IL-17 blocked development of the SLE phenotype, but resulted in a significant lymphoproliferative disease characterized by splenomegaly and the expansion of total and double-negative T cells [144].

Mohamed et al. [145] showed that IL-17A levels in patients were reduced in advanced stages of diabetic kidney disease. In a streptozotocin model, IL-17A deficiency resulted in more severe disease progression relative to wild-type mice, and administration of low dose IL-17A reduced macrophage infiltration and the development of renal fibrosis. In our laboratory, RORyT mutant rats showed reduced sensitivity to AKI following I/R vs. wild-types rats. However, an increase in ischemic time in RORyT mutants resulted in failure to recover from AKI [86]. Administration of IL-17A facilitated recovery of postischemic RORyT mutant rats to a similar state as wild-type controls. Recovery from AKI due to IL-17 treatment was associated with inhibition of M1 macrophage infiltration, which remained elevated in untreated RORyT mutant rats for up to 4 days following I/R [86]. Taken together, these data suggest that the balance of Th17 cells plays an important role in immune homeostasis and may play an unappreciated role in feedback to suppress inflammation under some experimental conditions.

**Concluding remarks**

Since the discovery of Th17 cells, an important contributory role for these cells in kidney injury and fibrosis has been identified. We reviewed the accumulated research data implicating Th17 activation in models of kidney disease and hypertension. In addition, we outlined evidence that the primary cytokine produced by Th17 cells, IL-17A, may interact with multiple inflammatory and resident cells to drive disease. Due to its pleiotropic effects on multiple target cell types (outlined in Fig. 2), IL-17 is an attractive therapeutic target in several kidney disorders. Several reviews have addressed potential strategies to target IL-17 in disease, and biologic agents are already in use for treatment of diseases such as psoriasis [146]. An addition to biologics, other agents directed at SOCCs, which influence Th17 activation, are under development [147] and it is conceivable that such interventions may have therapeutic efficacy in patients with kidney disorders.

**Conflicts of interest**

All authors have no conflicts of interest to declare.

**Funding**

Work from the authors presented in this paper was supported by National Institutes of Health grant DK-063114 and a Bridge Funding award from the Indiana University Research Foundation (DPB). Purvi Mehrotra was supported by an Indiana University Showalter Fellowship.
Authors’ contributions

Conceptualization: All authors
Writing–original draft: All authors
Writing–review & editing: All authors
All authors read and approved the final manuscript.

Acknowledgements

We would like to thank Dr. Robert Bacallao for critical review of this manuscript and Ms. Barbara Sturonas-Brown for assistance with illustrations.

ORCID

David P. Basile, https://orcid.org/0000-0003-4649-3464
Md Mahbub Ullah, https://orcid.org/0000-0002-5712-6750
Jason A. Collet, https://orcid.org/0000-0002-0492-0926
Purvi Mehrotra, https://orcid.org/0000-0003-3102-4358

References

receptor related molecule IL-17RC as the receptor for IL-17F. *J Immunol* 2007;179:5462–5473.


133. Evasovic JM, Singer CA. Regulation of IL-17A and implications for TGF-β1 comodulation of airway smooth muscle remodeling.


A Korean perspective on the 2019 Kidney Disease Outcomes Quality Initiative guidelines for vascular access: what has changed and what should be changed in practice?

Hyung Seok Lee, Sung Gyun Kim

Division of Nephrology, Department of Internal Medicine, Hallym University Sacred Heart Hospital, Anyang, Republic of Korea

The Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines are developed by the National Kidney Foundation in the United States; however, the guidelines have an impact on most international societies, including those in Korea. The KDOQI recently released the updated 2019 guidelines for vascular access based on numerous papers and controversies concerning vascular access since 2006, when the first guidelines were published. The new KDOQI guidelines have undergone significant changes compared to previous guidelines, including a change in the philosophy regarding a patient-centered approach using an end-stage kidney disease “Life-Plan.” In addition, there are newly developed or revised definitions and some key differences from previous guidelines. The process of adapting guidelines needs to be individualized to hemodialysis practice in each country, while agreeing with general principles and philosophy; therefore, we summarize changes in the updated guidelines and discuss the application and implementation of the new principles and concepts of the guidelines for vascular access care in Korea.

Keywords: Arteriovenous fistula, Guideline, Kidney Disease Outcomes Quality Initiative, Renal dialysis

Introduction

Hemodialysis (HD) continues to be the most common treatment modality for patients with end-stage kidney disease (ESKD) in Korea [1]. The longevity of HD patients is closely related to the quality of dialysis treatment and depends on reliable and durable vascular access (VA), which is often referred to as the lifeline of HD patients. Furthermore, the medical cost of care for arteriovenous (AV) access continues to increase [2].

In addition to these medical and economic demands, the optimal care of VA based on new evidence from substantial research, technical improvements in devices, and changes in patient demographics has improved since the release of VA guidelines by the National Kidney Foundation (NKF) Kidney Disease Outcomes Quality Initiative (KDOQI)
in 2006 [3]. The KDOQI guidelines for VA were updated and released in 2019 [4] and contain many changes from previous guidelines. These changes are not only based on new information but also include information regarding the recalibration of evidence on which the previous guidelines were based (Table 1).

The 2019 guidelines were developed according to the GRADE (Grade of Recommendations Assessment, Development, and Evaluation) Evidence to Decision (EtD) framework [5,6], which is a more advanced step of the GRADE approach used in the development process of the prior guidelines. In that process, a higher level of evidence review was required, and it was led by an independent evidence review team (ERT). This team pooled the evidence through strict criteria with high standards, leading to the recalibration of previous evidence, which had implications for the 2006 guidelines. Some evidence previously classified as high-level evidence was downgraded to moderate- or low-level evidence by the ERT. As a result, these guidelines have a more significant evidence base for their recommendations and suggestions. For example, when a statement indicates that “There is inadequate evidence for KDOQI to make a recommendation,” the Work Group cannot make any recommendation, suggestion, or other evidence-based guidance based on the very low, low, or inadequate quality of evidence amassed by the ERT. However, this should not be interpreted as “do not recommend” or “do not suggest.” This simply indicates that the level of evidence is not sufficient to be a guideline for the rating, but that it is an important topic that needs to be included, so further research is needed.

There is underreported data that revision of the evidence could not counter. For example, there is no literature regarding vessel preservation, so new guidelines qualify for expert opinion statements. When the guidelines state that “KDOQI considers it is reasonable” or “considered reasonable,” this indicates expert opinions. To avoid misunderstanding of the revised guidelines, it is necessary to understand the GRADE approach before evaluating specific statements.

For the past several years, the optimal care of VA has been of paramount concern in Korean societies. In particular, nephrologists who were interested in VA care formed the Korean Society of Diagnostic and Interventional Nephrology (KSDIN) in 2010, which is supported by the Korean Society of Nephrology (KSN). The KSDIN has tried to establish the

| Table 1. Changes in the new guidelines compared to the previous guidelines |
|-----------------------------|-----------------------------|
| **Concept** | Fistula first, catheter last | AV access first, catheter last |
| **Definition** | AV access dysfunction and complications | AV access dysfunction and complications |
| | Thrombotic flow-related | Thrombotic flow-related |
| | Nonthrombotic flow-related | Nonthrombotic flow-related |
| | Infectious | Infectious |
| **Mature fistula** | Defined by satisfaction of rule of 6s | Defined as one that can provide prescribed dialysis consistently with two needles for >2/3 dialysis sessions within 4 consecutive weeks |
| **Catheter dysfunction** | Defined as a failure to attain and maintain an extracorporeal blood flow of 300 mL/min or greater at a prepump arterial pressure more negative than –250 mmHg | Defined as a failure to maintain the prescribed extracorporeal blood flow for adequate HD without lengthening the prescribed HD treatment |
| **Diagnostic criteria of catheter-related bacteremia** | Require blood draws from the peripheral vein | Allow blood draws from the HD circuit |

(Continued to the next page)
Key differences in guidance

Modality education
Patients with a GFR less than 30 mL/min/1.73m² (CKD stage 4) should be educated on all modalities of kidney replacement therapy options.

2019 KDOQI guidelines
Adult and pediatric patients with an eGFR less than 30 mL/min/1.73 m² (CKD G4) with progressive decline in kidney function (including failing transplant or PD) should be educated on all modalities of kidney replacement therapy options.

Timeline for AV access creation
AVF should be placed at least 6 months before anticipated HD start.

2019 KDOQI guidelines
In nondialysis CKD patients, AVF should be created 6–9 months before anticipated HD start.

Preoperative evaluation
Vascular mapping should be performed in all patients before placement of an access.

2019 KDOQI guidelines
Selective preoperative ultrasound in patients with high risk of AV access failure rather than routine vessel mapping in all patients.

Postoperative care
None.

2019 KDOQI guidelines
Adjuvant far-infrared therapy is suggested to improve AVF primary patency be based on individual circumstances.

AV access type & location
AVF are preferred; wrist > elbow > transposition

Then, AVG; forearm loop > upper arm AVG > necklace or lower extremity AVG

2019 KDOQI guidelines
Create AVF or AVG consistent with patient Life-Plan and overall goals of access care.

Site dependent on patient’s Life-Plan and anticipated duration of HD

Surveillance
Recommends organized monitoring/surveillance approach with regular assessment of clinical parameters of the AV access and HD adequacy.

2019 KDOQI guidelines
Does not suggest routine AVG surveillance by measuring access flow, pressure monitoring or imaging.

Inadequate evidence to support AVF surveillance beyond physical examination.

AV access maintenance
Preemptive PTA may be indicated in certain cases of abnormal physical findings.

2019 KDOQI guidelines
Does not recommend preemptive angioplasty of AV access with stenosis not associated with clinical indicators.

Intraluminal agents to prevent CVC dysfunction or CRBSI
None.

2019 KDOQI guidelines
Suggests that the selective use of once weekly prophylactic CVC locking with a thrombolytic agent (recombinant TPA) can be considered in patients in need of long-term CVCs.

Suggests that the selective use of prophylactic antibiotic locks can be considered in patients in need of long-term CVC who are at high risk of CRBSI (e.g., multiple prior CRBSI).

New technologies
The efficacy of stent grafts for the salvage of AVGs has not been compared with other strategies, but may provide better long-term results.

2019 KDOQI guidelines
Stent graft is suggested for treatment of clinically significant graft-vein anastomotic stenosis of AVG in preference to angioplasty alone when the stent-graft is used appropriately in view of patient ESKD Life-Plan and overall goals and targets.

Stent graft is suggested to treat in-stent restenosis in AVG and AVF for overall better 6-month post intervention outcomes.

Early cannulation graft is an option when a patient urgently starts HD without sufficient prior time to plan creation of AV access.

AV, arteriovenous; AVF, arteriovenous fistula; AVG, arteriovenous graft; CKD, chronic kidney disease; CRBSI, catheter-related bloodstream infection; CVC, central venous catheter (tunneled hemodialysis catheter); eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; GFR, glomerular filtration rate; HD, hemodialysis; KDOQI, Kidney Disease Outcomes Quality Initiative; PD, peritoneal dialysis; PTA, percutaneous transluminal angioplasty; TPA, tissue plasminogen activator.
best care for patients based on the data and situation in Korea. In line with this, we summarize the new guidelines, focusing on what has changed, and discuss how Korean experts will adopt the new principles and philosophy of the guidelines and apply those to patients in Korea.

**Change in concepts and definitions**

**Change in concepts (from ‘fistula first’ to ‘patient first’)**

The updated guidelines present a new concept of VA care based on the fact that each patient’s lifetime experience with chronic kidney disease (CKD) is very different. Therefore, we need an individualized approach to meet their needs. The previous KDOQI guidelines promoted the concept of ‘fistula first’; however, many studies have raised serious questions regarding this one-size-fits-all approach to VA, finding substantial heterogeneity across patients in the benefit derived from the creation of an arteriovenous fistula (AVF) [7–9].

Therefore, the new guidelines have emphasized a more patient-centered approach, which considers the complications and solutions according to the needs and preferences of each patient, and recommends establishment of an ‘ESKD Life-Plan’. The Life-Plan takes into account the next treatment modality for the individual patient along with dialysis access. While ‘fistula first’ is still important and should be supported when appropriate, ‘fistula first and catheters last’ is not the only message; getting the right access to the right patient at the right time for the right reasons is crucial.

Therefore, an approach that considers the next steps alongside the planning of the first VA has been emphasized. This planning provides many advantages, such as preserving the blood vessels necessary for the successful formation of dialysis vessels in the future and avoiding unnecessary procedures and complications. Therefore, the updated KDOQI focused on the P-L-A-N (Establish Patient Life-Plan, and then consider the corresponding Access Needs) approach for individual patients (Fig. 1). The “Patient Life-Plan” should be considered, including “Access Needs” for ‘What is next?’, such as a creation plan, contingency plan, and succession plan even before the initial VA is placed. The new KDOQI guidelines recommend an annual review and update of the patient’s individualized ESKD Life-Plan as well as a minimum quarterly review of VA functionality, complications, risks, and access options, which is a nephrologist’s responsibility. Hence, more active participation of nephrologists will be required for planning VA, rather than leaving it in the hands of the vascular surgeon.

**New and revised definitions of access use**

The new or updated definitions align with more modern practices for our dialysis patients. The old KDOQI guidelines presented the ‘rule of 6s’, which we were familiar with for over a decade. The new guidelines, however, state that a mature fistula is one that can provide the prescribed dialysis consistently with two needles for over two-thirds of dialysis sessions within 4 consecutive weeks. In Korea, adequate HD efficacy was clinically obtained in many cases, even though the prescribed blood pump flow was somewhat lower than in the United States or Europe. Therefore, even if the VA did not reach the 6s threshold, it was still often used successfully for HD.

In the previous KDOQI guidelines, catheter dysfunction was defined as the failure to attain an extracorporeal blood flow of 300 mL/min or greater with a prepump arterial pressure more negative than 250 mmHg. However, the

![Fig. 1. Individualized P-L-A-N (Patient Life-Plan and their Access Needs). The 2019 Kidney Disease Outcomes Quality Initiative guidelines for vascular access suggest considering the patient first, followed by planning vascular access consistent with their individual ESKD Life-Plan, which is the anticipated continuum of kidney replacement treatments (peritoneal dialysis, hemodialysis, transplantation, or conservative care). “Access Needs” include three main components: an access creation plan, access contingency plan, and access succession plan. Concurrently, there must always be a vessel preservation plan, to ensure viability for future access. ESKD, end-stage kidney disease.](https://www.krcp-ksn.org)
new guidelines define catheter dysfunction as a failure to maintain the prescribed extracorporeal blood flow required for adequate HD without lengthening the prescribed HD treatment. Prescribing HD treatment without prolonged HD time should be considered significant, and sometimes flow in the catheter at 250 to 270 mL/min is not regarded as a malfunction in Korea.

The definition of catheter-related infections incorporates the Centers for Disease Control and Prevention (CDC) [10] and Infectious Diseases Society of America (IDSA) [11] guidelines. It also considers the circumstances of the HD unit and patients, which made it more practical. Now, blood can be taken from dialysis circuits, which is an easier and faster way to make the diagnosis compared to venipuncture, which can further damage the native veins.

Access dysfunction is a very general term that is not specific with regard to the etiology of dysfunction. Therefore, the definitions of dysfunctions and complications have been divided more specifically and replaced with three terms; thrombotic flow-related, nonthrombotic flow-related, or infectious. This definition was also applied to complications. For example, stenosis or thrombosis is a thrombotic flow-related complication, and AV access aneurysm or steal syndrome is a nonthrombotic complication. The Work Group wanted to distinguish AV access dysfunction due to stenosis or thrombosis from other causes of dysfunction, such as aneurysm or steal syndrome.

Finally, infiltration injury was defined as vessel injury related to cannulation or the dialysis procedure and was categorized as minor, major, or severe cannulation injury according to the recovery period or the necessity for more active treatments, such as transfusion, hospitalization, and endovascular or surgical intervention. It is now recommended to report infiltration injury according to the classification in the new guidelines.

**Key differences in the statements of 2019 guidelines**

**Preparation for dialysis access and education on ESKD modalities**

When we talk about preparing our patients who are transitioning to dialysis either for peritoneal dialysis (PD) or a transplant, the old KDOQI guidelines support the idea that patients with a glomerular filtration rate (GFR) of <30 mL/min/1.73m² or with stage-4 CKD should be educated on all the modalities of kidney replacement therapy, including transplantation. However, the new guidelines state that adult and pediatric patients with GFRs of <30 mL/min/1.73m² and with progressive decline in kidney function, including kidney failure, transplant, or PD should be educated on all the modalities of kidney replacement therapy. This recommendation is derived from the fact that multiple papers support the idea that the patients who failed a transplant actually went back on catheter for multiple reasons. These included denial by the patient that their transplant was failing and the lack of preparation on the nephrologist’s part for access care and referring the patient in a timely fashion for permanent access [12]. In addition, the old KDOQI guidelines state that AV fistulation should be placed at least 6 months before the anticipated start of dialysis, whereas the new guidelines recommend a slightly longer interval of 6 to 9 months before the anticipated dialysis. We all acknowledge that it is difficult to estimate when a patient initiates dialysis, but we have some framework to help us.

**Preoperative evaluation**

The previous KDOQI guidelines suggested that vascular mapping should be performed in all patients before placement of AV access. One of the major changes that the new KDOQI guidelines presented is that selective preoperative ultrasound should be performed in patients who are at a high risk of AV access failure, rather than routine vessel mapping in all patients. High-risk patients include those who are elderly, female, or who have a history of central venous catheters or peripherally inserted central catheter lines, cardiac rhythm devices, peripheral vessel damage due to venipuncture, or comorbidities such as peripheral vascular disease and coronary artery disease. It is reasonable to individualize the mapping for certain patients, but considering the increase in elderly CKD patients, most patients would be included in the high-risk group. In addition, there are no absolute criteria for minimal vessel diameter in planning the creation of an AV fistula in the new guidelines. We are familiar with the idea that 2.0 to 2.5 mm for the vein and 2 mm for the artery were the recommended diameters for fistula creation [13–15]. The KDOQI guidelines note that there is a lack of evidence to support those
recommendations; however, it is crucial to assess the vessel wall condition along with vessel distensibility and calcification before the creation of AV access. Thus, the new guidelines state that it is reasonable to evaluate multiple characteristics of vessel quality for AVF creation (size, distensibility, flow, etc.).

**Order of preferences**

According to the concept of ‘patient first,’ which promotes individualized decision-making regarding access placement, the arteriovenous graft (AVG) or long-term catheter can be the first access option in some circumstances with valid reasons. Korea has one of the fastest-growing populations of elderly HD patients in the world, and more than 90% of patients start renal replacement therapy with HD. Therefore, whether the “fistula first” approach should also be applied in elderly patients is a crucial issue in Korea. AVFs have fewer complications once they mature, but they take more time to mature and are associated with a competing risk of death until the patient begins to derive benefits. Therefore, patient life expectancy becomes a significant concern. The survival benefit of AVF decreases as patient age increases \[16\]; therefore, individualized VA selection that considers patient morbidity, short life expectancy, and personal preference are necessary.

We are used to the idea of “catheter last” and the avoidance of long-term catheters if possible. The new KDOQI guidelines state that the use of tunneled or nontunneled catheters is actually reasonable in valid circumstances, which requires a substantial change of mindset.

The preference of ‘distal, nondominant arm’ emphasized in the previous guidelines remains an important principle, but it depends on the ESKD Life-Plan, vascular condition, and preference of the individual patient. The new guidelines state that the type and location of AV access be considered depending on whether the patient’s life expectancy is more than one year and whether the situation is urgent or not.

Site recommendations are dependent on the Life-Plan and anticipated duration of dialysis. Thus, placement of a forearm AVF, forearm loop AVG or proximal forearm AVF could be a reasonable choice for patients anticipated to live more than a year, while a forearm loop AVG, brachiocephalic AVF, or upper arm AVG could be a reasonable choice for patients anticipated to live less than a year. This idea is ideal, but the current tools for predicting estimates of the anticipated HD duration need more studies, so choosing access type and location should be based on the operator’s discretion and best clinical judgment in consideration of the patient’s ESKD Life-Plan. For urgent HD initiation, an early cannulation graft or catheter can be considered. Although the early cannulation graft is not available yet in Korea, we anticipate this will make significant changes in preparing for maintenance HD in the future.

**Monitoring and surveillance**

The updated guidelines do not suggest routine AVG surveillance and note that there is insufficient evidence supporting fistula surveillance beyond physical examination \[17–21\]. From the available data, the Work Group found that it is inadequate to make a recommendation for routine AVF surveillance through the assessment of access blood flow, pressure monitoring, or imaging for stenosis in addition to routine clinical monitoring to improve access patency. The new guidelines place a greater emphasis on monitoring and training regarding its application than on surveillance. The 2006 KDOQI guidelines recommended AV access imaging, as well as preemptive correction of stenotic lesions with more than 50% stenosis when critical AV access flow (Qa) values were present in addition to clinical findings. However, the 2019 KDOQI guidelines cast doubts on the diagnostic value and validated diagnostic thresholds of surveillance that are able to accurately predict stenosis leading to future thrombosis, and emphasize that monitoring should be the primary tool and surveillance should be used in a supportive role. Hence, nephrologists and dialysis staff responsible for HD treatment and VA care need to be properly trained in physical examination of AV access to monitor and recognize clinical indicators of AV access dysfunction \(\text{Table 2}\) \[4\]. However, there is ongoing debate regarding the role of surveillance; thus, this is one of the controversial changes in the new KDOQI guidelines. It is reasonable to believe that an effective surveillance method or validated threshold has yet to be found, rather than assuming that surveillance itself is ineffective or useless. Therefore, further research is mandatory to identify more reliable and reproducible surveillance techniques or indicators.
Indications for preemptive intervention

In the updated KDOQI guidelines, preemptive angioplasty of AV access (AVF or AVG) is not recommended for stenosis not associated with clinical indicators. Together with the statements on surveillance, this is the most notable change in the new guidelines which could impact the clinical practice of access care in South Korea, where percutaneous transluminal angioplasty (PTA) for the preventive purpose is still commonly implemented [2].

The 2006 KDOQI Work Group previously recommended AV access surveillance with preemptive angioplasty of stenosis for improving AV access outcomes. However, detection of stenosis in isolation is not clinically meaningful without inspecting the effect of intervention on clinically important outcomes, such as AV access thrombosis, patency, and intervention rates. Some studies on the outcomes of preemptive angioplasty that were rated as high quality in the 2006 guidelines were found to be underpowered in the updated 2019 guidelines, which contributed to the change in the recommendations for AV access surveillance and preemptive angioplasty. More clinical studies are necessary as the current data is not solid enough to show improved outcomes such as AV access patency after a prophylactic intervention on stenosis without clinical indicators. For AVF, the data were unclear, and for AVG, the data did not demonstrate improved patency with surveillance and subsequent preemptive intervention on graft with no clinical indicators when compared to routine clinical examinations [22,23]. Because the controversy of preemptive angioplasty is in part caused by an ambiguous definition, the new KDOQI guidelines attempt to clarify this by discussing prophylactic correction by focusing on its implementation for the stenosis with or without a clinical indicator [24].

Thus, it is emphasized in the topic as ‘do not intervene’ on a stenotic lesion if the stenosis is detected via surveillance in the absence of clinical indicators. In terms of AV access maintenance, the new KDOQI guidelines provide room for preemptive angioplasty, which is reasonable for patients with consistently persistent clinical indicators and underlying AV access stenosis to undergo preemptive angioplasty of their AV access to reduce the risk of thrombosis and loss of AV access. If not, preemptive correction of AV access should only be performed if it is associated with clinical indicators.

Clinically, it is important to refer patients timely for intervention through early recognition of clinical indicators from significant stenosis as well as to refrain from regular PTA scheduled regardless of clinical indicators. In Korea, therefore, it is crucial to educate health practitioners related to HD treatment on the application of monitoring to clinical indicators of AV access in addition to convincing physicians involved in PTA to intervene only if the clinical indicators meet the recommendations in the new guidelines.

Pharmacological primary and secondary prevention of arteriovenous-access flow dysfunction

The former guidelines did not discuss pharmacological

---

**Table 2. Clinical indicators (signs and symptoms) suggesting underlying clinically significant lesions during access monitoring**

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Clinical indicator</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical examination or check</td>
<td>Ipsilateral extremity edema &lt;br&gt; Alterations in the pulse, with a weak or resistant pulse, difficult to compress, in the area of stenosis &lt;br&gt; Abnormal thrill (weak and/or discontinuous) with only a systolic component in the region of stenosis &lt;br&gt; Abnormal bruit (high pitched with a systolic component) in the area of stenosis &lt;br&gt; Failure of the fistula to collapse when the arm is elevated (outflow stenosis) and lack of pulse augmentation (inflow stenosis) &lt;br&gt; Excessive collapse of the venous segment upon arm elevation</td>
</tr>
<tr>
<td>Dialysis</td>
<td>New difficulty with cannulation when previously not a problem &lt;br&gt; Aspiration of clots &lt;br&gt; Inability to achieve the target dialysis blood flow &lt;br&gt; Prolonged bleeding beyond usual for that patient from the needle puncture sites for three consecutive dialysis sessions &lt;br&gt; Unexplained (&gt;0.2 units) decrease in the delivered dialysis dose (Kt/V) on a constant dialysis prescription without prolongation of dialysis duration</td>
</tr>
</tbody>
</table>

primary and secondary prevention of AV access flow dysfunction, but the 2019 KDOQI guidelines included new information.

The KDOQI guidelines do not suggest the use of fish oil or aspirin for preventing AVF flow dysfunction. There was also inadequate evidence for making a recommendation on the use of oral simvastatin and ezetimibe for reducing AVF interventions or thrombosis. However, KDOQI evaluated the potential of the use of adjuvant far-infrared therapy for improving AVF primary patency and suggested its use according to individual circumstances, feasibility, and the clinician’s best judgment and expertise. Currently, adjuvant far-infrared therapy has been introduced limitedly in a small number of centers in Korea \[25\], but it is expected that more centers will implement adjuvant far-infrared therapy based on individual circumstances in the future.

**New technology**

While early cannulation graft, which is a new recommendation related to new technologies, is not yet available in Korea, a stent-graft (Covera Vascular Covered Stent; Bard Peripheral Vascular Inc., Tempe, AZ, USA) has recently become available. However, the stent-graft can be covered by insurance only in the usage for vessel rupture during endovascular treatment in Korea, while it is recommended for stenosis in the graft-venous anastomosis of AVG in the new KDOQI guidelines. We cannot predict insurance coverage for the application of stent-graft in the stenotic lesions in Korea, but we look forward to the use of stent-graft in the venous anastomosis of AVGs to reflect the new guidelines in the near future. In addition, the early cannulation graft should be introduced in Korea as it can help patients to avoid central venous catheter placement or reduce its duration.

**Korean perspective on the 2019 NKF-KDOQI guidelines for vascular access**

From a Korean nephrologist’s viewpoint, the patient-centered ESKD Life-Plan strategy is unfamiliar; the role of the

### Table 3. Korean perspective on the updated KDOQI guidelines for vascular access

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Key issues relevant to the clinical practice of Korean Nephrologists</th>
</tr>
</thead>
<tbody>
<tr>
<td>Access planning</td>
<td>An expansion of understanding the multidisciplinary approach for establishing an ESKD Life-Plan is necessary. More active involvement of nephrologists in the establishing the ESKD Life-Plan, planning VA, and enhancing interdepartmental cooperation is important for improving access care in Korea.</td>
</tr>
<tr>
<td>Preoperative evaluation</td>
<td>The population of elderly incident HD patients has increased in Korea, and most incident HD patients who need planning of VA creation may have one of the risk factors. In addition, Doppler US examination for access mapping is covered by national insurance in Korea, hence preoperative US mapping is anticipated to be performed in general.</td>
</tr>
<tr>
<td>Postoperative care</td>
<td>Currently, adjuvant far-infrared therapy is implemented in a limited fashion in a small number of centers in Korea, but it is expected that more centers will try adjuvant far-infrared therapy based on individual circumstances in the future.</td>
</tr>
<tr>
<td>Monitoring and surveillance</td>
<td>Currently, it is mandatory to measure the static venous pressure every month by the regular national assessment for dialysis adequacy in Korean hospitals, but this will need to be reconsidered in the future according to the new guidelines. In Korea, surveillance using UDT and Doppler US is covered by reimbursements from the national health insurance system, so it is increasingly being implemented. However, monitoring is primary, and surveillance should be applied as a supplementary method.</td>
</tr>
<tr>
<td>AV access maintenance</td>
<td>AV access stenosis is suggested to fall under two categories: stenosis associated with a clinical indicator or stenosis not associated with a clinical indicator. PTA should be considered only for stenosis accompanied by clinical indicators. It is not recommended except for patients with consistently persistent clinical indicators to undergo preemptive angioplasty, and timely surgical correction could be considered to comply with the goals and targets of VA care. There should be &lt;3 interventions to maintain AV access use per year. Regular scheduled PTAs, regardless of the presence of clinical indicators, are not suggested.</td>
</tr>
<tr>
<td>New technologies</td>
<td>Stent grafts for AV access became available in Korea recently, but these are reimbursed by the national insurance system only for the treatment of ruptured stenotic segments of AV access. Currently, early cannulation grafts are not available in Korea.</td>
</tr>
<tr>
<td>Future research</td>
<td>Currently, clinical trials for drug-coated balloons (KCT0003654) and plastic cannulation (KCT0003745) are underway in Korea, and are anticipated to report results in the next year.</td>
</tr>
</tbody>
</table>

AV, arteriovenous; ESKD, end-stage kidney disease; HD, hemodialysis; KDOQI, Kidney Disease Outcomes Quality Initiative; PTA, percutaneous transluminal angioplasty; UDT, ultrasound dilution technique; US, ultrasound; VA, vascular access.
nephrologist in the multidisciplinary team remains vague, and some of the statements or new technologies in the updated guidelines are currently not available (Table 3). To apply this new strategy in Korea and to develop a multidisciplinary approach, Korean nephrologists, who are directly involved in dialysis treatment and responsible for ESKD patients, should have an updated insight on the optimal care of VA considering their patient’s Life-Plan. Despite recognizing the importance of healthy VA for patients, clinical decisions on access care largely depend upon interventional radiologists or surgeons; therefore, VA management by nephrologists has been fragmented and limited in Korea. However, in 2010 with the support of the KSN, the KSDIN was established so that nephrologists could have a more active role in access care through different activities, including hands-on training with Doppler ultrasound for AV access, educating on the standards of dialysis access care suitable in Korea, developing academic programs for interventional nephrology fellowship, promoting research capabilities and building a registry cohort of VA procedures, and collaborating with national and international scientific communities. To broaden the understanding of the updated guidelines for health practitioners involved in dialysis access care, the KSDIN translated the 2019 KDOQI guidelines for vascular access into Korean and distributed it publicly. Therefore, more nephrologists have become interested in diagnostic and therapeutic procedures for VA; as a result, Doppler ultrasound examinations, tunneled HD catheter placements, and endovascular procedures by nephrologists have steadily increased in Korea [26]. In line with an increasing concern of nephrologists and along with the rapid growth of patients requiring HD in Korea, the new guidelines are expected to have a significant impact on patient care for VA, patient education, and training programs. Although the updated guidelines are based on limited clinical data from Korea and include a number of statements that cannot be currently practiced, the patient-centered approach based on the ESKD Life-Plan strategy will be introduced into our clinical practice through our strenuous effort for best practice of access care.

Summary

The new KDOQI guidelines outline the best-individualized care through a standardized process by review of the latest evidence and recalibrating previous data through the advanced GRADE-EtD format with high-quality standards. Although some controversies remain, the Work Group makes room for new evidence and provides suggestions for future research in the updated guidelines.

Table 4. Goals\(^a\) and targets

<table>
<thead>
<tr>
<th>ESKD Patient on HD Life-Plan Target</th>
<th>All ESKD patients on HD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Life-Plan goal: Establish and Document the Patient’s P-L-A-N, to be reviewed and updated annually. Component:</td>
<td></td>
</tr>
<tr>
<td>a) Patient Life-Plan: 1–2 year (short term) and 5-year plan (long term)</td>
<td></td>
</tr>
<tr>
<td>b) Access Needs: i) creation plan, ii) contingency plan, iii) succession plan</td>
<td></td>
</tr>
<tr>
<td>AV Access (Fistula or Graft) Target</td>
<td>All AV access (Fistula or Graft)</td>
</tr>
<tr>
<td>Intervention goal = “1-2-3” intervention as follows;</td>
<td></td>
</tr>
<tr>
<td>1. For each 1 AV access creation</td>
<td></td>
</tr>
<tr>
<td>2. There should be ≤2 interventions to facilitate AV access use</td>
<td></td>
</tr>
<tr>
<td>3. There should be ≤3 interventions to maintain AV access use per year</td>
<td></td>
</tr>
<tr>
<td>Access use refers to successful use of AV access with two-needle cannulation to achieve prescribed dialysis.</td>
<td></td>
</tr>
<tr>
<td>Central Venous Catheter Target</td>
<td>All CVC, regardless if the CVC is cuffed or not, tunneled or not, or the “final CVC” or not;</td>
</tr>
<tr>
<td>Infection goal = catheter-related bloodstream infection rate of &lt;1.5/1,000 catheter days</td>
<td></td>
</tr>
</tbody>
</table>

AV, arteriovenous; CVC, central venous catheter; ESKD, end-stage kidney disease; HD, hemodialysis.
\(^a\)Overarching goal: to achieve reliable, functioning, complication-free dialysis access to provide prescribed dialysis while preserving future dialysis access site options as required by the individual patient’s ESKD Life-Plan.

The new guidelines are less prescriptive than the previous 2006 guidelines in targeting the fine details in each area due to differences in practice patterns, thereby leaving more to the clinician’s discretion, but the guidelines also emphasize the importance of high-quality standards with defined targets for achieving the overarching goal of VA care (Table 4).

An emphasis is made across the entire document that all clinicians should be aware of the patient’s unique circumstances and needs, and apply a patient-centered approach for access care. Therefore, nephrologists in Korea should be actively involved in the planning and maintaining of VA based on the best clinical judgment, with careful application of the guidelines in order to achieve optimal patient outcomes.

The 2019 KDOQI guidelines for vascular access request that nephrologists have extensive experience and insight in coordinating and integrating multidisciplinary VA teams based on the patient’s ESKD Life-Plan. This will help us to attain the “right access, in the right patient, at the right time, for the right reasons,” providing new challenges and opportunities for the nephrology society in Korea.

Conflicts of interest

All authors have no conflicts of interest to declare.

Acknowledgments

We would like to thank all the members of the Korean Society of Diagnostic and Interventional Nephrology for supporting the review of 2019 KDOQI guidelines for vascular access and for their dedicated efforts and time in translating the updated guidelines into Korean.

Authors’ contributions

Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Visualization: HSL, SGK
Writing—original draft: HSL, SGK
Writing—review & editing: HSL, SGK
All authors read and approved the final manuscript.

ORCID

Hyung Seok Lee, https://orcid.org/0000-0001-6380-9243

Sung Gyun Kim, https://orcid.org/0000-0002-5034-0527

References


Pediatric acute kidney injury: new advances in the last decade

Sidharth K. Sethi¹, Timothy Bunchman², Ronith Chakraborty³, Rupesh Raina³,⁴

¹Department of Pediatric Nephrology, Kidney Institute, Medanta-The Medicity Hospital, Gurgaon, India
²Departments of Pediatric Nephrology and Transplantation, Children’s Hospital of Richmond at VCU, Richmond, VA, USA
³Akron Nephrology Associates and Cleveland Clinic Akron General Medical Center, Akron, OH, USA
⁴Department of Nephrology, Akron Children’s Hospital, Akron, OH, USA

Pediatric acute kidney injury (AKI) is a frequently missed complication. AKI has a significant impact on both short- and long-term outcomes in children. Within the last decade, there have been major landmark developments in this field of critical care pediatric nephrology. The topic was searched by two independent researchers using Google Scholar and PubMed and related studies published in the last 10 years. The terms used for the search were ‘pediatric acute kidney injury,’ ‘pediatric acute renal failure,’ ‘pediatric dialysis,’ ‘biomarkers,’ ‘nephrotoxins,’ ‘nephrotoxicity in children,’ and ‘pediatric critical care nephrology.’ We found that AKI is common in critically ill neonates and children. Among the various definitions, the Kidney Disease: Improving Global Outcomes (KDIGO) definition is most commonly used. In addition, it is imperative to risk stratify sick children at admission in the hospital to predict AKI and worse outcomes as this aids in early management. There are now major landmark trials that describe the epidemiology, prevention, and management guidelines in this field and health care professionals need to be aware they should diagnose AKI early. Overall, this review highlights the landmark studies in the last decade and shows that early diagnosis and management of AKI in ‘at risk’ children can improve outcomes.

Keywords: Acute kidney injury; Biomarkers; Critical care; Dialysis

Introduction

Acute kidney injury (AKI) is a common complication, affecting almost one-third of critically sick children and also noncritically ill children admitted to wards [1,2]. In the last decade, there has been a better understanding of outcomes in the field of pediatric AKI, which include higher morbidity, increased length of stay, duration of ventilation, and mortality [3,4]. There are newer studies on pediatric AKI epidemiology, clearly delineated definitions, newer biomarkers, and new criteria for risk stratification of children admitted in emergency situations. Additionally,
definitions and the understanding of neonatal AKI have undergone a drastic change due to recent studies [5]. There is now novel research on machines made especially for smaller children with smaller extracorporeal volume [6–8]. This review includes the major advances in the field of pediatric AKI in the last decade that have made a significant impact on learning and practice in this field (Fig. 1). This is a particularly important area of nephrology, where the clinical and translational advances have been performed first in pediatrics, much before the adult nephrology field.

**Changing epidemiology of pediatric acute kidney injury**

There is increasing evidence that the incidence and awareness of pediatric AKI is rising. In infants and children undergoing cardiac surgery, the incidence varies from 30% to 50% [9–12]. Additionally, it is common in pediatric intensive care units (ICUs) and has an incidence of 10% to 35% [13–15]. The rate is higher in children who are ventilated and are on inotropes [16]. AKI is also common in wards, especially in children receiving aminoglycosides and multiple nephrotoxins during their hospital stay [17,18].

The first prospective study on pediatric AKI, the Assessment of Worldwide Acute Kidney Injury, Renal Angina and Epidemiology (AWARE) study, was done over a 3-month observational period and included 4,683 children [19]. This study showed that AKI was seen in 26.9% of children, and severe AKI was seen in 11.6% of children within 7 days of ICU admission. This increase in AKI severity was associated with a stepwise increase in mortality. Additionally, cardiovascular and respiratory disorders had a higher association with severe AKI.

Among the neonate subgroup, the largest retrospective study in the neonatal population, known as Assessment of Worldwide Acute Kidney Injury Epidemiology in Neonates (AWAKEN), was performed in 2017. This study included more than 2,000 newborns in four different countries admitted to the neonatal ICU before 14 days of life, who received intravenous fluids for at least 48 hours. AKI was
seen in 30% of all newborns and was differently stratified per gestational age, with a higher incidence in extreme preterm birth infants. AKI was also associated with mortality and increased length of stay after adjusting for confounding variables [5].

Additionally, the etiology of AKI varies based on the geographic setting. In the developed world, the setting of AKI has shifted from primary glomerular disorders to hospital-acquired AKI, with common causes being nephrotoxins, critically ill status, postsurgical, posttransplantation, and malignancy [20,21]. In the developing world, especially in rural regions, the etiological factors remain as dehydration, sepsis, and hemolytic uremic syndrome [22].

**Newer definitions of pediatric acute kidney injury**

The ability of serum creatinine (SCr) to accurately estimate kidney function in a sick child has been problematic. This has resulted in the use of more than 35 definitions of AKI in clinical studies, ranging from changes in SCr to dialysis requirement. Earlier studies employed nonstandard AKI definitions without any grading (defining AKI as the doubling of SCr), thereby excluding early-stage AKI. Since there was no consensus in definitions, comparisons among studies were difficult, resulting in a wide range of quoted epidemiology, morbidity, and mortality rates within the pediatric AKI literature [23].

The Kidney Disease: Improving Global Outcomes (KDIGO) definition and staging system is the most recent and preferred definition even in pediatric AKI literature [24]. Other classification systems include pRIFLE (pediatric Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease) and a subsequent modification proposed by the Acute Kidney Injury Network (AKIN) [25,26] (Table 1). Each definition confers its own set of advantages and disadvantages. For example, pRIFLE can diagnose a greater number of mild AKI cases that are usually missed by the other two systems but requires patient height and baseline SCr value, which might not be readily available. In pRIFLE, the estimated creatinine clearance (CCI) is based on the original Schwartz formula to quantitate the change in glomerular filtration rate (GFR) rather than absolute changes in SCr used in the adult RIFLE criteria. Furthermore, the pRIFLE classification has outperformed the AKIN, KDIGO, and conventional grading criteria in predicting AKI in several pediatric patient populations. Zapitelli et al. [27] found that AKI prevalence increased when changes in estimated GFR (eGFR) (pRIFLE) were accounted for rather than changes in SCr (AKIN) in pediatric inpatients. Additionally, Sutherland et al. [23] recently demonstrated notable differences in incidences and substantial disparities in staging resulting from the use of these three definitions on the same cohort of hospitalized children. The AKIN definition appears more specific and does not require height and baseline SCr values; however, it has the most restrictive diagnostic timeframe. The AKIN system, which defines AKI

<table>
<thead>
<tr>
<th>Classification</th>
<th>Staging</th>
<th>Creatinine criteria</th>
<th>Urine output criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>pRIFLE</strong></td>
<td>Risk</td>
<td>eGFR decreased by ≥25%</td>
<td>0.5 mL/kg/hr for 8 hr</td>
</tr>
<tr>
<td></td>
<td>Injury</td>
<td>eGFR decreased by ≥50%</td>
<td>0.5 mL/kg/hr for 16 hr</td>
</tr>
<tr>
<td></td>
<td>Failure</td>
<td>eGFR decreased by ≥75% (or &lt;35 mL/min/1.73 m²)</td>
<td>0.3 mL/kg/hr for 24 hr or anuria for 12 hr</td>
</tr>
<tr>
<td></td>
<td>Loss</td>
<td>Persistent failure &gt;4 wk</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ESRD</td>
<td>Persistent failure &gt;3 mo</td>
<td></td>
</tr>
<tr>
<td><strong>AKIN</strong></td>
<td>1</td>
<td>Increase in creatinine of ≥50% or an absolute increase in creatinine of 0.3 mg/dL over 48-hr period</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>Increase in creatinine of ≥100%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>Increase in creatinine of ≥200%</td>
<td></td>
</tr>
<tr>
<td><strong>KDIGO</strong></td>
<td>1</td>
<td>SCr rise ≥0.3 mg/dL within 48 hr or an increase in creatinine of ≥50% within 7 day</td>
<td>&gt;0.5 and ≤ 1 mL/kg/hr</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>Increase in creatinine of ≥100%</td>
<td>&gt;0.3 and ≤ 0.5 mL/kg/hr</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>Increase in creatinine of ≥200% or SCr ≥4 mg/dL or receipt of dialysis or eGFR&lt;35 mL/min/1.73 m² (neonatal cut-off, SCr ≥2.5 mg/dL)</td>
<td>≤ 0.3 mL/kg/hr</td>
</tr>
</tbody>
</table>

AKIN, Acute Kidney Injury Network; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; KDIGO, Kidney Disease: Improving Global Outcomes; pRIFLE, pediatric Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease; SCr, serum creatinine.
showing that the urine and plasma levels are significantly
of NGAL have been done in children post cardiac surgery, gelatinase-associated lipocalin (NGAL)
and validated early biomarker in children is neutrophil
novel biomarkers that appear in urine or plasma well before
show that it is an early predictor biomarker of AKI
estimation of GFR. Moreover, there is now pediatric data to
12 months of age
muscle mass, and are identical in adults and children over
glomerulus, and is catabolized by the proximal tubule.
The plasma cells are not affected by sex, age, diet, or
increased filtration, decreased tubule reabsorption, and
proximal tubule cell TIMP2/IGFBP7 urinary leakage seem to
be the most likely mechanisms [38].

There is recent interest in patients who are ‘biomarker
positive; creatinine negative’ which means their urinary
or serum early biomarkers are high while SCr is normal.
Two recent studies enrolled more than 4,000 cardiac
surgical, critically ill and emergency patients [39,40]. Both
studies showed almost >20% of patients had only elevated
NGAL in urine. These ‘subclinical AKI’ patients in fact had
two- to three-fold higher risk of death and need for renal
replacement therapy (RRT). Even in patients with very high
creatinine, markedly high tubular markers in urine had a
worse prognosis.

Hence, NGAL and a panel of urinary or serum biomarkers
may help clinicians make an early diagnosis of AKI and
plan supportive care early. Moreover, structural biomarkers
may further help in reliably classifying AKI in a mechanistic
manner. The various functional and structural markers are
illustrated in Table 2.
While fluid overload in children itself is not a direct marker of mortality, the adverse effects lead patients to become vulnerable to an increased risk of morbidity and mortality. It also puts patients at risk of being underdiagnosed with AKI and delays treatment, raises odds for mortality associated with complications, can lead to increased hospital and ICU stays, and can prolong ventilator support in the critically ill population [52].

Furosemide stress test to risk stratify patients
Clinicians have access to limited tools that predict which patients with early AKI will progress to more severe stages. In early AKI, urine output after a furosemide stress test (FST), which involves intravenous administration of furosemide (1.0 or 1.5 mg/kg), can predict the development of stage-3 AKI [53]. There are recent studies which suggest use of this test alone or in combination with biomarkers may predict progression to a severe stage of AKI in sick patients. Using an FST in patients with increased biomarker levels may improve risk stratification [53].

Newer laboratory tests in acute kidney injury differentiation
Automated urine technology and centralized laboratory testing are becoming the standard for providing urinalysis data to clinicians. It is critical to remember that urine sediment examination remains a time-honored test that provides a wealth of information about the patient’s underlying kidney disease. This test performs very favorably as a urinary “biomarker” for a number of acute kidney diseases. Prerenal AKI from true or effective volume depletion is generally not associated with tubular injury/necrosis. In this setting, urine sediment is usually bland with no/few cells and casts. On the other hand, urine examination is one of the most useful tests in the diagnosis of acute interstitial nephritis and acute nephritic syndrome [54].

In addition to the tests that are commonly used in diagnosing etiology and complications of AKI, urinary indices, especially the fraction excretion of urea (FeUrea),

### Risk stratification at admission: application of ‘Renal Angina Index’

Renal Angina Index (RAI) combines objective parameters of kidney dysfunction (change in Scr and percent change in fluid overload [%FO]) and patient characteristics (AKI risk factors) to ascertain renal angina and has been successfully validated as a functional risk stratification tool in critically ill patients with AKI. An RAI of ≥8 within the first 12 hours of ICU admission has shown to entail very high sensitivity and negative predictive value for AKI development or persistence at 72 hours of ICU admission in children [41,42]. RAI is a risk discrimination model that enhances the pretest probability of AKI. It renders context to biomarker measurement and significantly optimizes their predictive performance, akin to the cardiac angina-troponin relationship. RAI has been shown to correlate with an increased need for RRT, prolonged mechanical ventilation, higher oxygenation index, and a higher risk of mortality when compared to children with a negative index score [43,44]. RAI entails moderate discrimination for predicting severe AKI prediction, but it improves after incorporation of biomarkers [45].

### Clinical examination

**Watch for fluid overload**

Over the last decade, there have been studies in the adult population [46,47] and pediatric population (composed of neonates [48], post cardiac surgery [49], children with multiple organ dysfunction [50], and those on dialysis [51]) that have shown that fluid overload is common and is detrimental in sick patients. It is now well practiced in the intensive care to look at the percent fluid overload in sick children.
have recently been studied. It is well known that the fractional excretion of sodium (FeNa) is >2% in children and >2.5% in neonates with a higher urine sodium >30 meq/L, which suggests tubular damage, e.g., acute tubular necrosis in the AKI setting. However, in certain situations of diuretic therapy or where the patient is on intravenous saline or presents with chronic kidney disease, FeNa may not be reliable. FeNa can then be substituted by FeUrea \[55\]. A FeUrea <35% implies prerenal AKI and FeUrea >50% suggests intrinsic AKI. A high FeNa and FeUrea >35% have a 95% negative predictive value for intrinsic AKI \[56\].

**Neonatal acute kidney injury: newer advances**

The major challenges confronted by clinicians involved in the care of neonates with AKI stem from numerous factors; unique renal physiology in term and preterm neonates, lack of a standardized AKI definition, and weight- and gestational age-dependent baseline SCr value in the neonates. Moreover, neonates usually have nonoliguric renal failure, making oliguria an insensitive marker of AKI in this cohort \[57\]. Neonatal AKI is further confounded by the reflection of maternal SCr levels in neonates for the first 3 days postbirth and the variable decline over days to weeks depending on gestational age \[58\].

The formation of the Neonatal Kidney Collaborative (NKC) was a giant leap forward which accomplished the heretofore unmet need of neonatal AKI quantification at a global level. The AWAKEN study retrospectively evaluated 2,022 neonates from 24 centers across the globe, which formed the NKC. The group concluded that neonatal AKI is common, with an incidence of 29.9%, and is an independent risk factor for mortality and prolonged hospital stay, independent of demographics, severity of illness, and existing comorbidities. The incidence of AKI was 43% in patients <29 weeks gestation, 18% in those between 29 and 36 weeks gestation, and 37% in those >36 weeks gestation \[5\].

Since maternal SCr is transmitted across the placental barrier and its clearance is dependent upon the infant’s gestational age, the KDIGO definition was modified in such a manner that baseline SCr was assumed to be the lowest SCr level noted in each infant. Also, the SCr threshold for stage-3 AKI was reduced to 2.5 mg/dL rather than usual KDIGO threshold of 4 mg/dL \[59\].

A recent secondary analysis from AWAKEN also showed that caffeine administration in preterm neonates is associated with reduced incidence and severity of AKI. Further studies should focus on the timing and dosage of caffeine to optimize the prevention of AKI \[60\]. Other ancillary studies from the same group include a report on the association of AKI and hypertension \[61\], a study showing the association between AKI and mortality in those with severe neonatal encephalopathy \[62\], the association of AKI and intraventricular hemorrhage \[63\], and the association of AKI and chronic lung disease in premature and near term/term infants \[64,65\].

**Neuwer machinery for smaller children**

In the last decade, major innovations have been made in designing dedicated machinery with less error for dialysis of newborns and children. The most notable are the Prismaflex HF20 filter (Gambro, Mézyieu, France), the CARDiorenal PEDiatric Emergency Machine (CARPEDIEM; Bellco-Medtronic, Mirandola, Italy), the Newcastle Infant Dialysis and Ultrafiltration System (NIDUS); and the Aquadex system (Baxter Corp., Minneapolis, MN, USA).

**Prismaflex HF20 filters**

Continuous RRT (CRRT) with Prisma or Prismaflex dialysis machines and M10 (50 mL) or HF20 (55 mL) filters with access via the internal jugular; 6.5 French hemodialysis (HD) catheters may be used. The Prismaflex HF20 set has recently been developed with relatively low circuit volume (60 mL) and is made of a polyarylethersulfone membrane, which is not associated with bradykinin release syndrome. There have been recent reports of successful use of HF20 filters in unstable infants \[66,67\].

**CARPEDIEM**

The challenge to design RRT equipment specifically intended for newborns and small infants weighing in the range of 1.5 to 10 kg led to development of the CARPEDIEM system. It received European certification in 2012 after thorough testing. It is a combination of hardware, software, and disposable circuits miniaturized and designed specifically for newborns and small infants with a reduced priming volume (27 mL including filter) with the roller pumps finely regulated by two precision scales accurate to 1 g. It was used for the first time on a neonate in 2013.
and can be used in situations when adequate convective clearance is insufficient due to limited blood supply like in hypercatabolic states, where there is a need for increased dialysis efficiency [68,69].

**NIDUS**

NIDUS evolved as a novel HD circuit driven by syringes and uncouples the baby’s blood flow capacity from requirements of the dialysis filter. The syringe-driven machine repeatedly withdraws 5 to 12.5 mL aliquots of blood from a single lumen central venous line, passes and returns it across a dialysis filter, and then returns it back to the baby. At a blood flow rate of 20 mL/min, this processes 5 mL of blood each minute [8]. A multicenter trial on the use of NIDUS is recruiting babies in the pediatric ICU with a body weight of 0.8 to 7.99 kg, who require continuous dialysis as part of their standard clinical care. The recruitment started in January 2015 and is proposed to continue till December 2020 in the UK [70].

**Aquadex**

In order to mitigate the concerns regarding use of large extracorporeal circuits, the Aquadex circuit was adapted to provide prefiler replacement fluid for continuous venovenous hemofiltration (CVVH). The filter is 0.12 m² and composed of a polysulfone membrane. Ultrafiltration rates of up to 500 mL/hr can be achieved for clearance of waste products. A recent pediatric experience of Aquadex has been published on ultrafiltration to provide a range of therapies, including CVVH, prolonged intermittent RRT, and slow continuous ultrafiltration. The group was able to initiate RRT with minimal complications, particularly in critically ill neonates [6].

**Better understanding in prevention of pediatric acute kidney injury**

**Drugs to prevent acute kidney injury**

**Furosemide and bumetanide**

In order to improve urine output in critically ill patients, furosemide has been used to maintain fluid balance. However, studies in adults have not provided any evidence that diuretics improve survival or help in recovery of AKI [71]. Studies in infants undergoing cardiac surgery have shown that furosemide infusion may be used instead of boluses to improve urine output [72]. Recently, bumetanide, a newer loop diuretic, has been used in preterm infants with oliguric AKI. While increasing urine output, there was a rise in SCr, highlighting the potential that loop diuretics can cause nephrotoxicity in this vulnerable population [73].

**Low-dose dopamine**

Low-dose dopamine in neonates and pediatric ICU patients failed to demonstrate an improvement in kidney function and urine output [74]. Moreover, there is recent evidence of worsening renal perfusion with this dose itself [75].

**Fenoldopam**

A recent study on fenoldopam, a selective dopamine A1 receptor agonist that decreases vascular resistance and increases renal blood flow, improved urine output in neonates requiring cardiac surgery with positive fluid balance despite diuretics [76]. Another recent study showed that a higher dose of 1 μg/kg/min during cardiac surgery may reduce the urinary NGAL and serum cystatin C levels, even without any changes in SCr [77]. However, the data is sparse on this drug.

**Theophylline**

During perinatal hypoxia in neonates, adenosine is released, which may cause vasoconstriction in the kidney causing a reduction in GFR [78]. Thus, nonspecific adenosine receptor antagonists, such as aminophylline and theophylline, may help in this specific setting. Three recent randomized trials showed a reduction in SCr and better urine output in severely asphyxiated neonates who were given a single dose of theophylline [78-81]. Based on these trials, KDIGO also recommends a single dose of theophylline for asphyxiated neonates since they are at risk of AKI [82]. However, there are concerns about neurological side effects, and more so the relevance of these drugs in the era where hypothermia is a standard of care in these neonates.

**Rasburicase**

There is a recent interest in rasburicase (a recombinant urate oxidase enzyme) with a retrospective study in seven neonates with AKI. A single bolus of rasburicase reduced SCr, blood urea, and urine output [83]. However, more evidence is needed for the use of this drug in the treatment of AKI in neonates and children.
Electronic hospital software alerts to help clinicians prevent acute kidney injury

Recently, electronic software integrated within hospital management servers has been successfully used to prevent AKI by alerting clinicians well in time. Nephrotoxic Injury Negated by Just-in-time Action (NINJA) is a prospective AKI monitoring program used in Cincinnati Children’s Hospital. It uses an automated program to extract data in real time and flags noncritically ill children who are admitted and are receiving three or more nephrotoxins. These children undergo a daily surveillance of SCR, and the center noted a 38% reduction in the rate of nephrotoxin exposure and a concomitant 64% reduction in AKI rates [84]. Recently, a Baby-NINJA initiative in multiple neonatal ICUs reported a reduction in high nephrotoxic medication exposures from 16.4 to 9.6 per 1,000 patient-days (p = 0.03) and a reduction in percentage of nephrotoxic medication-AKI from 30.9% to 11.0% (p < 0.001) [85].

Newer advances in dialysis for children

RRT modalities for pediatric AKI have expanded from peritoneal dialysis (PD), HD to CRRT and sustained low-efficiency dialysis (SLED). Advancements in use of RRT in children have led to a higher standard of care for young and critically ill patients [86]. Since no difference in survival outcomes has been seen with any dialysis method, the optimal RRT modality to be chosen for children with AKI is based on the patient’s size, overall clinical status, on the performance of the dialytic modality, and the availability of resources and expertise [87].

PD is the most common and simple method of providing solute and water removal in the ICU. It is easy to perform, can be easily learned, and does not require vascular access or anticoagulation. In a recent worldwide survey by Raina et al., 68.5% of respondents in developing countries preferred PD for treating infant AKI while only 29.1% of physicians in developing countries and 22.2% in developed countries favored PD to treat AKI [88]. Additionally, certain modifications to PD have been made recently to improve ultrafiltration, namely continuous equilibration PD, high volume PD, tidal PD, and continuous flow PD [89].

HD is the most efficient method of dialysis with rapid solute and fluid removal. It is ideal for managing pulmonary edema, hyperkalemia, intoxications, hyperammonemia, and acute tumor lysis syndrome [90]. However, patient hemodynamic stability is a must for a child to be put on HD. It does require a vascular access, careful evaluation of the extracorporeal blood volume (in the circuit and the dialyzer), and the need for anticoagulation [90]. Recently, the Pediatric Continuous Renal Replacement Therapy Foundation (PCrRT) gave recommendations on how to avoid intradialytic hypotension in children [91].

CRRT is the preferred modality for the management of AKI and fluid overload in critically ill children. It can be used with both or one of the diffusion or convection strategies. It is a complex dialysis modality that requires expertise and systemic heparin or regional citrate anticoagulation. The Prospective Pediatric CRRT Registry Group has published guidelines for dialyzing children with sepsis and multiorgan dysfunction in the last decade [51,92,93].

SLED is an alternative to CRRT in hemodynamically unstable pediatric patients with AKI. It utilizes conventional dialysis machines with low blood pump and dialysate flow rates for ≥6 hours daily. Recently, Sethi et al. [94,95] published a retrospective and prospective experience of SLED in unstable pediatric patients utilizing heparin-free dialysis and prefiltre convective replacement fluid.

Conclusion

Management of AKI is challenging in critical infants and children. Over the past decade, revolutionary landmark studies and machineries have evolved, greatly improving the diagnosis, early detection, and management of renal support in this population. The pediatric nephrology community is working together closely to provide more scientific data to improve renal support in smaller critically sick children.

Conflicts of interest

All authors have no conflicts of interest to declare.

Authors’ contributions

Conceptualization: SKS, TB, RR
Data curation: All authors
Formal analysis: All authors
Investigation: All authors
Methodology: All authors  
Project administration: All authors  
Writing-original draft: SKS, RC, RR  
Writing-review & editing: SKS, RC, RR  
All authors read and approved the final manuscript.

ORCID

Sidharth K. Sethi, https://orcid.org/0000-0002-1516-3393  
Timothy Bunchman, https://orcid.org/0000-0002-1781-0398  
Ronith Chakraborty, https://orcid.org/0000-0003-1865-9682  
Rupesh Raina, https://orcid.org/0000-0003-3892-8376

References


74. Prins I, Plötz FB, Ulterwaal CS, van Vught HJ. Low-dose...


Trends in epidemiologic characteristics of end-stage renal disease from 2019 Korean Renal Data System (KORDS)

Yu Ah Hong¹, Tae Hyun Ban¹, Chae-Yeong Kang², Sun Deuk Hwang³, Sun Ryoung Choi⁴, Hajeong Lee⁵, Hee-Yeon Jung⁶, Kyeongmin Kim⁷, Young Eun Kwon⁸, Su Hyun Kim⁹, Tae Hee Kim¹⁰, Ho-Seok Koo¹⁰, Chang-Yun Yoon¹¹, Kiwon Kim¹², Jongha Park¹³, Yong Kyun Kim¹

¹Department of Internal Medicine, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea
²The Korean Society of Nephrology, Seoul, Republic of Korea
³Department of Internal Medicine, Inha University College of Medicine, Incheon, Republic of Korea
⁴Department of Internal Medicine, Hallym University Dongtan Sacred Heart Hospital, Hwaseong, Republic of Korea
⁵Department of Internal Medicine, Seoul National University Hospital, Seoul, Republic of Korea
⁶Department of Internal Medicine, School of Medicine, Kyungpook National University, Kyungpook National University Hospital, Daegu, Republic of Korea
⁷Department of Internal Medicine, Daegu Eulji Medical Center, Eulji University, Daegu, Republic of Korea
⁸Department of Internal Medicine, Myongji Hospital, Hanyang University College of Medicine, Goyang, Republic of Korea
⁹Department of Internal Medicine, Chung-Ang University Hospital, Seoul, Republic of Korea
¹⁰Department of Internal Medicine, Inje University College of Medicine, Busan, Republic of Korea
¹¹Yoon’s Medical Clinic Dialysis Center, Seoul, Republic of Korea
¹²Seoul One Clinic, Anyang, Republic of Korea
¹³Department of Internal Medicine, Ulsan University Hospital, University of Ulsan College of Medicine, Ulsan, Republic of Korea

Background: The Korean Society of Nephrology (KSN) has maintained a nationwide end-stage renal disease (ESRD) registry data from Korean Renal Data System (KORDS) since 1985, as the representative registry of ESRD patients in Korea. This review is aimed to update the status of domestic ESRD and to provide evidence on the direction of dialysis therapy.

Methods: The KORDS Committee of KSN has collected data on dialysis centers and patients through an online registry program, and the data from 1986 to 2019 were analyzed.

Results: The incidence and prevalence of ESRD patients in Korea are increasing. The ESRD population numbered more than 100,000 in 2019, doubling during the 10 years since 2010. The proportion of diabetes mellitus as a major cause of ESRD seems to
Introduction

The incidence and prevalence of end-stage renal disease (ESRD) requiring renal replacement therapy (RRT) either by dialysis or kidney transplantation (KT) have progressively increased in countries around the world, including Korea [1,2]. Identifying ESRD incidence and prevalence is of vast importance so that policymakers and health care providers can develop public health care plans for ESRD patients. The Korean Society of Nephrology (KSN) launched a nationwide ESRD patient registry, Korean Renal Data System (KORDS), in 1985, which has continued for over 35 years. The goals of the KORDS are as follows: (1) to estimate the numbers and distributions of ESRD patients; (2) to determine the characteristics of ESRD and dialysis therapy and their complications or outcomes based on scientific evidence; and (3) to improve the quality of dialysis therapy and support public health decisions related to ESRD [3]. Every year, the KSN releases an annual report from KORDS, which presents an overview of the incidence and prevalence of RRT including KT, the characteristics of patients, and the survival of patients on RRT in Korea. In this article, we provide a summary of the 2019 KORDS annual report. This article presents the most recent data on the epidemiology of RRT for ESRD, which focuses on the incidence and prevalence of RRT and ESRD mortality trends in Korea. More detailed data from the KORDS are available through the KSN website (http://www.ksn.or.kr).

Methods

The KORDS was populated with responses from mailed paper questionnaires from 1985 to 1994. An electronic questionnaire with dial-up modem file transfer or diskette mailing was used from 1995 to 2000 [4]. An internet-based questionnaire for dialysis patient registry has been administered by the KSN since 2001 via an online registry program on the KSN website and is updated yearly [5]. Enrollment in the registry is voluntarily updated by members of the KSN. The registry program has collected data throughout the years, and the collected data include dialysis center information, dates of hemodialysis (HD) or peritoneal dialysis (PD) initiation, newly developed comorbid diseases, vascular access, dialysis doses, medications including erythropoiesis-stimulating agents and phosphorus-controlling agents, laboratory data, dialysis adequacy, rehabilitation status, and outcomes for each patient on HD, on PD, or who had undergone KT. Among these data, this study analyzed the changes in incidence and prevalence rates and outcomes in ESRD patients from 1986 to 2019. Because the survival data from 1986 to 2000 were insufficient, the analyses of incidence and prevalence of ESRD patients were performed from 1986 to 2019, but the analyses of outcomes were performed from 2001 to 2019. The KT recipients were excluded from outcome analysis. A flow diagram for patient selection is presented in Supplementary Fig. 1 (available online). Trends in mortality rates are presented for the patients treated each year according to the number of patient-years at risk. Unadjusted survival rates were calculated using the Kaplan-Meier method, and absolute mortality rates were presented per 1,000 person-years of follow-up. All statistical analyses of survival data were analyzed using SAS (version 9.4; SAS Institute, Cary, NC, USA) and R (version 4.0.1; R Foundation for Statistical Computing, Vienna, Austria).

Conclusion: The incidence and prevalence of Korean ESRD patients have increased over time, although patient survival has also steadily increased. The establishment of a surveillance method to address the major cause of mortality in ESRD patients will help improve outcomes.

Keywords: Chronic kidney failure, Incidence, Mortality, Prevalence
Results

Incidence and prevalence of RRT in adults in Korea

At the end of 2019 in Korea, the total number of new patients who started RRT for ESRD was 18,642, comprising 15,587 (83.6%) with HD, 762 (4.1%) with PD, and 2,293 (12.3%) with KT (Fig. 1A). The total number of patients starting RRT was more than 10,000 in 2011, illustrating the continuously increasing trend. In particular, the proportion of ESRD patients who selected HD as the initial treatment modality was steadily growing. The percentage of incident HD patients increased from less than 70% before 2008 to more than 80% after 2014 and was maintained at around 85% in 2019 (Fig. 1B). The number of incident PD patients decreased significantly compared to the past and has remained around 800 in recent years, a 4% incidence. Although the number of KT recipients gradually increased, the proportion was maintained at 12% to 14%.

Consistent with the trend of ESRD incidence, the prevalence of RRT was increasing (Fig. 1C), finally surpassing 100,000 patients at the end of 2019. Among a total of 108,873 patients receiving RRT, 81,760 (75.1%) were receiving HD, 5,960 (5.5%) PD, and 21,153 (19.4%) KT. The prevalence of ESRD has doubled since 2010, with Korea ranking sixth in the world with an incidence of 1,816 per million population (Fig. 1D, data extracted from the United States Renal Data System Annual Report [1]).

Underlying causes of ESRD and status of the elderly dialysis population

Over the past three decades, the three leading causes of ESRD in Korea were diabetes mellitus (DM), hypertension (HTN), and chronic glomerulonephritis (GN). The proportion of DM patients increased from 1992 (19.5%) to 2012 (50.6%). Currently, DM (48.4%) is the most common cause of ESRD in Korea (Fig. 2A). Although this increase has plateaued since 2012, it was still higher than that in Japan or the United States [1,6]. The percentage of ESRD patients who had a kidney disease of unknown origin still exceeds 10% in recent years. In addition, the percentages of primary diseases such as polycystic kidney disease and miscellaneous diseases have remained constant.

Figure 1. Incidence and prevalence of renal replacement therapy in Korea. (A) Annual incidence of RRT in Korea. (B) Proportion of renal replacement modalities (annual incidence from 1986 to 2019). (C) Annual prevalence of RRT in Korea. (D) The current status of RRT (per million population) in Korea through internal comparisons.
HD, hemodialysis; KT, kidney transplantation; PD, peritoneal dialysis; RRT, renal replacement therapy.
and the country is rapidly approaching a super-aged society. Statistics Korea forecast that Korea will be a super-aged society in 2025 [7]. Regarding this aging trend, the dialysis population was consistent with the general population. The mean age of the overall dialysis population was 65.0 years in 2019 (Fig. 2B). The mean ages of patients who required dialysis due to DM and HTN were 67.2 and 66.1 years, respectively, higher than the 59.0 years reported by chronic GN. Finally, the proportion of dialysis patients over 65 years of age in Korea exceeded 50% in 2019 (51.9%) (Fig. 2C). The proportion of dialysis patients aged 65 years and older increased from approximately 25% in 2005 to more than 50% in 14 years. The proportion of patients on dialysis for more than 10 years was 9.0% for HD and 2.9% for PD 20 years ago, increasing to 19.3% for HD and 12.5% for PD 10 years later.

At present, about 40% of HD patients and 50% of PD patients have been on dialysis for more than 10 years.

Distribution of dialysis machines

The increased total number of ESRD patients was mainly related to the rapid increase in HD patients, which led to an increase in the number of HD centers in Korea. At the end of 2019, the number of HD centers exceeded 1,000, and the number of HD machines exceeded 30,000 (Fig. 3). The number of HD machines per HD center has been maintained at 27 to 29 for about 10 years.

All-cause mortality and survival rates by treatment modality

A total of 149,947 eligible incident and prevalent dialysis patients between 1 January 2001 and 31 December 2019 was analyzed. During the median follow-up period of 34.8 months, 30,852 patients undergoing HD (23.8%) and 8,429 patients undergoing PD (33.0%) died, and mortality rates were 50.7 for HD and 89.3 for PD per 1,000 patient-years, respectively. In 2001, the unadjusted mortality rate for overall dialysis patients was 122.5 per 1,000 patient-years. By dialysis modality, mortality rates were 119.3 for HD patients and 121.6 for PD patients per 1,000 patient-years. In 2018, the unadjusted mortality rate for dialysis patients was 45.18 per 1,000 patient-years, and mortality rates by dialysis modality were 45.10 for HD patients and 51.33 for PD patients per 1,000 patient-years (Fig. 4A). The 5-year

![Figure 2. Prevalent percentages based on underlying cause of end-stage renal disease and age distribution in Korea. (A) Underlying causes of ESRD. (B) Mean ages of dialysis patients according to primary renal disease. (C) The proportion of dialysis patients over 65 years old. DM, diabetes mellitus; ESRD, end-stage renal disease; GN, glomerulonephritis; HTN, hypertension.](image-url)
Figure 3. Numbers of hemodialysis (HD) centers and HD machines in Korea.

Figure 4. Unadjusted all-cause mortality for all-dialysis patients, 2001 to 2018. (A) Treatment modality, (B) sex, (C) age, and (D) primary renal diseases.

DM, diabetes mellitus; GN, glomerulonephritis; HD, hemodialysis; HTN, hypertension; PD, peritoneal dialysis.

Patient survival rate of dialysis patients after the onset of ESRD in 2001 was 69.0% in HD patients and 52.4% in PD patients. The 5-year patient survival rate after the onset of ESRD gradually increased from 2001 to 2013 in both HD and PD. Since 2013, the patient survival rate after the onset of ESRD in PD has been similar to that in HD. In 2016, the 3 month- and 1-, 2-, and 3-year patient survival rates after the onset of ESRD were 99.3%, 96.7%, 91.6%, and 86.4% in HD, respectively, and 99.2%, 98.0%, 94.5%, and 88.1% in PD. In 2019, the 3 month- and 1-year patient survival rates after the onset of ESRD were 99.2% and 98.0% in HD, and 99.3% and 98.4% in PD.
onset of ESRD were 99.4% and 97.2% in HD, respectively, and 99.5% and 95.6% in PD (Table 1).

Comparison of mortality rates by sex, age, and primary renal disease

There was no significant difference between males and females in mortality rates for overall dialysis patients, and the change in mortality rates from 2001 to 2018 was similar between males and females. In 2001 and 2018, the unadjusted mortality rates per 1,000 patient-years were 125.0 and 48.6 for males, respectively, and 119.3 and 40.7 for females (Fig. 4B). The mortality rates of dialysis patients over 65 years of age were significantly higher than those of dialysis patients younger than 65 years from 2001 to 2018 (Fig. 4C). In 2001 and 2018, the unadjusted mortality rates per 1,000 patient-years were 174.7 and 67.3 for older patients, respectively, and 104.4 and 24.4 for younger patients. The mortality rates gradually decreased in both older and younger patients from 2001 to 2018. The mortality rates for diabetic patients were significantly higher than those of nondiabetic patients from 2001 to 2018. In 2001 and 2018, the unadjusted mortality rates per 1,000 patient-years were 184.9 and 59.4 for diabetic patients, respectively, and 96.3 and 35.5 for nondiabetic patients. The mortality rates of DM as a cause of ESRD were significantly higher than those of HTN and chronic GN from 2001 to 2018 (Fig. 4D). In 2001 and 2018, the unadjusted mortality rates per 1,000 patient-years were 184.9 and 59.4 for DM, 104.8 and 39.6 for HTN, and 76.5 and 19.0 for chronic GN, respectively.

Cause-specific mortality rates

The largest category of known cause-specific mortality for dialysis patients was death due to cardiac disease (35.8%) in 2019. Non-uremic cardiac arrest, uremic cardiac arrest, and coronary artery disease were included in the category of cardiac disease. Non-uremic cardiac arrest, uremic cardiac arrest, and coronary artery disease comprised 15.3%, 12.9%, and 7.6% of known causes of death among dialysis patients, respectively. Infection-related disease (22.9%) was the second most prevalent category of known cause-specific mortality for dialysis patients. Sepsis, pneumonia, tuberculosis, and peritonitis comprised 11.2%, 8.2%, 0.6%, and 0.1% of known causes of death among dialysis patients, respectively. Vascular disease (11.2%) was the third most common cause of mortality for dialysis patients. Vascular disease consisted of cerebrovascular accident, pulmonary embolism, gastrointestinal hemorrhage, gastrointestinal embolism, and other vascular diseases. Treatment refusal, suicide, and treatment withdrawal for other reasons were included in social causes of death, and malnutrition, malignancy, accident, and uncertain cause were included in miscellaneous causes of death. Cerebrovascular accidents comprised 6.5% of known causes of death, malignancy accounted for 5.0%, liver failure for 2.3%, suicide for 0.8%, and treatment refusal for 0.3%. The cause of death information was missing or unknown for 19.0% of dialysis patients (Fig. 5). The trends of cause-specific death from 2001 to 2019 are presented in Fig. 6. The proportion of cardiac disease increased slightly and the proportion of vascular disease decreased. Consequently, the proportion of cardiovascular disease-related death has changed little from 2001 to 2019 among the known causes of death in dialysis patients. The proportion of infection-related death has slightly increased over 20 years (Fig. 6).

Discussion

In the 2019 report of the KORDS, major findings included rapid growth in the overall number of patients undergoing

<table>
<thead>
<tr>
<th>Year</th>
<th>3 Mo</th>
<th>12 Mo</th>
<th>24 Mo</th>
<th>36 Mo</th>
<th>60 Mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemodialysis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2001</td>
<td>98.7</td>
<td>93.9</td>
<td>86.4</td>
<td>80.1</td>
<td>69.0</td>
</tr>
<tr>
<td>2004</td>
<td>98.4</td>
<td>94.8</td>
<td>88.6</td>
<td>82.2</td>
<td>71.1</td>
</tr>
<tr>
<td>2007</td>
<td>99.0</td>
<td>95.8</td>
<td>90.4</td>
<td>84.7</td>
<td>73.4</td>
</tr>
<tr>
<td>2010</td>
<td>99.0</td>
<td>95.8</td>
<td>91.5</td>
<td>87.0</td>
<td>77.5</td>
</tr>
<tr>
<td>2013</td>
<td>99.4</td>
<td>96.4</td>
<td>91.9</td>
<td>87.1</td>
<td>77.0</td>
</tr>
<tr>
<td>2016</td>
<td>99.3</td>
<td>96.7</td>
<td>91.6</td>
<td>86.4</td>
<td>-</td>
</tr>
<tr>
<td>2019</td>
<td>99.4</td>
<td>97.2</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Peritoneal dialysis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2001</td>
<td>97.6</td>
<td>92.2</td>
<td>82.7</td>
<td>73.0</td>
<td>52.4</td>
</tr>
<tr>
<td>2004</td>
<td>98.1</td>
<td>91.9</td>
<td>82.6</td>
<td>72.7</td>
<td>58.2</td>
</tr>
<tr>
<td>2007</td>
<td>99.0</td>
<td>95.4</td>
<td>86.5</td>
<td>77.5</td>
<td>63.7</td>
</tr>
<tr>
<td>2010</td>
<td>98.6</td>
<td>96.0</td>
<td>91.1</td>
<td>83.7</td>
<td>70.9</td>
</tr>
<tr>
<td>2013</td>
<td>99.2</td>
<td>96.6</td>
<td>90.9</td>
<td>84.5</td>
<td>71.5</td>
</tr>
<tr>
<td>2016</td>
<td>99.2</td>
<td>98.0</td>
<td>94.5</td>
<td>88.1</td>
<td>-</td>
</tr>
<tr>
<td>2019</td>
<td>99.5</td>
<td>95.6</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>
Figure 5. Unadjusted relative percentages for cause of death of dialysis patients in 2019. (A) Major causes of death and (B) detailed cause-specific death.

Figure 6. Trends for proportions of causes of death during the incident year, 2001 to 2019.

dialysis, the proportion of elderly patients, and the overall number of patients undergoing long-term dialysis. The proportion of diabetic ESRD patients was maintained at around 50%, and a consistent decrease in the proportion of PD patients was observed in recent years. Among ESRD patients, the HD proportion in the study period increased to 84%, and the PD proportion decreased to 4%. Over the past two decades, the mortality of dialysis patients gradually
decreased, but the mortality of diabetic dialysis patients was higher than that of dialysis patients with HTN or chronic GN. Recently, the patient survival rates in HD were similar to those in PD. Taken together, the survival improvement of dialysis patients and the increase in the proportion of long-term dialysis patients might contribute to the increase in the mean age of dialysis patients.

The incidence and prevalence of ESRD patients in Korea have been increasing over the past three decades, and the prevalence has doubled in the last 10 years. Although the prevalence of predialysis chronic kidney disease (CKD) stage 3 to 5 patients has remained constant during the same period [8], the number of ESRD patients requiring RRT showed a recent rapid increase. As a result, Korea is now ranked sixth in the world for prevalence of ESRD [9].

Although the data from KORDS in 2013 reported that the prevalence of ESRD patients did not appear to reach the inflection point [10], the value has been continually increasing and has now exceeded those of Japan and the United States. At present, the trend resembles that of Taiwan, where the overall number of ESRD patients increased at the greatest rate among global countries [9]. The data from KORDS showed that most ESRD patients underwent HD. In the future, the aging trend will contribute to a progressively higher modality rate of HD compared to PD and KT. Under such circumstances, the numbers of HD centers and dialysis machines are likely to increase.

To reduce the number of ESRD patients, it is necessary to improve adherence through the proper administration of prescribed agents and lifestyle modifications according to the causative disease and to reduce complications through nephrologist counseling from the early stage of CKD. In addition, the rate of ESRD cases of unknown origin remains high, which must be resolved to reduce ESRD in the long term. Fortunately, regular health screenings via school, workplace, and regional systems have been expanded in Korea [11]. Therefore, if a patient does not miss a regular health examination, data of unknown origin will gradually decrease through diagnosis of the causative disease.

Another interesting finding was that the reduction in mortality risk was greater for patients treated with PD than those treated with HD in the past two decades, and that the survival of patients treated with PD and HD is similar in Korea for recent years. Comparisons between the long-term survival rates of patients with HD and PD in the past two decades were first reported in 2019 using the KORDS. In Korea, a previous population-based, large-scale study using Korean Health Insurance Review and Assessment data suggested that the mortality rate was significantly higher in incident PD patients than in incident HD patients in the period from 2005 to 2008 [12]. On the other hand, PD was associated with better survival than HD in the early period of dialysis in a national prospective cohort study performed since 2009 [13]. The present data from KORDS showed higher overall mortality rates in PD patients than in HD patients in the 2000s. Although the reason why PD patients have shown recent improvement in outcomes is not clear, it may be attributed to increased reimbursement for PD in the national health insurance program, the development of PD education programs, and the use of biocompatible PD solutions. Recent nationwide cohort data also indicated that PD and in-center HD provide similar survival in Europe and the United States [1,14]. Because statistical analyses for outcomes in this registry data were conducted without adjustment for confounding variables, further research is needed to assess the exact trends of mortality rates by treatment modality in Korean ESRD patients.

Despite a substantially decreasing trend of mortality rates in the last 20 years, the absolute mortality risk remains high in dialysis patients due to cardiovascular events and infections. In the KORDS for cause-specific death, cardiovascular disease was the most common, accounting for 47.0% of deaths (cardiac disease, 35.8% and vascular disease, 11.2%). Infection accounted for 22.9% of deaths and malignancy accounted for 5.0% of deaths in 2019. Trends in cause of death over time remained unchanged for cardiovascular disease and exhibited a mild increase for infection from 2001 to 2019. Other nationwide registry data demonstrated a decrease in cardiovascular mortality in dialysis patients over time in Japan and Europe [6,15]. However, survival analyses of the KORDS have some limitations, including relatively low enrollment rates, a lack of information on patient survival, and misclassification of cause-specific death, due to data collection based on voluntary enrollment. Therefore, it is necessary to consider a plan to increase the enrollment rate of the KORDS.

In conclusion, the KSN ESRD registry showed substantial increases in ESRD incidence and prevalence, especially in elderly and diabetic groups. These data highlight the need to pay attention to the high mortality rates of elderly and
diabetic dialysis patients in Korea. These data also indicate the need for evidence-based treatment approaches for elderly and diabetic patients to prevent the progression of kidney disease. Although recent survival rates were similar between HD and PD patients, the proportion of prevalent PD patients gradually decreased. Therefore, further research may be needed for the individualized risk prediction of mortality regarding the selection of dialysis modality in patients who will start RRT.

Conflicts of interest

All authors have no conflicts of interest to declare.

Funding

This work was supported by a National Research Foundation of Korea grant funded by the Korean government (MSIT) (2018R1C1B5045006). Acknowledgements

The ESRD Registry Committee of the KSN thanks all of the medical doctors and nurses of the dialysis centers in Korea for participating in this registry.

Authors’ contributions

Conceptualization: JP, YKK
Data curation: CYK
Formal analysis: SDH, SRC, HL
Investigation: HYJ, KK (Kyeongmin Kim), YEK
Methodology: SHK, THK
Visualization: HSK, CYY, KK (Kiwon Kim)
Writing–original draft: YAH, THB
Writing–review & editing: JP, YKK
All authors read and approved the final manuscript.

ORCID

Yu Ah Hong, https://orcid.org/0000-0001-7856-4955
Tae Hyun Ban, https://orcid.org/0000-0002-2884-4948
Chae-Yeong Kang, https://orcid.org/0000-0001-8587-7765
Sun Deuk Hwang, https://orcid.org/0000-0003-0074-6972
Sun Ryoung Choi, https://orcid.org/0000-0002-9668-3349

Hajeong Lee, https://orcid.org/0000-0002-1873-1587
Hee-Yeon Jung, https://orcid.org/0000-0003-0232-7202
Kyeongmin Kim, https://orcid.org/0000-0002-5414-4339
Young Eun Kwon, https://orcid.org/0000-0002-0843-9857
Su Su Hyun Kim, https://orcid.org/0000-0003-3382-528X
Tae Hee Kim, https://orcid.org/0000-0002-3001-234X
Ho-Seok Koo, https://orcid.org/0000-0001-7856-8083
Chang-Yun Yoon, https://orcid.org/0000-0001-8545-9344
Kiwon Kim, https://orcid.org/0000-0002-2885-0053
Jongha Park, https://orcid.org/0000-0002-1461-9483
Yong Kyun Kim, https://orcid.org/0000-0002-1871-3549

References


Comparison of chronic kidney disease trial designs and analysis strategies

John Lawrence

Office of Biostatistics, Center for Drug Evaluation and Research, U.S. Food and Drug Administration, Silver Spring, MD, United States

Background: Despite the large burden of chronic kidney disease (CKD), it is challenging to conduct adequately powered clinical trials in this setting. Sound and efficient trials are needed to advance treatment. Various analysis strategies can be used to compare the efficacy of a parallel trial design with that of three two period trial designs.

Methods: The type 1 error rates and powers of various trial designs were calculated using simulated data from models fit to two recent CKD trials. In addition, we assessed the influences of a variety of analysis strategies and of the presence of a carryover effect.

Results: The parallel and crossover designs (with analysis of change from baseline to the off treatment value) maintained the target type 1 error rate in all scenarios. In some scenarios, an open label design yielded inflated type 1 error rates. In many scenarios, the open label and delayed start designs had unacceptably low power and high type 1 error rates. Overall, the crossover design had the highest power by far, and always controlled the type 1 error rate.

Conclusion: The recommended approach to a CKD trial is a two period design with an endpoint that is the rate of change in estimated glomerular filtration rate from pretreatment to off treatment. As compared to a parallel trial, a crossover study involves a considerably smaller sample size and shorter total follow-up duration. A crossover design may also be preferable for patients, and facilitates recruitment of a sufficient number of subjects.

Keywords: Bioethics, Computing methodologies, Kidney diseases, Treatment switching

Introduction

Chronic kidney disease (CKD) affects an estimated 8% to 16% of adults worldwide [1]. Despite its wide prevalence, it has been challenging to run large and adequately powered randomized trials in patients with CKD [2]. Large, multi-year trials are expensive to conduct. Trials of patients with kidney disease often exclude a large proportion of the potential subjects. Finally, a high level of nonadherence among enrolled subjects can sharply reduce a study’s statistical power. A sound and efficient trial design that can handle missing data is essential to conducting a successful trial that advances treatment.
CKD progresses slowly. Therefore, definitive clinical endpoints, such as the need for dialysis or kidney transplant, have been replaced by surrogate endpoints that are related to kidney function or damage. These surrogate endpoints can be measured in a shorter follow-up time than that required for more definitive endpoints like the need for dialysis. A meta analysis of over 60,000 subjects in 47 randomized clinical trials [3] concluded that the slope of the estimated glomerular filtration rate (eGFR) is a viable surrogate for clinical endpoints in CKD trials. Indeed, the U.S. Food and Drug Administration supports the use of eGFR slope as a surrogate endpoint in trials of therapies for rare types of CKD [4].

Various approaches have been suggested to analyze data on the eGFR slope in randomized controlled trials [3]. For clinical trials, acute slope is defined as that ‘from randomization to the first 3 months in follow-up,’ while the chronic slope is that ‘from 3 months to end of the trial.’ Finally, the total slope is that ‘from randomization to 1, 2, 3, or 4 years.’ Many factors can influence the decision to use chronic slope versus the total slope in a clinical trial. Acute effects can complicate the interpretation of the treatment effect on both chronic and total slopes. A negative acute effect can attenuate or reverse the statistical power advantages of the total slope compared to the clinical end point. A negative acute effect can also increase the risk that use of the chronic slope as a surrogate end point could lead to a type 1 error relative to the clinical end point. Therefore, the acute, chronic and total slopes may all need to be assessed. One approach is to compare the chronic slopes by excluding the first 3 months of data from both arms, and then fitting a mixed effects model to the remaining data and testing for a difference in the mean slopes. An alternative method is to analyze all of the data with an acute effect term in the model so that the data are assumed to arise from a mixed effects model comprising two different slopes (a piecewise linear model). After this model is fit, the total slope is estimated by dividing the predicted mean change from baseline by the duration of treatment. This estimate is not technically a slope, because the mean trajectory is not a straight line but rather a rate of change. Both of these approaches assume that subjects stay on the treatments to which they were randomized for the duration of follow-up.

A different approach to estimating the rate of change (without the acute effect) is to have all of the subjects withdraw from the study drug at the end of a fixed period. Then, one can make end of trial measurements after the acute effect has worn off. This approach was successfully used in the Replicating Evidence of Preserved Renal Function: an Investigation of Tolvaptan Safety and Efficacy (REPRISE) trial in autosomal dominant polycystic kidney disease (ADPKD) [5]. The REPRISE trial was also notable for its use of two run in phases in order to minimize loss to follow up. Although some subjects discontinued the study drug during the trial, 96% of randomized subjects stayed in the trial and attended the final visit at 12 months. The subjects who withdrew from the trial were included in the analysis. Their annualized rate of change was estimated at the time of withdrawal by dividing their change in eGFR from baseline by their duration of follow-up.

In this study, the efficacy of a traditional randomized controlled trial design (parallel trial) with that of three two period trial designs was compared (Fig. 1). In each of the two period designs, the eGFR was measured at baseline, at the end of period 1, and at the end of period 2. A withdrawal phase at the conclusion of each trial period permits off drug measurement of the eGFR. The first design is the open label trial, during which all subjects receive the experimental drug during the trial, 96% of randomized subjects stayed in the trial and attended the final visit at 12 months. The subjects who withdrew from the trial were included in the analysis. Their annualized rate of change was estimated at the time of withdrawal by dividing their change in eGFR from baseline by their duration of follow-up.

Using simulated data from models fit to two recent trials of CKD treatments, the type 1 error rates and the powers of these trial designs were calculated. The influence of these data on the results of a variety of analysis strategies and on the presence of a carryover effect were assessed. The objective of this work is to compare different designs in terms of the number of patients and total follow-up duration needed to achieve the objectives of a clinical trial under different scenarios. Wherever appropriate, recommendations are given for trial designs with their respective rationales.
Methods

Data were simulated using a mixed effects model of the following form:

\[ Y_{ij} = X_i + \beta_1(t_{ij}) + \beta_2 u_{ij} + \beta_3 \times (t_{ij} - u_{ij}) I(u_{ij} > 0) + b_1i + b_2i t_{ij} + e_{ij} \]

In this model, \( Y_{ij} \) is the observed eGFR of subject \( i \) at time \( t_{ij} \); \( X_i \) is the ideal unobserved GFR for subject \( i \) at baseline; \( u_{ij} \) is the amount of time up to time \( t_{ij} \) that the subject was on treatment; \( I(u_{ij} > 0) \) is 1 if \( u_{ij} > 0 \), and 0 otherwise. \( \beta_1, \beta_2, \) and \( \beta_3 \) are fixed effects terms. \( \beta_1(\cdot) \) is a function that describes the trajectory in the placebo group. When there is a constant rate of change, this term can be replaced by \( \beta_1 \times t_{ij} \). \( \beta_2 \) is the effect of the treatment on the chronic slope and \( \beta_3 \) is the carryover effect; \( b_1i \) and \( b_2i \) are random effects assumed to be normally distributed with a mean of zero. In order to illustrate the difference between \( t_{ij} \) and \( u_{ij} \), assume patient \( i \) is assigned to the treatment in period 1 and that the duration of treatment is \( T \). Then, \( u_{ij} = T \) whenever \( t_{ij} > T \). The residual error terms in the model, \( e_{ij} \), are assumed to be mutually independent and normally distributed as \( N(0, \sigma^2) \); they are also assumed to be independent of the random effects. No acute effect is used in the model, because it is assumed that all of the measurements were made while the patient was off of treatment.

The data from the Tolvaptan Efficacy and Safety in Management of Autosomal Dominant Polycystic Kidney Disease and its Outcomes (TEMPO) 3-4 study [5] and REPRISE trials [7] were used to identify reasonable parameter values to simulate data from trials of each design. These trials studied patients with ADPKD. ADPKD causes bilateral, progressively enlarging kidney cysts. Despite progressive growth of the kidney cysts over a patient’s lifetime, the early course of ADPKD is actually characterized by hyperfiltration and relatively normal GFR for many decades. This feature of ADPKD makes GFR an insensitive marker of underlying renal parenchymal damage. It may be necessary to consider the cause of kidney disease when determining an individual patient’s response. The parameters were also modified to investigate different possible scenarios under the null hypothesis (no treatment effect) and the alternative hypothesis (beneficial treatment effect). The parameter values used are shown in Supplementary Appendix 1 (available online). The rate of change during placebo treatment was \(-4\) mL/min per 1.73 m\(^2\) annually, while that during experimental treatment was \(-3\), for a chronic treatment effect of 1. The exception was in the case of a carryover effect in the crossover design (explained below).

In the TEMPO trial, subjects were randomized to receive the experimental drug or placebo, and were followed for 3 years before continuing to an open label extension. In
In the REPRISE trial, the subjects were followed for 1 year. Therefore, it was assumed that the follow-up duration is 2 years per period. This follow-up is the average of the 1- and 3-year follow-up periods in the two referenced studies. For two-period designs, it is ethical and feasible for patients to consent to at least 2 years of follow-up on experimental treatment and at most 2 years on placebo.

In all designs, two eGFR measurements were assumed at baseline and at each timepoint when all subjects were off the study treatment. In the parallel and delayed-start designs, two measurements were taken at baseline and two at the end of the study. In the other two period designs, two measurements were taken at baseline, two at the end of period 1, and two at the end of period 2.

For the crossover design, two different scenarios are considered for the potential carryover effect. This design was meant to allow for the possibility that the drug imparts a structural change that persists after the drug is stopped. The first scenario was the absence of a carryover effect. In the second scenario, there was a moderately large carryover effect equal to 25% of the chronic effect in period 1. In other words, one quarter of the effect of the drug on the chronic slope was assumed to remain in period 2 for the subjects who were randomized to the experimental drug in period 1. In addition, those subjects’ mean slope in period 2 (when they were not taking the drug) increased by 25% of the increase in period 1 (when they were taking the drug).

Analysis

For the parallel and delayed-start designs (Fig. 1), we averaged each subject’s two baseline values and the two end of study values. A subject’s change from baseline was the difference between the two average values. The annualized rate of change was the change from baseline divided by the duration of follow-up. Finally, a two sample t test is used to compare the two arms.

For the crossover design (Fig. 1), three analysis strategies were used. The first strategy was to fit a mixed effects model that included a common chronic effect for the treatments in periods 1 and 2. The null hypothesis was that the chronic treatment effect is zero. The likelihood ratio test was used to test this null hypothesis. In the other two analysis strategies, we first calculated the averages of the two measurements taken at baseline, at the end of period 1, and at the end of period 2. Next, a single value for period 1 was calculated by subtracting the baseline from the end of period 1 value, and then dividing by the duration of follow-up. A single value for period 2 was calculated by subtracting the end-of-period 1 value from the end-of-period 2 value and then dividing by the duration of follow-up. Finally, either a pooled test or two stage test was performed [8]. The two stage test started by testing for a statistically significant carryover effect that was large enough to analyze based on the data of period 1 being more powerful than are the pooled data from periods 1 and 2. If a significant carryover effect was observed, then the period 1 data were used alone as if it were a parallel trial. The significance level must be adjusted to evaluate the treatment effect in the second period (unpublished data). The preliminary test for carryover is correlated with the test of treatment effect from the first period alone. Therefore, the actual significance level of the two-stage procedure is higher than is nominal level \( \alpha \), even when there is no residual carryover.

For the two-period open-label design, the first averages of the two measurements taken at baseline (at the end of period 1) and at the end of period 2 were calculated. Next, a single value for period 1 was calculated by subtracting the baseline from the end of period 1 value and dividing by the duration of follow-up. A single value was calculated for period 2 by subtracting the end of period 1 value from the end-of-period 2 value and dividing by the duration of follow-up. The treatment effect for each subject was calculated by subtracting the annualized rate of change in period 2 from that in period 1. This is mathematically equivalent to the following formula: 
\[
\left[ 2 \times \{ \text{end-of-period 1 value} \} - \{ \text{baseline value} \} - \{ \text{end-of-period 2 value} \} \right] / [\text{duration of each period}] 
\]

The numerator can also be rewritten as follows: 
\[
\left[ \{ \text{end-of-period 1 value} \} - \{ \text{baseline value} \} - \{ \text{end-of-period 2 value} \} - \{ \text{end-of-period 1 value} \} \right] \]

Therefore, the numerator was the difference of the treatment effect between the two periods. A one-sample t test was then performed to determine whether the mean treatment effect across subjects was greater than zero.

Asymptotic relative efficiency

When the treatment effect is small, a large sample size is needed to achieve a given power. The ratio of the sample...
sizes needed is termed the asymptotic relative efficiency (ARE). The ARE was calculated to compare several trial designs and analysis strategies.

**Type 1 error rate**

Three different scenarios in which there was no treatment effect are considered. The natural history of subjects in a trial will depend on their characteristics, including disease stage and external factors. These factors cannot necessarily be predicted in advance or controlled by the trial’s eligibility criteria. Renal function estimating equations are not linear functions of age.

Therefore, a constant rate of change cannot always be expected. In scenarios in which there is no treatment effect, \( \beta_2 = \beta_3 = 0 \). In the first scenario, a constant rate of change over time was assumed (decline of 4); that is \( \beta_2(t_{ij}) = -4 t_{ij} \). In the second scenario, the natural history of the rate of change was assumed to decline slightly over time. This rate of change was defined by a decline of 4.0 annually in period 1 and 3.5 annually in period 2, as follows: \( \beta_2(t_{ij}) = -4 t_{ij} \) when \( t_{ij} \leq 2 \) and \( \beta_2(t_{ij}) = -8 - 3.5(t_{ij} - 2) \) when \( t_{ij} > 2 \). The third scenario assumed an increasing rate of change over time. This rate of change was defined by a decline of 4.0 annually in period 1 and 4.5 annually in period 2, as follows: \( \beta_2(t_{ij}) = -4 t_{ij} \) when \( t_{ij} \leq 2 \) and \( \beta_2(t_{ij}) = -8 - 4.5(t_{ij} - 2) \) when \( t_{ij} > 2 \). The targeted type 1 error rate used for the hypothesis tests was the conventional one sided 0.025.

**Power**

Two different scenarios were investigated, including those with and without a carryover effect. The placebo arm was assumed to have a constant decline of 4. If there were no carryover effect, the chronic effect would be equal to 1. If there were a carryover effect, the treatment decline would be 3.75 (for a carryover effect of 0.25).

**Results**

**Type 1 error rate**

All of the designs and analyses had the target type 1 error rate, with the exception of the open label two period design with an increasing rate of change (Table 1). Therefore, when the rate of change is not constant over time (even by a small margin), there can be a marked effect on the type 1 error rate. This phenomenon is unrelated to any potential bias caused by unblinding. It is only the result of different rates of change in periods 1 and 2. It was assumed that the experimental treatment was given in period 1; however, the problem related to an inconstant rate of change can also occur if the experimental treatment is applied in period 2.

**Table 1. Type 1 error rate (n = 500)**

<table>
<thead>
<tr>
<th>Design and analysis</th>
<th>Rate of change scenario</th>
<th>Constant</th>
<th>Declining</th>
<th>Increasing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parallel</td>
<td>0.025</td>
<td>0.025</td>
<td>0.025</td>
<td></td>
</tr>
<tr>
<td>Open-label two-period</td>
<td>0.025</td>
<td>0.000</td>
<td>0.605</td>
<td></td>
</tr>
<tr>
<td>Delayed start</td>
<td>0.025</td>
<td>0.025</td>
<td>0.025</td>
<td></td>
</tr>
<tr>
<td>Crossover mixed effects</td>
<td>0.025</td>
<td>0.025</td>
<td>0.025</td>
<td></td>
</tr>
<tr>
<td>Crossover pooled</td>
<td>0.025</td>
<td>0.025</td>
<td>0.025</td>
<td></td>
</tr>
<tr>
<td>Crossover two-stage</td>
<td>0.025</td>
<td>0.025</td>
<td>0.026</td>
<td></td>
</tr>
</tbody>
</table>

100,000 simulated trials; margin of error \( \leq 0.001 \).

**Table 2. Power by study design (n = 500)**

<table>
<thead>
<tr>
<th>Design and analysis</th>
<th>Scenario</th>
<th>No carryover effect</th>
<th>Carryover effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parallel</td>
<td>0.826</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Open-label two-period</td>
<td>0.993</td>
<td>0.916</td>
<td></td>
</tr>
<tr>
<td>Delayed start</td>
<td>0.471</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Crossover mixed effects</td>
<td>0.995</td>
<td>0.977</td>
<td></td>
</tr>
<tr>
<td>Crossover pooled</td>
<td>0.994</td>
<td>0.964</td>
<td></td>
</tr>
<tr>
<td>Crossover two-stage</td>
<td>0.989</td>
<td>0.963</td>
<td></td>
</tr>
</tbody>
</table>

100,000 simulated trials; margin of error \( \leq 0.003 \).

NA, not applicable.
to the patients with two observations. The mixed effects model also appropriately handles variability in the timing of observations. For example, if period 1 ends at 2 years and one patient has two end of period 1 measurements (taken at visits on days 710 and 740), the mixed effects model uses those exact days in the model, while other analyses do not. However, the efficiency of the mixed effects model comes at the cost of assuming that the correct model is used. Other analyses do not make any strong model assumptions. The mixed effects model is a likelihood based method. Other recommended methods (that were not considered here) include multiple imputation and Bayesian approaches [9].

Asymptotic relative efficiency

The mathematical calculations for the ARE are provided in Supplementary Appendix 1. We assumed that two measurements were taken at baseline and two at the end of the study in order to assess the impact of multiple measurements at each time point in the parallel design. If only one measurement was made at each time point, then approximately 56% more subjects would be needed to achieve adequate power (than if two measurements were made at each point). The ARE was calculated at 1.56.

In comparing the crossover design with pooled analysis to the parallel design, the ARE was approximately 2.38. The gain in efficiency of the crossover design was in part a result of the additional follow-up of each subject. This gain in efficiency was also attributable to the elimination of the between subject variability in the random slope. Importantly, a crossover design involves a twofold greater duration of follow-up for each subject. Therefore, in order to achieve the same power in a trial of parallel design to one in a crossover design, the total duration of follow-up would need to be 19% greater (2.38-fold the number of subjects, each of whom was followed up for half as much time).

Discussion

The crossover design is recommended in CKD trials because of its efficiency, control of the type 1 error rate, ethicality of all subjects receiving active treatment, and its appeal to patients. For any given type 1 error rate and power, the crossover design requires fewer patients than does a parallel design or delayed start design. The two period open label design is not recommended because it does not control the type 1 error rate in some scenarios. The delayed start design may be attractive to patients with conditions for which no effective treatment is available, because all patients in a given trial are guaranteed to receive the experimental therapy (either from the start or after the end of period 1). The crossover design also has this benefit. The delayed start design has considerably lower power than does either the parallel design or the crossover design.

Of the analysis strategies compared here, the mixed effects model analysis is expected to be most efficient if the assumed model is correct, and the subjects have various patterns of missing data. If all of the subjects have the same number of observations at each time point, then the mixed effects model is expected to be similarly efficient to the pooled analysis strategy. If there is a possibility of a large carryover effect, a two stage analysis may be more powerful than is pooled analysis. In the alternative scenario shown in Table 2, there was a moderate amount of carryover (25% of the treatment effect). In that scenario, two stage analysis and pooled analysis had approximately equivalent power. If the carryover effect were larger, the two stage test would have greater power.

One frequent concern in CKD trials is missing data. This issue can be mitigated by providing incentives for subjects to remain in a trial, even if they no longer wish to take the study drug. Regardless, a portion of subjects in any CKD trial will die, undergo kidney transplantation, or start dialysis. A concern with parallel trials is that the two groups may not be comparable after a large number of subjects is lost to follow up. However, in a crossover trial (in which each subject serves as his/her own control), the estimate of the treatment effect is not confounded by differences in covariate distribution between the two groups.

In future trials of CKD treatments, a two period design is recommended with an endpoint of the rate of change in eGFR. Our simulations and theoretical calculations generally agree with the empirical observations of Lathyris et al. [10]. Based on their review of meta-analyses (that included both crossover and parallel studies), Lathyris et al. concluded that crossover trials tend to agree with parallel arm trials. However, the group also found that parallel arm trials tended to make more conservative treatment effect estimates than did crossover trials. We also recommend a longer duration of total follow-up and a much smaller sample size in crossover
trials compared to those of parallel trials. Finally, a crossover trial may be ethically preferable to a parallel trial, because all of the subjects will receive the study drug. This feature may also facilitate subject recruitment.

**Conflicts of interest**

The author has no conflicts of interest to declare.

**Acknowledgments**

The authors thank Graeme A. O’May, PhD and J. Rick Turner, PhD, DSc of DRT Strategies, Inc. for editorial assistance.

**ORCID**

John Lawrence, https://orcid.org/0000-0002-9892-2753

**References**

Serum interferon-γ and urinary monocyte chemoattractant peptide-1 are important factors in the pathogenesis of immunoglobulin A nephropathy

Sang Youb Han¹, Kyung Hwan Jeong², Chun-Gyoo Ihm², Young Sun Kang³, Dae Ryong Cha³

¹Department of Internal Medicine, Inje University Ilsan Paik Hospital, Goyang, Republic of Korea
²Department of Internal Medicine, College of Medicine, Kyung Hee University, Seoul, Republic of Korea
³Department of Internal Medicine, Korea University Ansan Hospital, Ansan, Republic of Korea

Background: Imbalance of T helper (Th) 1/2 cells has been shown to contribute to the development of immunoglobulin A nephropathy (IgAN). To address the inconsistent results on the role of Th1/Th2 polarization, we evaluated the levels of Th1/Th2 cytokines in various samples from patients with IgAN.

Methods: Thirty-one patients with biopsy-proven IgAN (age, 34.48 ± 12.10 years) and 25 healthy controls (age, 44.84 ± 13.72 years) were enrolled. We evaluated the relationship between the levels of Th1/Th2 cytokines and the response to glucocorticoid treatment.

Results: The levels of serum interferon-gamma (IFNγ) and urinary monocyte chemoattractant peptide (MCP)-1 were higher in the IgAN group than in the control group. The levels of MCP-1 in urine and secreted by peripheral blood mononuclear cells (PBMCs) were significantly different among three groups categorized based on daily proteinuria. The level of urinary MCP-1 was significantly correlated with proteinuria. The levels of urinary MCP-1, serum interleukin (IL)-4, IFNγ, and IL-2 secreted by PBMCs and intrarenal IL-1 messenger RNA (mRNA) were significantly correlated with the ratio of proteinuria at 6 months to baseline proteinuria in patients undergoing glucocorticoid treatment. MCP-1 mRNA and protein levels were significantly upregulated in mesangial cells stimulated with IFNγ among representative Th1/Th2 cytokines.

Conclusion: IFNγ was shown to be a key cytokine in the pathogenic processes underlying IgAN, and its upregulation induced an increase in urinary MCP-1 production. These findings suggest that Th1 cytokines may play an important role in the development of IgAN.

Keywords: Chemokine CCL2; IGA glomerulonephritis; Interferons; T helper 1 cells; T helper 2 cells
Introduction

Immunoglobulin A nephropathy (IgAN) is characterized by the deposition of circulating immune complexes containing undergalactosylated IgA in the glomerular mesangium [1]. Several lines of evidence have shown the involvement of systemic immune dysregulation in the pathophysiology of IgAN. For instance, IgAN has a recurrence rate of 50% after renal transplantation [2]. Moreover, IgAN resolved after bone marrow transplantation in a patient with IgAN and chronic myeloblastic leukemia [3].

The imbalance in T helper (Th) cells, which are involved in adaptive immune responses, has been suggested to play an important role in the pathogenesis of several diseases [4], including IgAN. Representative Th1/Th2 cytokines, interferon-gamma (IFN\(\gamma\)), and interleukin (IL)-4 were found to be involved in the pathogenesis, development, and progression of IgAN [5-7]. The Th1/Th2 cytokine polarity has been shown to play a key role in these processes; however, the results of these studies have not been consistent. Furthermore, in previous studies [5-7], the cytokine profile of specific specimens, such as serum, urine, kidney, or tonsil, was determined, but a global understanding of the cytokine landscape is currently lacking.

To address the inconsistency of previous results, we evaluated the levels of Th1/Th2 cytokines in various samples, including serum, urine, kidney, peripheral blood mononuclear cells (PBMCs), and mesangial cells (MCs), from patients with IgAN. These measurements may more clearly reveal the relationships of cytokines with clinical parameters. We also evaluated the correlation of cytokine levels and the response to glucocorticoid treatment in patients with IgAN.

Methods

Participants

Thirty-one patients with biopsy-proven IgAN and 25 healthy controls from three different hospitals were enrolled in this study. Patients with the following systemic diseases were excluded: autoimmune diseases, diabetes, hepatic diseases, and malignancies. IgAN was diagnosed based on the following pathologic findings; presence of mesangial proliferation assessed by light microscopy and mesangial IgA deposition assessed by immunofluorescence. All patients were treated with renin-angiotensin system blockade. Patients with proteinuria of >500 mg/day were treated with the following glucocorticoid regimen; 1 mg/kg/day at the beginning for 2 months and tapering for another 4 months. A 24-hour urine sample was collected to measure proteinuria. Blood and urine (for the measurement of cytokines) were immediately processed. Samples were centrifuged at 3,000 \(\times\) g for 10 minutes, and aliquots were stored at -80°C until analysis. This study was approved by the Institutional Review Board of the Korea University (No. R0803121). Informed consent was obtained from all participants in compliance with the Helsinki Declaration.

Data collection

We collected data on patient demographics and comorbidities. The baseline laboratory examination included serum creatinine, cholesterol, high-density cholesterol, triglycerides, fasting blood glucose, hemoglobin, white blood cell count, platelets, and urine analysis.

Cytokine measurement

The simultaneous assessment of the concentration of IFN\(\gamma\), IL-2, IL-4, IL-10, IL-13, monocyte chemoattractant peptide (MCP)-1, and tumor necrosis factor alpha (TNF-\(\alpha\)) in the serum and urine was performed using commercially available multiplex bead-based sandwich-based immunoassay kits (MPXHCYTO-60K-07; Millipore, Billerica, MA, USA) following the manufacturer’s instructions. The concentration of urinary cytokines was standardized against that of urinary creatinine. The assays were performed in duplicate. Secreted cytokines in culture supernatants were also measured using the same method. The levels of all cytokines are expressed relative to the total protein concentration.

Quantitative reverse transcription-polymerase chain reaction (RT-PCR)

Total RNA from renal core biopsy tissues or cultured MCs were extracted using Trizol reagent (ThermoFisher Scientific Inc., Waltham, MA, USA) and reverse transcribed into cDNA using SuperScript II Reverse Transcriptase (Invitrogen, Carlsbad, CA, USA) as described elsewhere [8]. Quantitative RT-PCR was performed on a Bio-Rad iCycler system (Bio-
Rad, Hercules, CA, USA) using SYBR Green (TaKaRa Bio, Tokyo, Japan) using the following cycling conditions; 50°C for 10 minutes, 95°C for 5 minutes, and then 45 cycles of denaturation at 95°C for 10 seconds and annealing with extension at 60°C for 30 seconds. The sequences of primers used in this study are shown in Supplementary Table 1 (available online). The expression of each gene was normalized to that of \( \beta \)-actin messenger RNA (mRNA).

**Peripheral blood mononuclear cells**

PBMCs were obtained using a Ficoll solution (Biochrom AG, Berlin, Germany) and resuspended in Dulbecco’s modified Eagle medium (Gibco BRL, Grand Island, NY, USA) supplemented with 5% fetal calf serum at 37°C for 2 hours. Nonspecific esterase staining was performed to confirm the identity of PBMCs. For PBMC activation, cells were treated with phorbol 12-myristate 13-acetate (Sigma Aldrich Corp., St. Louis, MO, USA) at a final dose of 25 ng/mL. After PBMCs were incubated for 48 hours, supernatants were collected and frozen at –80°C for subsequent experiments.

**Mesangial cell culture**

To access the production of cytokines by MCs, the normal renal cortex of human kidneys was obtained immediately after nephrectomy as previously described [9]. To test the response of MCs to Th1/Th2 cytokines, MCs were incubated in medium containing IL-2 (10 ng/mL), TNF-\( \alpha \) (25 ng/mL), or IFN\( \gamma \) (1,000 IU/mL) for 24 hours. MCP-1 protein level was determined according to the manufacturer’s recommendation (MPXHCYTO-60K-07;Millipore).

**Statistical analysis**

Statistical analyses were performed using the IBM SPSS Statistics version 25.0 (IBM Corp., Armonk, NY, USA). The statistical significance of differences was determined by ANOVA or the Student t-test. The nonparametric Kruskal-Wallis test was performed if assumption of normality of the data was not suitable. The correlation between cytokine gene expression and clinicopathological data was analyzed by the Spearman test. A p-value of <0.05 was regarded as significant. All data are presented as mean ± standard deviation.

**Results**

**Baseline characteristics**

The mean ages of participants in the IgAN group (14 males, 17 females) and control group (11 males, 14 females) were 34.48 ± 12.10 years and 44.84 ± 13.72 years, respectively. Participants in the IgAN group presented higher systolic blood pressure, grade of hematuria, and proteinuria and lower estimated glomerular filtration rate (eGFR) and hemoglobin levels than the control group (Table 1).

**Cytokine measurements in patients with IgA nephropathy and healthy controls**

Plasma and urine cytokine levels are shown in Supplementary Table 2 (available online). Notably, the levels of serum IFN\( \gamma \) and urinary MCP-1 were significantly higher in the IgAN group than in the control group (Fig. 1). Moreover, serum IL-4 and IL-10 levels tended to be increased in the IgAN group compared with the control group.

**Baseline physicochemical and cytokine differences between 24-hour urinary proteinuria-based groups**

Patients were divided into three groups based on the 24-hour proteinuria; 500 mg, 500 to 1,000 mg, and ≥1,000 mg. Serum creatinine, the grade of hematuria, and blood pressure were higher in patients with proteinuria of >500 mg/day than those in patients with proteinuria of <500 mg/day.

The levels of MCP-1 in urine (p = 0.030) and secreted by PBMCs (p = 0.046) were significantly different among the three groups (Fig. 2). The level of several cytokines, namely serum TNF-\( \alpha \), and MCP-1 and IL-13 secreted by PBMCs, also tended to differ among the three groups. Furthermore, the levels of the following cytokines were correlated with baseline proteinuria; urinary MCP-1 (r = 0.451, p = 0.002), TNF-\( \alpha \) (r = 0.362, p = 0.015), serum IL-10 (r = 0.595, p < 0.001) and TNF-\( \alpha \) (r = 0.398, p = 0.008).

The intrarenal levels of IL-10 and nuclear factor kappa B (NF-\( \kappa \)B) mRNA were significantly different among the three groups (Fig. 2). The levels of MCP-1 and IL-2 also tended to differ among the three groups. In addition, the levels of IL-10 (r = 0.659, p = 0.020) and NF-\( \kappa \)B (r = 0.608, p = 0.010) were
**Table 1. Baseline characteristics of patients**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Control</th>
<th>IgAN</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients (male:female)</td>
<td>25 (11:14)</td>
<td>31 (14:17)</td>
<td>0.004</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>44.84 ± 13.72</td>
<td>34.48 ± 12.10</td>
<td>0.004</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>63.40 ± 12.29</td>
<td>60.50 ± 11.05</td>
<td>0.358</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>23.61 ± 3.44</td>
<td>22.00 ± 3.32</td>
<td>0.081</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>112.64 ± 11.55</td>
<td>121.67 ± 16.73</td>
<td>0.026</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>73.08 ± 11.20</td>
<td>76.13 ± 10.87</td>
<td>0.308</td>
</tr>
<tr>
<td>WBC (/µL)</td>
<td>5,782.00 ± 1,246.32</td>
<td>6,591.94 ± 1,749.12</td>
<td>0.056</td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>13.98 ± 1.20</td>
<td>12.94 ± 2.09</td>
<td>0.034</td>
</tr>
<tr>
<td>Platelet (×10³/µL)</td>
<td>271.28 ± 73.82</td>
<td>256.22 ± 78.87</td>
<td>0.468</td>
</tr>
<tr>
<td>Cholesterol (mg/dL)</td>
<td>186.17 ± 53.91</td>
<td>178.10 ± 42.96</td>
<td>0.543</td>
</tr>
<tr>
<td>HDL (mg/dL)</td>
<td>45.63 ± 15.38</td>
<td>52.08 ± 17.36</td>
<td>0.172</td>
</tr>
<tr>
<td>Triglyceride (mg/dL)</td>
<td>137.54 ± 94.36</td>
<td>118.89 ± 73.18</td>
<td>0.426</td>
</tr>
<tr>
<td>FBS (mg/dL)</td>
<td>100.0 ± 20.03</td>
<td>95.31 ± 12.72</td>
<td>0.323</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>0.83 ± 0.25</td>
<td>1.07 ± 0.44</td>
<td>0.017</td>
</tr>
<tr>
<td>24-hr proteinuria (mg/day)</td>
<td>137.40 ± 84.73</td>
<td>1,476.29 ± 1,607.35</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Data are presented as number only or mean ± standard deviation.

BP, blood pressure; FBS, fasting blood sugar; HDL, high-density lipoprotein; IgAN, immunoglobulin A nephropathy; WBC, white blood cell.

**Figure 1. Level of cytokines in the serum and urine.** Comparison was performed between healthy controls and patients with IgAN. Data are presented as mean ± standard deviation. *p < 0.05 vs. control group.

IgAN, immunoglobulin A nephropathy; IL, interleukin; INFγ, interferon-gamma; MCP-1, monocyte chemoattractant peptide-1.
correlated with baseline proteinuria in patients with IgAN.

Baseline physicochemical and cytokine differences in groups according to estimated glomerular filtration rate

Patients were divided into two groups (high and low eGFR) based on an eGFR of 60 mL/min/1.73 m². Patients with low eGFR presented lower body mass index and hemoglobin and higher proteinuria than those with high eGFR. The levels of urine IL-13, MCP-1, and TNF-α and TNF-α secreted by PBMCs were significantly increased in patients with low eGFR concentration. Moreover, the levels of urine IFNγ, serum IL-10 and MCP-1, and IL-2 secreted by PBMCs also tended to be higher in patients with low eGFR concentration (Supplementary Fig. 1, available online).

Clinical and cytokine changes in patients undergoing corticosteroid treatment

Among the 31 patients, 17 patients were treated with glucocorticoids. Thirteen patients responded to glucocorticoid treatment, as indicated by a reduction in proteinuria of >50% compared with baseline proteinuria levels. Two patients did not respond to treatment, and another two patients were not followed up until 6 months after the treatment.

To determine parameters significantly related to
proteinuria reduction in patients undergoing glucocorticoid treatment, the correlation between the percentage of proteinuria reduction and various parameters was analyzed. The levels of urine MCP-1 (r = 0.722, p = 0.012), serum IL-4 (r = 0.930, p < 0.001), and IFNγ (r = 0.882, p = 0.002) and IL-2 secreted by PBMCs (r = 0.866, p = 0.003) were significantly correlated with the proteinuria at 6 months to baseline proteinuria ratio. Furthermore, the intrarenal IL-1 mRNA level (r = 0.731, p = 0.040) was also correlated with proteinuria reduction (Supplementary Table 3, available online).

**Interferon-gamma-stimulated monocyte chemoattractant peptide-1 production in mesangial cells**

To assess inflammatory responses, MCs were stimulated with different Th1/Th2 cytokines. The MCP-1 mRNA level was significantly upregulated in MCs stimulated by IFNγ treatment. The MCP-1 protein level in supernatants was also increased exclusively by IFNγ (Fig. 3).

**Discussion**

In this study, we found that levels of serum IFNγ and urinary MCP-1 were significantly higher in patients with IgAN compared with levels in healthy controls. Urinary MCP-1, serum IL-10, and TNF-α levels were higher in patients with high proteinuria or correlated with the proteinuria level. Furthermore, the urinary MCP-1 level was significantly increased in patients with low eGFR. In vitro experiments also showed that among different tested Th1/Th2 cytokines, only IFNγ induced MCP-1 synthesis in cultured patient-derived MCs. Therefore, IFNγ was found to be a key cytokine in the pathogenetic processes of IgAN; in turn, the upregulation of IFNγ induced an increase in urinary MCP-1 levels. Consequently, upregulated MCP-1 was related to clinical findings, such as proteinuria and eGFR levels, and further correlated with responsiveness to glucocorticoid treatment.

The importance of Th1/Th2 polarization in the pathogenesis of IgAN remains unclear. Some reports point to a Th1 predominance in patients with IgAN and animal models for IgAN [5,10,11]. Moreover, the IgA-containing immune complex was found to induce the secretion of IL-1 and IL-6, subsequently leading to inflammatory reactions [12]. Other studies showed that IFNγ, TNF-α, and IL-6 increased the expression of Fcα receptors in MCs and the interaction of IgA with Fcα receptors induced the expression of NF-κB and MCP-1 [13,14]. INFγ polymorphisms were also related to the development of IgAN [15]. These findings support a relationship between Th1 cytokines and proinflammatory cytokines. In our study, we could not demonstrate definitive polarization of Th1/Th2 cells, but the IFNγ levels were predominantly increased in the serum of patients with IgAN and IFNγ stimulated MCP-1 expression in MCs from IgAN patients. Therefore, IFNγ might be a key cytokine in the development of IgAN.

MCP-1 plays an important role in IgAN as well as other glomerulonephritides. Previous studies showed that MCP-1 reflects the disease activity, proteinuria, and severity of chronic histologic changes in IgAN [16,17]. In another study,

![Figure 3](image-url)
urinary MCP-1 levels independently predicted renal survival [18]. Although the pathogenetic mechanism of MCP-1 in IgAN is unclear, some reports have shone light on the role of MCP-1 in this disease. Proteinuria and activation of IFNγ were suggested as the main stimuli to MCP-1 [17,19]. In our study, MCP-1 expression was highly upregulated in several samples from patients with IgAN, especially those with high proteinuria and low eGFR. In addition, the urine MCP-1 level was further correlated with responsiveness to glucocorticoid treatment. These results suggest that MCP-1 might be a valuable marker for determining the disease activity and treatment response in patients with IgAN.

Notably, few studies have shown the relationship between cytokines and disease severity in IgAN. In addition to MCP-1, various proinflammatory (TNF-α, IL-1β), Th1 (IFNγ, IL-2), and Th2 (IL-4, IL-10) cytokines are related to disease activity in IgAN [7,20,21]. In accordance with these findings, we found that the levels of TNF-α, IL-10, IL-13, and NF-κB in various samples were significantly related to disease activity.

Glucocorticoids inhibit various cytokines, but their effect in patients with IgAN is still controversial. Several cytokines, especially IL-6, were found to be suppressed in IgAN after steroid treatment [22]. However, Kalliakmani et al. [23] reported that levels of IL-6, a profibrotic cytokine, were unchanged in patients with IgAN after steroid treatment. In our study, levels of urine MCP-1, serum IL-4, and IFNγ and IL-2 secreted by PBMCs were significantly correlated with the percentage of proteinuria reduction in patients with IgAN after glucocorticoid treatment. Furthermore, the intrarenal IL-1 mRNA level was correlated with proteinuria reduction, in agreement with the findings of Pathak et al. [24]. These results highlight the usefulness of cytokine levels assessed in various samples, including PBMCs, in predicting responses to steroid treatment.

Our study has several limitations. First, the small number of patients enrolled in this study does not allow the characterization of disease status based on pathology and the determination of treatment responses. Second, longitudinal data were not enough to determine the relationship between clinical prognosis and cytokine levels. Third, we measured only the intrarenal levels of cytokine mRNA, not that of proteins, which does not reflect the actual expression of cytokines.

Regardless of these limitations, the present study offers a comprehensive view of the cytokine profile of patients with IgAN, as it was simultaneously performed in serum, urine, kidney tissue, PBMC, and MC samples.

In conclusion, IFNγ was found to be a key cytokine in the specific pathogenetic processes of IgAN. The upregulation of IFNγ induced increased urinary MCP-1 production, which in turn correlated with several clinical findings and reduction of proteinuria in patients with IgAN after glucocorticoid treatment. Our data suggest that an integrated analysis of various tissue samples from patients with IgAN would be of utmost importance to further clarify the pathogenetic mechanism underlying this disease.

Conflicts of interest

All authors have no conflicts of interest to declare.

Funding

This study was supported by a cooperative research fund from the Korean Society of Nephrology (2008).

Authors’ contributions

Conceptualization: CGI, DRC
Data curation: SYH, KHJ, YSK
Formal analysis: SYH, CGI, DRC
Funding acquisition: KHJ, CGI, YSK
Methodology: SYH, CGI, DRC
Project administration: CGI, DRC
Writing—original draft: all authors
Writing—review & editing: all authors
All authors read and approved the final manuscript.

ORCID

Sang YoubHan, https://orcid.org/0000-0003-3312-0597
Kyung Hwan Jeong, https://orcid.org/0000-0003-1492-8021
Chun-Gyoo Ihm, https://orcid.org/0000-0002-6397-4481
Young Sun Kang, https://orcid.org/0000-0002-4061-386X
Dae Ryong Cha, https://orcid.org/0000-0003-0663-2844

References


www.krcp-ksn.org 75


Histopathologic and clinicopathologic classifications of antineutrophil cytoplasmic antibody-associated glomerulonephritis: a validation study in a Korean cohort

Jeong-Hoon Lim¹,², Man-Hoon Han³, Yong-Jin Kim³, Yena Jeon⁴, Hee-Yeon Jung¹,⁸, Ji-Young Choi¹,², Jang-Hee Cho¹,⁸, Chan-Duck Kim¹,⁸, Yong-Lim Kim¹,⁸, Hajeong Lee⁶,⁷, Dong Ki Kim⁶,⁷, Kyung Chul Moon⁸, Sun-Hee Park¹,⁵

¹Department of Internal Medicine, School of Medicine, Kyungpook National University, Daegu, Republic of Korea
²Department of Internal Medicine, Kyungpook National University Chilgok Hospital, Daegu, Republic of Korea
³Department of Pathology, School of Medicine, Kyungpook National University, Kyungpook National University Hospital, Daegu, Republic of Korea
⁴Department of Statistics, Kyungpook National University, Daegu, Republic of Korea
⁵Department of Internal Medicine, Kyungpook National University Hospital, Daegu, Republic of Korea
⁶Department of Internal Medicine, Seoul National University School of Medicine, Seoul, Republic of Korea
⁷Department of Internal Medicine, Seoul National University Hospital, Seoul, Republic of Korea
⁸Department of Pathology, Seoul National University College of Medicine, Seoul, Republic of Korea

Background: Antineutrophil cytoplasmic antibodies (ANCA)-associated glomerulonephritis (AAGN) is a common cause of rapidly progressive glomerulonephritis and requires prompt and proper immunosuppressive therapy to improve renal prognosis. This study aimed to evaluate the predictive value of two different classifications for renal outcomes in Korean AAGN patients.

Methods: Ninety-two patients who were diagnosed with AAGN at two tertiary hospitals between 2004 and 2018 were retrospectively analyzed. The histopathologic classification according to glomerular pathology and the clinicopathologic classification according to normal glomeruli ratio, degree of interstitial fibrosis/tubular atrophy, and baseline renal function were evaluated using the Cox proportional hazards model.

Results: Forty-five patients (48.9%) progressed to end-stage kidney disease (ESKD) during the observation period. The mean age was 61.0 ± 15.3 years, and most patients had myeloperoxidase-ANCA (93.5%). In the histopathologic classification, the best renal survival occurred in the focal class, whereas the sclerotic class had the worst renal survival (sclerotic class vs. focal class; adjusted hazard ratio [aHR], 5.05; 95% confidence interval [CI], 1.32–19.31; p = 0.018). The mixed class had intermediate renal outcomes (mixed class vs. focal class; aHR, 4.23; 95% CI, 1.23–14.58; p = 0.022). In the clinicopathologic classification, the high-risk group had poor renal outcomes compared with the low-risk group (aHR, 6.56; 95% CI, 1.25–34.26; p = 0.026), but renal outcomes did not differ between the low- and medium-risk groups.

Received: October 8, 2020; Revised: November 11, 2020; Accepted: November 22, 2020
Editor: Beom Jin Lim, Yonsei University, Seoul, Republic of Korea
Correspondence: Sun-Hee Park
Department of Internal Medicine, School of Medicine, Kyungpook National University, Kyungpook National University Hospital, 130 Dongdeok-ro, Jung-gu, Daegu 41944, Republic of Korea. E-mail:sh-park@knu.ac.kr
ORCID: https://orcid.org/0000-0002-0953-3343
Copyright © 2021 by The Korean Society of Nephrology
This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial and No Derivatives License (http://creativecommons.org/licenses/by-nc-nd/4.0/) which permits unrestricted non-commercial use, distribution of the material without any modifications, and reproduction in any medium, provided the original works properly cited.
Conclusion: In Korean AAGN patients, histopathologic and clinicopathologic classifications had predictive value for renal outcomes, especially in the sclerotic class or the high-risk group with higher risk of progression to ESKD despite treatment.

Keywords: Antibodies, Antineutrophil cytoplasmic, Classification, Glomerulonephritis, Kidney failure, Chronic, Pathology

Introduction

Antineutrophil cytoplasmic antibodies (ANCA)-associated vasculitis (AAV) is characterized by necrotizing inflammation of small vessels and consists of a group of multisystemic diseases, such as microscopic polyangiitis, granulomatosis with polyangiitis, eosinophilic granulomatosis with polyangiitis, and renal limited vasculitis [1,2]. AAV commonly involves the kidneys and is a common cause of rapidly progressive glomerulonephritis [3]. Despite treatment, renal survival and patient survival are poor in patients with ANCA-associated glomerulonephritis (AAGN) [4,5]. Prompt diagnosis and immediate proper immunosuppressive therapy are necessary to prevent the progression of end-stage kidney disease (ESKD). However, immunosuppression can also cause an increased in short-term or long-term mortality, mainly by infection [6].

To prevent excessive immunosuppression and reduce complications, several studies have been conducted to find the histopathologic or clinical predictors for renal prognosis at the time of diagnosis. Various parameters, such as age, baseline renal function, percentage of normal/globally sclerotic glomeruli, and degree of interstitial fibrosis/tubular atrophy (IF/TA), have been identified as possible predictors [4,5,7,8]. However, they have limitations in predicting renal outcomes and have not been validated. Berden et al. [9] developed a simple histopathologic classification of AAGN divided into four classes (focal, crescentic, mixed, and sclerotic) according to glomeruli and crescent types. More recently, Brix et al. [10] accentuated the limitations of the histopathologic classification that reflects only glomerular findings. They developed a new classification according to the ANCA kidney risk scoring system that reflects not only histopathologic but also clinical findings.

Both classifications were developed using data from western AAV patients. Although there are Chinese and Japanese validation studies for histopathologic classification [11,12], no studies have used a Korean cohort. Also, there are still no studies on the ANCA kidney risk score for Asian AAGN patients. Therefore, this study aimed to evaluate the predictive value of the histopathologic and clinicopathologic classifications for renal outcomes among Korean AAGN patients.

Methods

Patients

This retrospective cohort study analyzed all patients diagnosed with AAGN at two university-based tertiary hospitals (Kyungpook National University Hospital and Seoul National University Hospital) from March 2004 to March 2018. Patients were eligible for inclusion if they met the following: (1) the criteria of the Chapel Hill Consensus Conference definition for AAV [2], (2) were positive serology for ANCA, (3) renal biopsy consistent with AAGN and the specimen contained ≥10 glomeruli [5,9], and (4) were followed up for ≥1 year. A total of 92 patients were included in this study. The study protocol was reviewed and approved by the Institutional Review Boards of Kyungpook National University Hospital (No. 2017-08-013-003) and Seoul National University Hospital (No. H1802-102-924). Informed consent was waived, as there was no infringement of the patients’ health or privacy during the study.

Data collection and definition

Data on patient demographics, comorbid diseases, and laboratory findings were surveyed at the time of renal biopsy from electronic medical records. Renal function was measured again at 1 year after diagnosis. The estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine equation [13]. Information on the development of ESKD and the last follow-up date was also collected. The development of ESKD was defined as requiring kidney transplantation, permanent hemodialysis, or peritoneal dialysis. Hypertension was defined as systolic blood pressure of ≥140 mmHg and/or diastolic blood pressure...
pressure of ≥90 mmHg or the use of antihypertensive medication. Diabetes was defined as the use of glucose-lowering agents, random glucose of ≥200 mg/dL, or hemoglobin A1c of ≥6.5%.

Two renal pathologists (MHH and YJK) who were blinded to the patient information independently evaluated the renal specimens. The details of the evaluated histopathologic information are as follows: the number of total/normal/crescentic (cellular or fibrous)/globally sclerotic glomeruli, histopathologic classification of AAGN using the algorithm developed by Berden et al. [9], and degree of IF/TA. The histopathologic classification was divided into four categories: focal class (≥50% normal glomeruli), crescentic class (≥50% cellular crescentic glomeruli), sclerotic class (≥50% globally sclerotic glomeruli), and mixed class (<50% normal, cellular crescentic, and globally sclerotic glomeruli) [9]. The detailed information and histopathologic images are shown in our previous report [14]. The interobserver variations of the histopathologic classification and the clinicopathologic score were identified (κ = 0.89 and κ = 0.95, respectively), and the discrepancies between the two observers were resolved by consensus meetings according to the recommendation [15]. The clinicopathologic classification was divided into three groups (low, medium, and high) according to the risk scores that consist of the histopathologic parameters (percentage of normal glomeruli: >25%, 0 points; 10%–25%, 4 points; <10%, 6 points and degree of IF/TA: ≤25%, 0 points; >25%, 2 points) and the laboratory variable (eGFR at the time of diagnosis: >15 mL/min/1.73 m², 0 points; ≤15 mL/min/1.73 m², 3 points) [10]. The risk groups were defined according to the sum scores: low-risk group, 0 points; medium-risk group, 2 to 7 points; and high-risk group, 8 to 11 points.

Treatment

Individual treatment information could not be retrieved in the data. The treatment was decided based on the general condition of the patient, comorbid diseases, and treatment protocols for AAGN [16,17]. Detailed information for general AAGN treatment has been described in a previous study [14]. In brief, high-dose intravenous methylprednisolone (500 mg/day for 3 days) with pulse intravenous or daily oral cyclophosphamide was used for induction. The steroid was then tapered to 1 mg/kg/day oral prednisolone for 4 to 6 weeks. Low-dose oral prednisolone and oral azathioprine were used for maintenance immunosuppression. Rituximab was used as induction immunosuppressive therapy for 21 patients (22.8%) since 2011.

Statistical analysis

Kolmogorov-Smirnov test was used to evaluate the normal distribution of variables. Continuous variables are presented as mean ± standard deviation or median (interquartile range, IQR) according to the distribution. Categorical variables are presented as number (percentage). Student t test or Mann-Whiney U test was used to compare the differences in continuous variables. Pearson chi-square test or Fisher exact test was used to compare the differences in categorical variables, as appropriate. Kaplan-Meier analysis was used to compare renal survival. A log-rank test was used to analyze the difference. Linear regression analysis was used to identify the associated factors for the 1-year change in eGFR. Cox proportional hazards regression analysis was performed to identify the predictors for renal survival. The statistic was used to evaluate the interobserver difference for the histopathologic classification. Statistical analyses were performed with IBM SPSS for Windows, version 22 (IBM Corp., Armonk, NY, USA). A p-value of <0.05 was considered statistically significant.

Results

Baseline characteristics

Among 92 AAGN patients, 45 (48.9%) had developed ESKD during a median of 475 days of follow-up (Table 1). The mean age was 61.0 ± 15.3 years at the time of diagnosis. Patients with ESKD had a tendency to be older than those without ESKD (63.4 ± 15.4 years vs. 57.1 ± 15.6 years; p = 0.055). Hypertension was more common in the ESKD group than in the non-ESKD group (46.7% vs. 21.3%; p = 0.010). Baseline eGFR was significantly lower among ESKD patients (8.6 mL/min/1.73 m² [7.0–13.2 mL/min/1.73 m²] vs. 24.0 mL/min/1.73 m² [12.9–40.2 mL/min/1.73 m²]; p < 0.001). Most patients had myeloperoxidase (MPO)-ANCA (86 of 92, 93.5%), and the proportion was similar between the ESKD and non-ESKD groups.

For the histopathologic findings, the median number of
In the clinicopathologic classification, the sum of the ANCA kidney risk score was significantly higher in the ESKD group than in the non-ESKD group (9.0 [6.0–11.0] vs. 2.0 [0.0–5.0]; p < 0.001). There was a larger proportion of the high-risk group and a lower proportion of the low-risk group in the ESKD group than in the non-ESKD group (ESKD vs. non-ESKD; high, 28 [62.2%] vs. 4 [8.5%]; low, 2 [4.4%] vs. 19 [40.4%]; p < 0.001).

Table 1. Baseline characteristics at the time of diagnosis

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total</th>
<th>ESKD</th>
<th>Non-ESKD</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>92</td>
<td>45</td>
<td>47</td>
<td></td>
</tr>
<tr>
<td>Age (yr)</td>
<td>61.0 ± 15.3</td>
<td>63.4 ± 15.4</td>
<td>57.1 ± 15.6</td>
<td>0.055</td>
</tr>
<tr>
<td>Male sex</td>
<td>46 (50.0)</td>
<td>24 (53.3)</td>
<td>22 (46.8)</td>
<td>0.532</td>
</tr>
<tr>
<td>Comorbid disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>11 (12.0)</td>
<td>6 (13.3)</td>
<td>5 (10.6)</td>
<td>0.690</td>
</tr>
<tr>
<td>Hypertension</td>
<td>31 (33.7)</td>
<td>21 (46.7)</td>
<td>10 (21.3)</td>
<td>0.010</td>
</tr>
<tr>
<td>Follow-up after diagnosis (day)</td>
<td>475.0 (87.0–1,268.0)</td>
<td>357.0 (68.0–1,344.0)</td>
<td>677.0 (320.0–1,175.0)</td>
<td>0.152</td>
</tr>
<tr>
<td>Laboratory data</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>eGFR (mL/min/1.73 m²)</td>
<td>13.2 (8.1–25.5)</td>
<td>8.6 (7.0–13.2)</td>
<td>24.0 (12.9–40.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Spot urine protein-to-creatinine ratio (g/g)</td>
<td>2.2 (1.5–3.9)</td>
<td>2.1 (1.5–4.1)</td>
<td>2.3 (1.5–3.8)</td>
<td>0.645</td>
</tr>
<tr>
<td>Immunology a</td>
<td></td>
<td></td>
<td></td>
<td>0.267</td>
</tr>
<tr>
<td>MPO-ANCA</td>
<td>86 (93.5)</td>
<td>41 (91.1)</td>
<td>45 (95.7)</td>
<td></td>
</tr>
<tr>
<td>PR3-ANCA</td>
<td>7 (7.6)</td>
<td>5 (11.1)</td>
<td>2 (4.3)</td>
<td></td>
</tr>
<tr>
<td>Histopathologic findings</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total glomeruli number</td>
<td>16.0 (12.0–23.0)</td>
<td>16.0 (12.0–24.0)</td>
<td>16.0 (12.0–22.0)</td>
<td>0.427</td>
</tr>
<tr>
<td>Normal glomeruli (%)</td>
<td>20.4 (8.3–39.1)</td>
<td>9.1 (0.0–18.6)</td>
<td>33.3 (20.8–50.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Crescentic glomeruli (%)</td>
<td>54.2 (30.8–70.4)</td>
<td>58.3 (32.4–76.1)</td>
<td>50.0 (30.0–69.2)</td>
<td>0.124</td>
</tr>
<tr>
<td>Globally sclerotic glomeruli (%)</td>
<td>14.8 (0.0–30.2)</td>
<td>23.3 (6.3–38.8)</td>
<td>8.3 (0.0–23.1)</td>
<td>0.004</td>
</tr>
<tr>
<td>IF/TA, &gt;25%</td>
<td>42 (45.7)</td>
<td>29 (64.4)</td>
<td>13 (27.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Histopathologic classification</td>
<td></td>
<td></td>
<td></td>
<td>0.003</td>
</tr>
<tr>
<td>Focal</td>
<td>18 (19.6)</td>
<td>3 (6.7)</td>
<td>15 (31.9)</td>
<td></td>
</tr>
<tr>
<td>Crescent</td>
<td>30 (32.6)</td>
<td>14 (22.2)</td>
<td>16 (34.0)</td>
<td></td>
</tr>
<tr>
<td>Mixed</td>
<td>32 (34.8)</td>
<td>18 (40.0)</td>
<td>14 (29.8)</td>
<td></td>
</tr>
<tr>
<td>Sclerotic</td>
<td>12 (13.0)</td>
<td>10 (22.2)</td>
<td>2 (4.3)</td>
<td></td>
</tr>
<tr>
<td>ANCA kidney risk score b</td>
<td>5.0 (2.0–11.0)</td>
<td>9.0 (6.0–11.0)</td>
<td>2.0 (0–5.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Clinicopathologic classification</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Low</td>
<td>21 (22.8)</td>
<td>2 (4.4)</td>
<td>19 (40.4)</td>
<td></td>
</tr>
<tr>
<td>Medium</td>
<td>39 (42.4)</td>
<td>15 (33.3)</td>
<td>24 (51.1)</td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>32 (34.8)</td>
<td>28 (62.2)</td>
<td>4 (8.5)</td>
<td></td>
</tr>
</tbody>
</table>

Data are expressed as number only, mean ± standard deviation, median (interquartile range), or number (%). ANCA, anti-neutrophil cytoplasmic antibody; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; IF/TA, interstitial fibrosis/tubular atrophy; MPO, myeloperoxidase; PR3, proteinase 3.

aOne patient (1 of 92, 1.1%) had positivity for both MPO- and PR3-ANCA.

bSum score of the clinicopathologic parameters (percentage of normal glomeruli, degree of IF/TA, and eGFR at the time of diagnosis).
Table 2. Rate of progression to end-stage kidney disease according to the classifications

<table>
<thead>
<tr>
<th>Variable</th>
<th>1 Year after diagnosis</th>
<th>p-value</th>
<th>Total follow-up period</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Histopathologic classification</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Focal</td>
<td>2/18 (11.1)</td>
<td>0.003</td>
<td>3/18 (16.7)</td>
<td>0.003</td>
</tr>
<tr>
<td>Crescentic</td>
<td>10/30 (33.3)</td>
<td></td>
<td>14/30 (46.7)</td>
<td></td>
</tr>
<tr>
<td>Mixed</td>
<td>15/32 (46.9)</td>
<td></td>
<td>18/32 (56.3)</td>
<td></td>
</tr>
<tr>
<td>Sclerotic</td>
<td>9/12 (75.0)</td>
<td></td>
<td>10/12 (83.3)</td>
<td></td>
</tr>
<tr>
<td><strong>Clinicopathologic classification</strong></td>
<td></td>
<td>&lt;0.001</td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Low</td>
<td>1/21 (4.8)</td>
<td></td>
<td>2/21 (9.5)</td>
<td></td>
</tr>
<tr>
<td>Medium</td>
<td>11/39 (28.2)</td>
<td></td>
<td>15/39 (38.5)</td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>24/32 (75.0)</td>
<td></td>
<td>28/32 (87.5)</td>
<td></td>
</tr>
</tbody>
</table>

Data are expressed as number (%).

<table>
<thead>
<tr>
<th>Variable</th>
<th>1 Year after diagnosis</th>
<th>p-value</th>
<th>Total follow-up period</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Histopathologic classification</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Focal</td>
<td>2/18 (11.1)</td>
<td>0.003</td>
<td>3/18 (16.7)</td>
<td>0.003</td>
</tr>
<tr>
<td>Crescentic</td>
<td>10/30 (33.3)</td>
<td></td>
<td>14/30 (46.7)</td>
<td></td>
</tr>
<tr>
<td>Mixed</td>
<td>15/32 (46.9)</td>
<td></td>
<td>18/32 (56.3)</td>
<td></td>
</tr>
<tr>
<td>Sclerotic</td>
<td>9/12 (75.0)</td>
<td></td>
<td>10/12 (83.3)</td>
<td></td>
</tr>
<tr>
<td><strong>Clinicopathologic classification</strong></td>
<td></td>
<td>&lt;0.001</td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Low</td>
<td>1/21 (4.8)</td>
<td></td>
<td>2/21 (9.5)</td>
<td></td>
</tr>
<tr>
<td>Medium</td>
<td>11/39 (28.2)</td>
<td></td>
<td>15/39 (38.5)</td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>24/32 (75.0)</td>
<td></td>
<td>28/32 (87.5)</td>
<td></td>
</tr>
</tbody>
</table>

Data are expressed as number (%).

Renal outcomes and changes in renal function

Thirty-six patients had progressed to ESKD at 1 year after diagnosis. The incidence of ESKD at 1 year was 11.1% (2 of 18), 33.3% (10 of 30), 46.9% (15 of 32), and 75.0% (9 of 12) in the focal, crescentic, mixed, and sclerotic classes, respectively (p = 0.003) (Table 2). The increasing trend with sequential category, focal, crescentic, mixed, and sclerotic classes, of the proportion of patients who developed ESKD, was also maintained during the total follow-up period (16.7% [3 of 18], 46.7% [14 of 30], 56.3% [18 of 32], and 83.3% [10 of 12], respectively; p = 0.003). In the clinicopathologic classification, the incidence of ESKD increased in the order of the low-, medium-, and high-risk groups both at 1 year after diagnosis and the entire follow-up period (1 year: 4.8% [1 of 21], 28.2% [11 of 39], and 75.0% [24 of 32]; total follow-up: 9.5% [2 of 21], 38.5% [15 of 39], and 87.5% [28 of 32], respectively; both p < 0.001).

As an index of therapeutic response, the changes in eGFR at 1 year after diagnosis (ΔeGFR1y) were compared (Fig. 1). In the histopathologic classification, ΔeGFR1y improved in the order of focal, crescentic, mixed, and sclerotic classes (Fig. 1A). ΔeGFR1y was significantly higher in the focal class than in the sclerotic class (p = 0.040). In the clinicopathologic classification, the high-risk group had worse ΔeGFR1y than both the low- and medium-risk groups (p = 0.034 and p = 0.001, respectively) (Fig. 1B). In the multiple linear regression analyses for ΔeGFR1y, the mixed and sclerotic classes showed a faster decline of eGFR than the focal class after adjusting for age, sex, diabetes, and hypertension (model 1 with the histopathologic classification; both p < 0.05) (Table 3). After adjusting for the same factors, the decline of eGFR was greater in the high-risk group than in the low-risk group (model 2 with the clinicopathologic classification; p = 0.008).
Table 3. Linear regression analysis of the change in eGFR during 1-year after diagnosis

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariate</th>
<th>Model 1</th>
<th>Model 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>β</td>
<td>p-value</td>
<td>β</td>
</tr>
<tr>
<td>Age</td>
<td>-0.33</td>
<td>0.007</td>
<td>-0.34</td>
</tr>
<tr>
<td>Sex (reference, female)</td>
<td>0.03</td>
<td>0.790</td>
<td>0.06</td>
</tr>
<tr>
<td>Diabetes</td>
<td>-0.02</td>
<td>0.894</td>
<td>0.02</td>
</tr>
<tr>
<td>Hypertension</td>
<td>-0.08</td>
<td>0.526</td>
<td>0.02</td>
</tr>
<tr>
<td>eGFR at diagnosis</td>
<td>0.11</td>
<td>0.375</td>
<td></td>
</tr>
<tr>
<td>Percentage of glomeruli</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>0.36</td>
<td>0.003</td>
<td></td>
</tr>
<tr>
<td>Crescentic</td>
<td>-0.10</td>
<td>0.418</td>
<td></td>
</tr>
<tr>
<td>Sclerotic</td>
<td>-0.29</td>
<td>0.018</td>
<td></td>
</tr>
<tr>
<td>Histopathologic classification</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Focal</td>
<td>Reference</td>
<td></td>
<td>Reference</td>
</tr>
<tr>
<td>Crescentic</td>
<td>-0.20</td>
<td>0.283</td>
<td>-0.25</td>
</tr>
<tr>
<td>Mixed</td>
<td>-0.39</td>
<td>0.021</td>
<td>-0.35</td>
</tr>
<tr>
<td>Sclerotic</td>
<td>-0.31</td>
<td>0.034</td>
<td>-0.36</td>
</tr>
<tr>
<td>Clinicopathologic classification</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>Reference</td>
<td></td>
<td>Reference</td>
</tr>
<tr>
<td>Medium</td>
<td>-0.01</td>
<td>0.943</td>
<td>0.03</td>
</tr>
<tr>
<td>High</td>
<td>-0.47</td>
<td>0.002</td>
<td>-0.42</td>
</tr>
</tbody>
</table>

eGFR, estimated glomerular filtration rate.


Prediction of renal survival

In the Kaplan-Meier analysis, renal survival was significantly different according to the histopathologic classification (log-rank p < 0.001) (Fig. 2). The mixed and sclerotic classes had worse renal outcomes than the focal class (p = 0.008 and p < 0.001, respectively). The crescentic class had a tendency for poorer renal survival than the focal class (p = 0.059). When dividing patients according to the cutoff of each parameter in the clinicopathologic classification, all three items (percentage of normal glomeruli, IF/TA, and baseline eGFR) were individually associated with renal survival (all log-rank p < 0.001), but normal glomeruli ratios of >25% and 10% to 25% did not differ in renal survival (p > 0.05; Fig. 3A-C). In the clinicopathologic classification, renal survival was decreased in the a low, medium, and high order of risk (log-rank p < 0.001) (Fig. 3D).

In the multivariate Cox regression analysis of renal outcome, the mixed and sclerotic classes were independent predictors for ESKD (vs. the focal class; mixed class: models (p < 0.05).
Figure 3. Kaplan-Meier curve for renal survival according to clinicopathologic classification and each included parameter. (A) Percentage of normal glomeruli. (B) Degree of interstitial fibrosis/tubular atrophy. (C) Estimated glomerular filtration rate (eGFR) at the time of diagnosis. (D) Clinicopathologic classification combining each parameter.

The high-risk group of the clinicopathologic classification was independently associated with the worse renal outcome (vs. low-risk; aHR, 6.56; 95% CI, 1.25–34.26; p = 0.026), but the medium-risk
Table 4. Predictors for progression to end-stage kidney disease in the Cox proportional hazards model

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariate HR (95% CI)</th>
<th>p-value</th>
<th>Model 1(^a) aHR (95% CI)</th>
<th>p-value</th>
<th>Model 2(^b) aHR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.03 (1.01–1.06)</td>
<td>0.015</td>
<td>1.02 (0.99–1.04)</td>
<td>0.210</td>
<td>1.01 (0.99–1.04)</td>
<td>0.263</td>
</tr>
<tr>
<td>Sex</td>
<td>1.22 (0.67–2.20)</td>
<td>0.514</td>
<td>1.23 (0.66–2.28)</td>
<td>0.520</td>
<td>1.32 (0.72–2.40)</td>
<td>0.372</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.42 (0.60–3.37)</td>
<td>0.425</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.85 (1.03–3.33)</td>
<td>0.039</td>
<td>0.95 (0.50–1.79)</td>
<td>0.871</td>
<td>1.15 (0.61–2.17)</td>
<td>0.674</td>
</tr>
<tr>
<td>eGFR at diagnosis</td>
<td>0.90 (0.86–0.95)</td>
<td>&lt;0.001</td>
<td>0.91 (0.87–0.96)</td>
<td>&lt;0.001</td>
<td>0.95 (0.91–1.00)</td>
<td>0.049</td>
</tr>
</tbody>
</table>

Percentage of glomeruli

<table>
<thead>
<tr>
<th></th>
<th>Reference HR (95% CI)</th>
<th>p-value</th>
<th>Reference aHR (95% CI)</th>
<th>p-value</th>
<th>Reference aHR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>0.96 (0.94–0.98)</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crescentic</td>
<td>1.01 (1.00–1.02)</td>
<td>0.156</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sclerotic</td>
<td>1.02 (1.01–1.04)</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Histopathologic classification

<table>
<thead>
<tr>
<th></th>
<th>Reference HR (95% CI)</th>
<th>p-value</th>
<th>Reference aHR (95% CI)</th>
<th>p-value</th>
<th>Reference aHR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Focal</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crescentic</td>
<td>3.40 (0.98–11.85)</td>
<td>0.054</td>
<td>2.45 (0.69–8.67)</td>
<td>0.165</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mixed</td>
<td>5.04 (1.48–17.19)</td>
<td>0.010</td>
<td>4.23 (1.23–14.58)</td>
<td>0.022</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sclerotic</td>
<td>9.88 (2.66–36.62)</td>
<td>0.001</td>
<td>5.05 (1.32–19.31)</td>
<td>0.018</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Clinicopathologic classification

<table>
<thead>
<tr>
<th></th>
<th>Reference HR (95% CI)</th>
<th>p-value</th>
<th>Reference aHR (95% CI)</th>
<th>p-value</th>
<th>Reference aHR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medium</td>
<td>4.40 (1.01–19.23)</td>
<td>0.049</td>
<td>2.56 (0.54–12.12)</td>
<td>0.237</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>18.63 (4.38–79.17)</td>
<td>&lt;0.001</td>
<td>6.56 (1.25–34.26)</td>
<td>0.026</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(aHR\), adjusted hazard ratio; CI, confidence interval; eGFR, estimated glomerular filtration rate; HR, hazard ratio.

\(^a\)Model 1 for histopathologic classification: adjusted for age, sex, hypertension, and eGFR at diagnosis.

\(^b\)Model 2 for clinicopathologic classification: adjusted for age, sex, hypertension, and eGFR at diagnosis.

Patients. Therefore, MPO-ANCA positive patients have a higher risk of renal failure [19–21]. In the histopathologic classification according to glomerular pathology, the focal class had the best renal survival, and the mixed and sclerotic classes had the worse and worst renal survival, respectively. However, the crescentic class did not differ in renal survival compared to the focal class. In the clinicopathologic classification according to the percentage of normal glomeruli, degree of IF/TA, and baseline renal function, the high-risk group had poor renal survival than the low- or medium-risk group; however, there was no difference in renal survival between the low- and medium-risk groups. These results demonstrated that the classifications that originated from western countries were moderate in predicting renal outcomes in Asian AAGN patients. In particular, they showed high predictability for renal outcomes in the worst prognosis groups, such as the sclerotic class or the high-risk group.

AAGN is the most common manifestation of AAV and is highly associated with morbidity and mortality [6,20]. There are several known prognostic factors for progression to ESKD in AAGN, but it is difficult to predict renal outcomes.

In addition, the associations of active inflammatory lesions in histopathology and renal outcomes are shown in Supplementary Table 1 (available online). Among the active inflammatory lesions, such as glomerular fibrinoid necrosis, peritubular capillaritis, tubulitis, and interstitial inflammation, moderate to severe interstitial inflammation was an independent predictor for ESKD after adjustment of age, sex, and hypertension (aHR, 2.40; 95% CI, 1.09–5.31; p = 0.031).

**Discussion**

This study evaluated the renal prognostic value of both histopathologic and clinicopathologic classifications among Korean AAGN patients. Unlike in western countries [9,10,18], the Korean AAGN cohort had a higher proportion of MPO-ANCA positive and higher incidence of progression to ESKD. Previous studies have shown that patients with MPO-ANCA have more abundant active and chronic lesions in renal histopathology than those of proteinase 3-ANCA positive patients. Therefore, MPO-ANCA positive patients have a higher risk of renal failure [19–21]. In the histopathologic classification according to glomerular pathology, the focal class had the best renal survival, and the mixed and sclerotic classes had the worse and worst renal survival, respectively. However, the crescentic class did not differ in renal survival compared to the focal class. In the clinicopathologic classification according to the percentage of normal glomeruli, degree of IF/TA, and baseline renal function, the high-risk group had poor renal survival than the low- or medium-risk group; however, there was no difference in renal survival between the low- and medium-risk groups. These results demonstrated that the classifications that originated from western countries were moderate in predicting renal outcomes in Asian AAGN patients. In particular, they showed high predictability for renal outcomes in the worst prognosis groups, such as the sclerotic class or the high-risk group.

AAGN is the most common manifestation of AAV and is highly associated with morbidity and mortality [6,20]. There are several known prognostic factors for progression to ESKD in AAGN, but it is difficult to predict renal outcomes.
accurately with any single factor [5,7,10]. Berden et al. [9] developed a simple histopathologic classification from European AAGN patients, which focused on the glomerular findings, except background tubulointerstitial findings and clinical findings. They reported that the focal class had a favorable outcome, the mixed class had an intermediate outcome, and the sclerotic class had the highest risk of not recovering renal function and progression to ESKD. Several western and Asian studies have also evaluated the prognostic value of the histopathologic classification [6,12,20,22,23]. Most studies, including a recent meta-analysis, showed similar outcomes: the best outcome in the focal class and the worst outcome in the sclerotic class [6,12,20,22,23]. Globally sclerotic glomeruli are not AAGN-specific findings. However, regardless of the AAGN disease activity, these chronic lesions indicate less response to treatment and a higher risk of progression to ESKD [7,24]. Unlike these classes, there is a controversy about the outcome of the crescentic and mixed classes. Some studies have reported that the crescentic class has a worse outcome than the focal or mixed class [6,23,25]. Others have reported a non-inferior outcome of the crescentic class compared to the focal class because of a good therapeutic response [9,12,20]. The results of this study are consistent with the latter—with Berden et al. [9] and the Japanese cohort studies [12]. Among Korean AAGN patients, the outcome of the crescentic class was relatively good and not inferior to the focal class. Recently, van Daalen et al. [26] reported a validation study for AAGN from patients worldwide. The ΔeGFR$_{2}$ was significantly higher in the crescentic class than in the mixed class despite similar renal function at the time of diagnosis, indicating that the crescentic class had a better treatment response. They explained that this would be related to the different composition of crescent types—that the crescentic class is characterized by a majority of cellular crescents and these are reversible lesions, but the mixed class has more heterogeneous crescent types, such as fibrocellular and fibrous crescents, with poor response to treatment [26,27]. These results may also be related to the association of different human leukocyte antigen by ethnicity in AAV patients [11]. Thus, based on the results of this study, Korean AAGN patients with the focal or crescentic class will need active treatment.

Brix et al. [10] developed a more complex classification using a calculation based on the ANCA kidney risk score. All three factors included in this classification (normal glomeruli ratio, degree of IF/TA, and baseline renal function) are well-established prognostic markers of AAGN in previous studies [4,5,7,15,24]. They determined the appropriate cutoff through rigorous analysis of the German AAGN cohort and divided the groups by scoring. The advantage of this classification is that it reflects both clinical laboratory (eGFR) and histopathologic (normal glomeruli and IF/TA) parameters. However, although these clinicopathologic variables were aggregated, the renal prognosis of the low- and medium-risk groups did not differ in the Korean cohort. A recent Turkish study also reported the same results as in this study [28]. There are some possible reasons for this inconsistent result. First, the cutoff value of the percentage of normal glomeruli was too low. Berden et al. [9] considered significance when the normal glomeruli percentage was higher than 50%, but Brix et al. [10] set the cutoffs at a lower rate of 10% and 25%. Hilhorst et al. [25] reported the worst survival in AAGN patients with normal glomeruli percentage of <25%. Tanna et al. [5] reported a significant difference in renal survival among normal glomeruli percentages of 0% to 20%, 21% to 50%, and >51%. There was no difference in renal survival between normal glomeruli percentages of 10% to 25% and >25% in the results of this study. Therefore, a modified cutoff of the normal glomeruli ratio is required to accurately predict survival among Korean AAGN patients.

Second, the proportion of patients who progressed to ESKD was much higher in this study. The cohort in this study had a lower baseline eGFR and a higher percentage of sclerotic glomeruli than the cohort studied by Brix et al. [10], and the proportion of MPO-ANCA positive was also higher. All these indicators suggest a higher risk of progression to ESKD. Additionally, ethnicity may have possibly contributed to the difference in results from the previous study.

In addition to the aforementioned histopathologic classification, an analysis of the association between histopathologic findings reflecting active lesions and renal survival revealed that moderate to severe interstitial inflammation independently increased the risk of ESKD. This result is consistent with a previous study that reported diffuse interstitial infiltration of inflammatory cells is a predictor for poor renal outcome in European patients with AAGN [4].

The incidence of AAGN increases with age. It is the second most common glomerulonephritis among Korean
patients aged above 70 years who underwent renal biopsy [29,30]. AAGN patients have a high risk of not only renal failure but also death, so prompt diagnosis and proper management are necessary. However, the mortality of AAV patients within the first 12 months after diagnosis was as high as 11%, and half of them died from infection [31]. Intensive immunosuppression also results in other adverse events, such as malignancy, bone marrow suppression, and gastrointestinal bleeding [31]. Thus, especially in elderly patients who are vulnerable to the adverse effects of immunosuppressive therapy, it is important to accurately predict the therapeutic response and provide an appropriate intensity of treatment. Neither the histopathologic nor the clinicopathologic classification perfectly predicts renal outcomes in Korean AAGN patients. However, both classifications showed high predictability of ESKD progression for patients in either the sclerotic class or the high-risk group. In these patients, treatment intensity should be adjusted to consider the worse renal prognosis with less therapeutic response. Also, background histopathologic findings such as interstitial inflammation need to be considered more to accurately predict the renal outcome. In a recently published study on crescentic glomerulonephritis patients, severe arteriosclerosis and tertiary lymphoid organ formation are independent predictors for renal survival after adjusting for age and baseline renal function [14]. By considering indicators that reflect chronic changes and inflammation activity, a more accurate prediction of renal outcomes will be possible.

The strength of this study is that it analyzed unselected patients who were diagnosed with AAGN at two university-based hospitals in Korea. For the first time in Korean AAGN patients, the predictive value of two European origin classifications was assessed. However, there are several limitations. First, this is a retrospective study, so there is a limitation to documenting the effectiveness of various treatments on renal outcomes. Second, the number of study patients was relatively small, although patients diagnosed with AAGN for a long period were included. This may reduce the validity. However, in both classifications, the number of patients was distributed appropriately in each class. Third, patients were treated at the discretion of the clinicians at each hospital. However, although there was no standard treatment, the Korean national health insurance system covers most medical expenses; therefore, treatment is performed according to the same national health insurance guidelines. Fourth, there is a possibility of sample bias. Partial tissue specimen cannot reflect the overall renal disease condition. However, like other AAGN studies [5,8], the bias was reduced by screening specimens that contained more than 10 glomeruli.

In conclusion, both histopathologic and clinicopathologic classifications were moderately able to predict the renal prognosis of Korean AAGN patients. For the sclerotic class or the high-risk group at diagnosis, the predictability for poor renal outcome was high due to poor response to treatment, and they had a high risk of progression to ESKD. Accordingly, clinicians need to balance the risks and benefits of treatment in Korean AAGN patients by identifying the group at high risk for renal outcomes.

Conflicts of interest

All authors have no conflicts of interest to declare.

Authors’ contributions

Conceptualization: JHL, SHP
Data curation: JHL, YJ, MHH, YJK
Investigation: JHL, HYJ, JYC, JHC, CDK, YLK, HL, DKK, KCM
Project administration: SHP
Writing-original draft: JHL, SHP
Writing-review & editing: All authors
All authors read and approved the final manuscript.

ORCID

Jeong-Hoon Lim, https://orcid.org/0000-0001-5517-9886
Man-Hoon Han, https://orcid.org/0000-0001-8856-553X
Yong-Jin Kim, https://orcid.org/0000-0002-9867-0752
Yena Jeon, https://orcid.org/0000-0002-4857-8616
Hee-Yeon Jung, https://orcid.org/0000-0003-0232-7202
Ji-Young Choi, https://orcid.org/0000-0002-9774-3665
Jang-Hee Cho, https://orcid.org/0000-0002-7031-5214
Chan-Duck Kim, https://orcid.org/0000-0002-4648-0324
Yong-Lim Kim, https://orcid.org/0000-0002-1344-3455
Hajeong Lee, https://orcid.org/0000-0002-1873-1587
Dong Ki Kim, https://orcid.org/0000-0002-5195-7852
Kyung Chul Moon, https://orcid.org/0000-0002-1969-8360
Sun-Hee Park, https://orcid.org/0000-0002-0953-3343
References


The comparative effects of intravenous iron on oxidative stress and inflammation in patients with chronic kidney disease and iron deficiency: a randomized controlled pilot study

Xenophon Kassianides¹, Andrew Gordon², Roger Sturme², Sunil Bhandari¹

¹Academic Renal Research Department, Hull University Teaching Hospitals NHS Trust and Hull York Medical School, Hull Royal Infirmary, Hull, UK
²Centre for Atherothrombosis and Metabolic Disease, Hull York Medical School, University of Hull, Hull, UK

Background: Concerns exist regarding the pro-oxidant and inflammatory potential of intravenous (IV) iron due to labile plasma iron (LPI) generation. This IRON-CKD trial compared the effects of different IV irons on oxidative stress and inflammation.

Methods: In this randomized open-label explorative single-center study in the United Kingdom, non-dialysis-dependent chronic kidney disease (CKD) patients with iron deficiency were randomized (1:1:1:1) to receive a single infusion of 200 mg iron dextran, or 200 mg iron sucrose (IS), or 200 mg or 1,000 mg ferric derisomaltose (FDI) and were followed up for 3 months. The primary outcomes measured were induction of oxidative stress and inflammation. Secondarily, efficacy, vascular function, quality of life, and safety were monitored.

Results: Forty patients were enrolled. No significant rise in oxidative stress existed, regardless of preparation or dose. There was a significant rise in LPI with 1,000 mg FDI at 2 hours that normalized within a week, not impacting oxidative stress or inflammation. A delayed rise in C-reactive protein was noted with IS. High-dose FDI produced a sustained serum ferritin increase (mean ± standard error of the mean of predose: 69.1 ± 18.4 μg/L, 3 months: 271.0 ± 83.3 μg/L; p = 0.007). Hemoglobin remained stable throughout. No adverse drug reactions were recorded during the study.

Conclusion: A single dose of IV iron in CKD patients does not trigger oxidative stress or inflammation biomarkers. Third-generation IV irons have a reassuring safety profile, and high-dose FDI produced a sustained serum ferritin rise and more efficient iron repletion, with no significant pro-oxidant or inflammatory signals when compared to a lower dose and other IV irons.

Keywords: Chronic kidney disease, Ferric derisomaltose, Intravenous iron, Iron deficiency, Oxidative stress
Iron deficiency anemia is a global condition co-existing with other medical comorbidities including chronic kidney disease (CKD), heart failure, inflammatory bowel disease, and malignancy [1,2]. It is associated with prognostic and financial implications and reduced quality of life [3,4].

Despite the broad availability of oral iron, issues remain with compliance and side effects [4]. Consequently, intravenous (IV) iron replacement has gained popularity and is incorporated in current clinical guidelines [5,6]. Several IV iron preparations are available including second-generation (e.g., iron sucrose [IS], low molecular weight iron dextran [ID]), and third-generation (e.g., ferric derisomaltose [FDI]) products.

Concerns exist regarding the risks of oxidative stress with parenteral iron administration [7–9]. Previous evidence suggests that the degree of oxidative stress caused by iron supplementation is relative to the labile plasma iron (LPI) released [10,11]. LPI can be involved in redox cycling and has a major role in the initiation and propagation of lipid peroxidation [12]. Works by Zager et al. [8,13,14] have indicated both a dose-related and a preparation-dependent association between iron and toxicity, especially with second-generation IV iron products (IVIPs). The amount of LPI released is related to the structural stability of the iron-carbohydrate complex; third-generation IV irons represent more tightly bound compounds than second-generation products [15]. This may explain why less stable IVIPs (e.g., IS) are linked to endothelial and renal dysfunction and inflammation [16–18].

This explorative study was designed to primarily assess the effect of different IV iron compounds and dosages on oxidative stress and inflammation in patients with non-dialysis-dependent CKD and absolute or functional iron deficiency.

Additionally, the effects of these IV iron treatments on hematinc profile and hemoglobin concentration, arterial stiffness, endothelial function, quality of life, and safety outcomes were investigated. We hypothesized that treatment with IV irons would primarily lead to variable effects on biomarkers of inflammation and oxidative stress and secondarily may result in differences in efficacy markers.

Methods

Study design and population

This was an open-label single-center prospective randomized explorative study. The study was carried out in accordance with Good Clinical Practice guidelines, the Declaration of Helsinki, and received ethical approval from NRES Committee Yorkshire & Humber in Leeds East, UK (No. 10/H1306/40).

Following acquisition of informed consent, the study enrolled patients with CKD stages 3 to 5 (estimated glomerular filtration rate of <60 mL/min/1.73 m²) with a serum ferritin (SF) level less than 200 μg/L and/or a transferrin saturation (TSAT) of <20%. Further information on the inclusion and exclusion criteria and methodology can be found in the published protocol (Supplementary Table 1, available online) [19].

Patients were recruited and randomly allocated in a 1:1:1:1 ratio to receive a single infusion of either 200 mg IS (Venofer, Vifor Pharma, Paris, France), 200 mg ID (Cosmofer, Pharmacosmos A/S, Holbaek, Denmark), or 200 mg or 1,000 mg FDI (Monofer, Pharmacosmos A/S) as per summary product characteristics and standard practice in our institution. They were followed up at 2 hours, 1 day, 1 week, and 1 and 3 months after infusion (Supplementary Table 2, available online).

Investigations

Oxidative stress, labile plasma iron, and inflammatory markers

Thiobarbituric acid reactive substances (TBARS) were measured as a by-product of lipid peroxidation and a surrogate marker of reactive oxygen species generation. The FerOS assay (Afferix, Tel Aviv, Israel) was used to measure LPI. This assay employs a selective chelator that blocks iron redox cycling leading to the identification of iron-mediated reactive oxygen species formation; this measures all forms of non-transferrin bound iron (NTBI), both redox active and not.

Interleukin (IL)-1β, IL-6, IL-8, and IL-10 were measured using enzyme-linked immunosorbent assays (ELISA) supplied by Thermo Fisher Scientific (Carlsbad, CA, USA). Beckman Coulter technology (Danaher Corp., Brea, CA, USA) was used for measurement of C-reactive protein (CRP) and albumin.
Hemoglobin and hematinics

Hemoglobin was analyzed with Sysmex XN technology (Sysmex UK, Milton Keynes, UK) as per local hospital pathology laboratory practice. SF and TSAT were measured spectrophotometrically using Beckman Coulter analyzers.

Vascular and endothelial function

The Enverdis Vascular Explorer (Enverdis GmbH Medical Solutions, Jena, Germany) was used to measure pulse wave velocity (PWV) and augmentation index as markers of arterial stiffness. The human CD62P ELISA kit (P-selectin; Abcam, Cambridge, UK) and the mouse E-selectin/CD62E Quantikine ELISA kit (R&D Systems, Minneapolis, MN, USA) were used to analyze P-selectin and E-selectin, respectively.

Quality of life

The Short Form (36) Health Survey (SF-36) was used. This is composed of 36 questions calculating patient-reported health status and has been established as a valid and reliable method for the assessment of quality of life in CKD-associated anemia [20].

Safety

Safety assessment took place throughout the study. Adverse events were recorded and analyzed regarding relationship to treatment with the investigational drug.

Statistical analysis

This was an explorative pilot study examining proof-of-concept; a power calculation was not required. The population used to assess safety included any randomized patient who received any amount of study drug. All analyses involved comparison of outcomes and changes in parameters during the study visits among all participants. Baseline population characteristics have been previously published [19,21] (Supplementary Table 3, 4; available online). The impact of iron treatment for each group individually and for a total combined group was examined for the outcome measures. Descriptive statistics and graphic correlations were employed for the analysis of hematinics, oxidative stress, and inflammatory markers. Numerical data were presented as the mean ± standard error of the mean. Statistical comparisons of continuous outcomes between the allocated treatment arms were performed using two-way ANOVA (R version 1.2.5019; R Foundation for Statistical Computing, Vienna, Austria). In addition, comparison of high-dose vs. low-dose iron was carried out for the primary and secondary outcome measures. A p-value of <0.05 was deemed statistically significant.

Results

Forty patients, with a mean age of 58.8 ± 2.2 years, were recruited and randomized from a total of 49 patients who attended screening. Twenty-three patients (57.5%) were male.

One participant commenced hemodialysis before the last visit, but follow-up was completed as per protocol; the patient was included in the analysis. One patient became pregnant within 1 month of receiving 1,000 mg FDI, while another individual randomized to the 1,000 mg FDI group required a second IV iron infusion during the study due to severe symptomatic anemia. The latter two participants were excluded from the 3-month analysis. The flow of participants is summarized in Fig. 1.

Oxidative stress and labile plasma iron

Administration of IV iron resulted in a rise in mean TBARS level within 2 hours (pre-infusion: 1,083.0 ± 117.1 nM, 2 hours post-infusion: 1,552.6 ± 156.0 nM; p = 0.060, all groups combined) (Fig. 2). The increased levels returned to baseline within 1 week. The greatest rise in TBARS was noted in the 1,000 mg FDI group, which was not statistically significant (pre-infusion: 846.0 ± 108.9 nM, 2 hours post-infusion: 1,865.0 ± 203.2 nM; p = 0.250). There was a non-statistically significant increase with IS that occurred 1 week post-infusion (pre-infusion: 906.3 ± 140.9 nM, 1 week post-infusion: 1,261.3 ± 369.3 nM; p = 0.990). There were no statistically significant differences for the effect on TBARS between products used or between the high-dose and low-dose FDI.

Mean LPI levels increased significantly within 2 hours of infusion and returned to baseline within 1 week (pre-infusion: 1.4 ± 0.5 ΔFU/min, 2 hours post-infusion: 7.4 ± 2.4 ΔFU/min; p = 0.006, all groups combined) (Fig. 3). LPI increased in the ID and IS groups, but these did not reach statistical significance. The concentration of LPI with 200 mg FDI remained constant and similar to the baseline level.
throughout the study. There was a significant increase in LPI with 1,000 mg FDI (pre-infusion: 0.33 ± 0.2 ΔFU/min, 2 hours post-infusion: 19.6 ± 7.1 ΔFU/min; p < 0.001), and the level at 2 hours post-infusion was significantly higher when compared to the 200 mg FDI group (19.6 ± 7.1 ΔFU/min vs. 1.6 ± 0.8 ΔFU/min; p < 0.001). These changes resolved within 1 week.

Inflammation

There was a rise in mean CRP level within a day of infusion, which returned to baseline levels within 1 month (pre-infusion: 7.5 ± 1.6 mg/L, 1 day post-infusion: 17.6 ± 8.0 mg/L; p = 0.400 / 1 month post-infusion: 7.5 ± 1.7 mg/L; p > 0.999, all groups combined). This rise was more evident in patients receiving IS (pre-infusion: 8.1 ± 3.3 mg/L, 1 day post-infusion: 36.1 ± 27.0 mg/L; p = 0.550). The changes in CRP did not

Figure 1. Consolidated Standards Of Reporting Trials (CONSORT) diagram. It indicates the flow of patients from point of identification to enrollment in the trial and also displays the patients who were included in the statistical analysis. FDI, ferric derisomaltose; ID, iron dextran; IS, iron sucrose.

Figure 2. Comparative effects on oxidative stress. Thiobarbituric acid reactive substances (TBARS) measurements are plotted as means with error bars representing standard error of the mean for all individual groups and for a total combined group. FDI, ferric derisomaltose; ID, iron dextran; IS, iron sucrose.

Figure 3. Comparative effects on labile plasma iron (LPI). LPI measurements are plotted as mean values for all groups individually and for a total combined group. Mean values are plotted and the error bars represent standard error of the mean. FDI, ferric derisomaltose; ID, iron dextran; IS, iron sucrose.
reach statistical significance for FDI at any dose (Fig. 4).

A transient fall in IL-10 within one month and a rise in IL-8 within 1 week of IV iron infusion were observed across the treatment groups; IL-6 was unaffected. IL-1β did not reach detectable levels during the study. A transient rise in IL-10 within 2 hours of infusion was noted with IS (Supplementary Fig. 1, 2; available online).

Serum albumin concentration remained unchanged throughout the study for all IVIPs (Supplementary Fig. 3, available online).

**Hemoglobin and hematinsics**

For all groups combined, hemoglobin concentration rose to its maximal level after one month and was sustained until the end of the study at 3 months (p > 0.999). The increase in hemoglobin concentration was not significantly different between the iron compounds, and no statistically significant difference was noted between high-dose and low-dose FDI (p > 0.999 throughout study) (Table 1).

TSAT increased within 2 hours post-infusion (up to 80%, all groups combined) and returned to baseline level by the first week (Fig. 5). This transient rise from baseline to 2 hours post-infusion was statistically significant in both the 1,000 mg FDI (17.8% to 98.7%; p < 0.001) and IS groups (21.1% to 91.4%; p < 0.001). High-dose FDI produced a significant change in TSAT at 2 hours and 1 day post-infusion when compared with low-dose FDI that persisted for 1 week (FDI of 1,000 mg vs. 200 mg; 2 hours post-infusion: 98.7% vs. 58.3%, p = 0.005; 1 day post-infusion: 100% vs. 51.8%, p < 0.001). There was no statistically significant difference between the different iron preparations at 2 hours post-infusion.

The mean SF level rose within 2 hours post-infusion to achieve its maximal mean concentration at 1 week (pre-infusion: 68.8 ± 8.0 μg/L, 1 week post-infusion: 216.2 ± 36.6 μg/L, 3 months post-infusion: 122.6 ± 23.1 μg/L; all groups

**Figure 4.** Comparative effects on CRP. CRP measurements plotted as means with error bars representing standard error of the mean for each individual group and for a total combined group. FDI, ferric derisomaltose; ID, iron dextran; IS, iron sucrose.

**Figure 5.** Comparative effects on transferrin saturation (TSAT). TSAT measurements are plotted as a mean percentage for each individual group and for a total combined group. Mean values are plotted with error bars representing standard error of the mean. FDI, ferric derisomaltose; ID, iron dextran; IS, iron sucrose.

**Table 1.** Analysis of hemoglobin concentration

<table>
<thead>
<tr>
<th>Concentration (g/L)</th>
<th>Baseline</th>
<th>2 Hr</th>
<th>1 Day</th>
<th>1 Wk</th>
<th>1 Mo</th>
<th>3 Mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iron sucrose, 200 mg</td>
<td>122.1 ± 4.6</td>
<td>125.6 ± 5.3</td>
<td>120.1 ± 4.6</td>
<td>125.4 ± 5.3</td>
<td>130.7 ± 5.9</td>
<td>129.0 ± 7.3</td>
</tr>
<tr>
<td>Iron dextran, 200 mg</td>
<td>129.6 ± 7.5</td>
<td>127.0 ± 7.5</td>
<td>124.9 ± 8.1</td>
<td>126.4 ± 7.4</td>
<td>127.8 ± 6.2</td>
<td>130.9 ± 7.4</td>
</tr>
<tr>
<td>Ferric derisomaltose, 1,000 mg</td>
<td>115.5 ± 4.5</td>
<td>117.8 ± 4.7</td>
<td>116.5 ± 4.5</td>
<td>114.8 ± 5.8</td>
<td>113.6 ± 5.5</td>
<td>120.0 ± 8.8</td>
</tr>
<tr>
<td>Ferric derisomaltose, 200 mg</td>
<td>123.0 ± 5.5</td>
<td>125.9 ± 5.8</td>
<td>122.3 ± 6.1</td>
<td>123.1 ± 6.2</td>
<td>126.0 ± 5.8</td>
<td>126.0 ± 6.1</td>
</tr>
<tr>
<td>Total</td>
<td>122.6 ± 2.8</td>
<td>123.7 ± 2.9</td>
<td>120.7 ± 2.9</td>
<td>122.7 ± 3.1</td>
<td>124.6 ± 3.0</td>
<td>127.2 ± 3.6</td>
</tr>
</tbody>
</table>

Data are presented as mean ± standard error of the mean.
The 1,000 mg FDI group produced the greatest and longest-lasting iron repletion (pre-infusion: 69.1 ± 18.4 μg/L, 1 week post-infusion: 505.9 ± 105.5 μg/L, 3 months post-infusion: 271.0 ± 83.3 μg/L), which remained significantly higher than baseline throughout the study (baseline to 1 week post-infusion, p < 0.001; baseline to 3 months post-infusion, p = 0.007). The 1,000 mg FDI dose achieved a statistically significantly greater change in SF when compared to the 200 mg FDI dose throughout the study (p < 0.001).

Vascular and endovascular function

There was a trend for a reduction in mean PWV throughout the study across all groups, which did not reach statistical significance (pre-infusion: 7.5 ± 0.4 m/sec, 3 months post-infusion: 6.7 ± 0.4 m/sec; p > 0.999). There was no significant difference between the compound used and improvement in PWV. No difference was noted between high-dose and low-dose FDI. A similar improvement tendency was observed for augmentation index (Supplementary Table 5, available online).

IV iron did not significantly affect E-selectin during the study, regardless of iron preparation or dose. A non-statistically significant decrease in mean P-selectin level was seen (pre-infusion: 75.0 ± 6.4 ng/mL; 2 hours post-infusion: 72.4 ± 6.5 ng/mL; 3 months post-infusion: 68.7 ± 6.9 ng/mL; p > 0.999, all groups combined); no significant differences in P-selectin were seen between the different IV iron groups or between different doses of FDI (Supplementary Table 5).

Quality of Life

There was a trend for improvement in all domains of the SF-36 following iron administration for all iron treatment groups combined and with each compound separately through the completion of the study. This was not statistically significant (Supplementary Table 6, available online).

Safety

One death occurred during the study due to myocardial infarction in a patient with significant cardiovascular comorbidities, 1 week following infusion of iron (1,000 mg FDI). The event was deemed unrelated to the study drug. There were no episodes of anaphylaxis or infusion reactions. No infection-related hospitalizations and no other cardiovascular events occurred.

Discussion

In this IRON-CKD study, we examined whether administration of IVIPs with different structural stability and risk of labile iron release would have differential impacts on biomarkers of oxidative stress and inflammation and on measures of efficacy, endothelial function, and safety in iron-deficient individuals with CKD. We also compared different doses of FDI, a commonly used third-generation IVIP with low risk of labile release, to identify any dosage-related differences.

Previously, it was assumed that a short-lived increase in oxidative stress was pathogenic. In this study, markers of oxidative stress returned to baseline within 1 week irrespective of iron preparation and dose. Here, despite a trend for increase in TBARS with high-dose FDI and IS, this did not reach statistical significance at any point. LPI rose in a dose-dependent manner, with a statistically significant rise noted with the high-dose FDI. Indeed, results from cellular studies with IVIP have commented on iron-induced increases in cellular stress that are possibly dose- and tissue-dependent; however, no duration of effect was evaluated [22]. The dose-dependent rise displayed here was short-lived and did not translate into systemic adverse effects nor a statistically significant increase in oxidative stress and inflammatory markers. The unchanged LPI from
baseline with 200 mg FDI potentially reflects the controlled iron delivery to iron-binding proteins with FDI. This results from the tight binding of iron in the carbohydrate matrix of FDI, which translates into a highly stable compound when compared to second-generation iron preparations such as IS [23]. Garbowski et al. [24] recently commented on two iron release modes; early (direct delivery of iron to transferrin in blood) and late (indirect release of iron from macrophages), with differences between IV irons dependent on their pharmacokinetic properties. They also concluded that FDI had a lower NTBI level compared to IS [24], similar to the findings in the current IRON-CKD study showing lower levels of NTBI with FDI vs. IS and ID at equivalent doses. The lack of impact on oxidative stress by FDI could explain the recent findings of the FERWON-NEPHRO trial where high-dose FDI (1,000 mg), when compared to IS (5 × 200 mg over 2 weeks), resulted in an improved incidence of cardiovascular events [25].

This can be inferred further through the transient rise in CRP with IS, a compound with weaker iron binding. The brief rise in IL-10 (an anti-inflammatory cytokine) caused by IS could represent part of a regulatory process in response to IL-12 (a pro-inflammatory cytokine) [26]. The lack of significant effect on inflammatory markers with third-generation IV iron, even at a high dose (FDI of 1,000 mg), may indicate that no LPI toxicity occurs with such compounds.

The rise in TSAT within hours in all groups demonstrates that current available iron preparations are efficacious, delivering iron rapidly and providing a source of circulating iron. SF achieved maximal rise after one week with 1,000 mg FDI, which provided the most significant and lasting elevation. This may reflect a greater iron repletion effect and highlights that a higher dose of IV iron is able to produce substantial and more effective iron repletion. It is important to underline that at maximal SF concentrations, achieved with high-dose FDI, there was no induced oxidative stress. These results reveal greater iron replenishment using high doses in a manner similar to the landmark PIVOTAL (Proactive IV Iron Therapy in Hemodialysis Patients) study [27]. The modest increase in hemoglobin is consistent with previous studies in non-anemic patients demonstrating little change [28].

IV iron did not aggravate arterial stiffness. This is consistent with other trials in patients receiving dialysis where no change in vascular reactivity was noted [29]. Here, treatment with IV iron resulted in a tendency for improvement in PWV and augmentation index.

Upregulation of selectins is associated with atherosclerosis and inflammation [30]. Evidence on the impact of iron on cell adhesion molecules such as E-selectin and P-selectin is scarce and conflicting [31,32]. In the current study, there were no significant changes in the expression of either E-selectin or P-selectin with any of the IVIPs or doses, suggesting that IV iron does not affect selectin-driven pathways.

This study has several limitations. It was open-label, which increases the risk of observer and participant bias. The study focused on non-smokers and may therefore not be representative of potential interactions of smoking (a powerful pro-oxidant factor) with IV iron treatment; however, it does not exclude any external effect of smoking. Moreover, the small number of participants in each of the four groups did not allow for stratification according to age and comorbidities, renal function, and medications, which are potentially important factors affecting oxidative stress. Additionally, as a pilot study it was not statistically powered for definitive conclusions; however, it can be used for hypothesis generation and for trend observation.

IRON-CKD provided a direct comparative assessment of the relative acute treatment effects of commonly used IV irons. The results indicate that, in the short term and following a single IV iron infusion, endothelial function and oxidative status are not affected. All studied preparations led to a rise in both stored and circulating iron, with more effective repletion with a higher dose. This translated into a small improvement in quality of life, in line with previous large cohort trials [4] underlining the impact of iron in non-anemic patients as witnessed in inflammatory bowel disease [33]. There were no infection-related hospital admissions with any of the preparations administered or with either low- or high-dose IV iron, which supports the good safety profile of high-dose iron and complements the findings in the PIVOTAL study where infection rates were identical irrespective of high- or low-dose IV iron treatment [34].

Additionally, this IRON-CKD study assessed the dose-dependent effects of FDI, complementing evidence on its efficacy from studies in CKD patients comparing FDI with oral iron and second-generation IVIP [35,36]. As third-generation IV iron compounds share different
pharmacodynamic properties from their predecessors [23], previous results on dose-associated toxicity cannot be necessarily extrapolated as indicated by this study.

Nuhu et al. [37] recently examined the mechanistic links between iron and CKD and concluded that the overall oxidation status in CKD is antioxidant. An interplay exists between iron homeostasis and oxidative stress in CKD that in turn impacts the effects of IV iron treatment [38]. It is believed that in CKD the system is primed with activation of both pro- and antioxidant pathways; iron deficiency may aggravate oxidative stress. It is, therefore, speculated that the resolution of iron deficiency with IV iron (despite a short transient increase in oxidative stress) provides an overall net antioxidant benefit due to mobilization of relevant enzymes [39].

The impact of multiple iron infusions and the long-term safety profile of IV iron require further research. Additional exploration of the impact of third-generation IVIP at comparative doses is needed, given their pharmacochemical differences and the potential impact on bone metabolism due to hypophosphatemia as reported with ferric carboxymaltose [40]. Such mechanistic evidence should be considered when incorporating IV iron therapy into other areas of medicine.

Although the patient sample size is too small to make any firm conclusions, this study provides evidence that currently available IV iron therapies are efficacious with a good safety profile. Additionally, this study revealed that high-dose FDI displays a trend of a greater treatment effect, resulting in higher SF and TSAT compared to a lower dose of FDI and to other IV iron preparations. This does not negatively affect oxidative stress, endothelial function, or inflammation. The successful IV iron repletion translates to improved quality of life and may positively affect arterial stiffness. Further larger studies are required to confirm the potential oxidative effects of IV iron and the impact of multiple doses in this patient group.

**Conflicts of interest**

The results presented in this paper have not been published previously in whole or part, except in abstract format following the ERA/EDTA-2020 Virtual Conference. Sunil Bhandari has received honorarium, consultancy fees, membership advisory board, and travel funding from Pharmacosmos A/S, Vifor Pharma, and Astellas. The rest of the authors have no conflicts of interest.

**Funding**

The IRON-CKD study received an unrestricted grant from Pharmacosmos A/S. The funder had no role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript.

**Acknowledgments**

The authors would like to thank Tracy Cathcart, Vikki Jubb, Ahmed Ziedan, and the Research and Development Team (Leanne Cox and Sarah Moffat) at the Hull University Teaching Hospitals NHS Trust for their support.

**Authors’ contributions**

Conceptualization: SB, RS
Data curation: XK
Formal analysis: XK
Funding acquisition: SB
Investigation: SB
Methodology: SB, AG, RS
Project administration: SB, AG
Visualisation: XK
Writing—original draft: XK
Writing—review & editing: XK, SB, AG, RS
All authors read and approved the final manuscript.

**Data statement**

Individual participant data that underlie the results reported in this article, after de-identification (text, tables, figures, and appendices), alongside protocols are available on request for 3 years following online publication to researchers with a methodologically sound proposal for the potential inclusion in meta-analysis. Requests should be directed to xenophon.kassianides@hey.nhs.uk.

**ORCID**

Xenophon Kassianides, https://orcid.org/0000-0002-1452-7757
Andrew Gordon, https://orcid.org/0000-0003-2770-6129
References


24. Garbowsk MW, Bansal SS, Porter JB, Burchhardt S, Hider R. NTBI is transiently generated from two compartments during a single dose of intravenous iron - a randomized controlled...


Clinical outcomes among hemodialysis patients with atrial fibrillation: a Korean nationwide population-based study

Yunmi Kang1, Hyung Yun Choi2, Young Eun Kwon3, Ji Hyeon Shin4, Eun Mi Won4, Ki Hwa Yang4, Hyung Jung Oh5,6, Dong-Ryeol Ryu6,7

1Department of Internal Medicine, Ewha Womans University Mokdong Hospital, Seoul, Republic of Korea
2The Korean Society of Nephrology, Seoul, Republic of Korea
3Department of Internal Medicine, Myongji Hospital, Hanyang University College of Medicine, Goyang, Republic of Korea
4Health Insurance Review and Assessment Service, Wonju, Republic of Korea
5Ewha Institute of Convergence Medicine, Ewha Womans University Mokdong Hospital, Seoul, Republic of Korea
6Research Institute for Human Health Information, Ewha Womans University Mokdong Hospital, Seoul, Republic of Korea
7Department of Internal Medicine, Ewha Womans University School of Medicine, Seoul, Republic of Korea

Background: The number of patients requiring dialysis is increasing worldwide, and the atrial fibrillation and atrial flutter (AF) prevalence among hemodialysis (HD) patients is higher than in the general population. There have been no studies of Korean AF patients undergoing HD that investigated how AF affects outcomes, such as all-cause mortality, hospitalization, and stroke events. We conducted a large-scale retrospective cohort study with data from the National Health Insurance System to determine how AF affects these outcomes.

Methods: In 2013, the Health Insurance Review and Assessment service, a Korean national health insurance scheme, collected data from 21,839 HD patients to evaluate the adequacy of dialysis centers. All-cause mortality, hospitalization, and stroke events were compared between patients with and without AF. Sub-analyses compared these outcomes between AF patients receiving warfarin and those not receiving warfarin.

Results: Cox regression analysis found that AF was a significant risk factor for death from any cause (hazard ratio [HR], 1.356; 95% confidence interval [CI], 1.222–1.506; p < 0.001), hospitalization (HR, 1.323; 95% CI, 1.225–1.430; p < 0.001), and hemorrhagic stroke (HR, 1.500; 95% CI, 1.050–2.141; p = 0.026). AF was not significantly associated with an increased risk of ischemic stroke. The use of warfarin was significantly associated with hemorrhagic stroke incidence (HR, 1.593; 95% CI, 1.075–2.360; p = 0.020), while there was no significant correlation between warfarin treatment and all-cause mortality, hospitalization, and ischemic stroke.

Conclusion: This cohort study of Korean dialysis patients showed that AF was a risk factor for multiple outcomes among HD patients.

Keywords: Atrial fibrillation, Hemodialysis, Hemorrhagic stroke, Hospitalization, Ischemic stroke, Mortality, Warfarin

Received: February 3, 2020; Revised: July 30, 2020; Accepted: September 10, 2020

Editor: Eun Hui Bae, Chonnam National University, Gwangju, Republic of Korea
Correspondence:
Hyung Jung Oh
Ewha Institute of Convergence Medicine, Ewha Womans University Mokdong Hospital, 1071 Anyangcheon-ro, Yangcheon-gu, Seoul 07985, Republic of Korea.
E-mail: ohjmd@naver.com
ORCID: https://orcid.org/0000-0002-4281-696X
Dong-Ryeol Ryu
Department of Internal Medicine, Ewha Womans University School of Medicine, 260 Gonghang-daero, Gangseo-gu, Seoul 07804, Republic of Korea.
E-mail: drryu@ewha.ac.kr

Copyright © 2021 by The Korean Society of Nephrology

This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial and No Derivatives License (http://creativecommons.org/licenses/by-nc-nd/4.0/) which permits unrestricted non-commercial use, distribution of the material without any modifications, and reproduction in any medium, provided the original works properly cited.
Introduction

Atrial fibrillation and atrial flutter (AF) is the most common arrhythmia in the general population, and its prevalence among end-stage renal disease (ESRD) patients undergoing hemodialysis (HD) is higher (ranges from 3.8% to 27%) \[1\] than that in general population (ranges from 2.5% to 3.5%) \[2,3\]. Moreover, the incidence of AF increases with age and dialysis duration among chronic HD patients \[4\]. AF commonly arises secondarily to comorbid conditions, such as coronary artery disease, pericarditis, mitral valve disease, cardiomyopathy, and HD itself, causes fluid swings that lead to heart failure and left atrial dilatation \[5,6\]. Thus, the occurrence of AF among chronic HD patients may carry a poor prognosis \[7\]. To the best of our knowledge, there have been no studies investigating the impact of AF on adverse clinical outcomes among Korean chronic HD patients.

Since AF is well known as a major cause of ischemic stroke in the general population, most physicians consider prescribing anticoagulants for patients at high risk of ischemic stroke. Likewise, among AF patients in the general population, anticoagulant therapy, usually with warfarin, has been used to prevent ischemic stroke among chronic HD patients. However, warfarin should be administered with caution because it can increase bleeding. Additionally, chronic HD patients require special care when taking warfarin because they are more likely to be at risk of bleeding. Thus, routine warfarin administration for chronic HD patients is not considered standard treatment. Moreover, AF in chronic HD patients likely does not increase the risk of stroke compared with AF in the general population. Therefore, Kidney Disease Improving Global Outcomes (KDIGO) guidelines do not advise AF patients to take anticoagulation agents routinely to prevent ischemic stroke when they are undergoing chronic HD \[8\]. In contrast, the American Heart Association/American College of Cardiology/Heart Rhythm Society (AHA/ACC/HRS) recommends warfarin administration for the HD population, similar to that for the general population \[9\].

This study aimed to investigate the impact of AF on adverse clinical outcomes (all-cause mortality, hospitalization, and ischemic or hemorrhagic stroke) among a large population of maintenance HD patients in Korea. Moreover, we examined the effects of warfarin use on clinical outcomes among AF patients undergoing chronic HD.

Methods

Study population and data collection

The National Health Insurance System (NHIS) in Korea is a single-payer system to which 98% of citizens belong. Under this system, medical providers request reimbursements from the NHIS. This nationwide cohort study relies on data from the Korean Health Insurance Review and Assessment (HIRA). We used the claim data between January 2013 and December 2017. Among members of the general population who used medical services during the period, we chose patients who were undergoing chronic HD. Chronic HD patients were identified by the International Classification of Disease, 10th revision (ICD-10) diagnoses and hospital billing records (O7020, O9991) for at least 90 days. Adults over 18 years who had been receiving conventional maintenance HD for at least 3 months were eligible for this study.

There is a regular national assessment for dialysis adequacy in Korean medical institutions where HD has been performed, and we enrolled a total number of 21,839 patients who were assessed for dialysis adequacy in 2013. Fig. 1 shows the process of subject selection. Between October and December 2013, a total of 53,607 patients under HD were charged with HD claims (O7020, O9991). During the same period, 50,397 patients with chronic HD including inpatient and outpatient were sorted. After removing patients who met the exclusion criteria, 21,839 patients were classified as subjects for the adequacy assessment.

There were a total of 735 institutions requesting adequacy assessment; 10 were excluded and 725 were evaluated. The criteria for selecting an institution to be evaluated were institutions that possess HD machines as of October 1, 2013 and those that produced HD billing codes (O7020, O9991). Conditions for exclusions included institutions that did not have an outpatient undergoing HD or was closed at the time of December 2013. Therefore, from October to December 2013, among the 735 dialysis centers that had HD machines and claimed medical codes related to HD, 725 centers (98.6%) were assessed.

We chose the following data because the follow-up duration of patients of the 2013 adequacy assessment was longer than that of the 2015 adequacy assessment. Baseline data, including demographics, comorbid diseases, and laboratory
data, were collected at the time of patient enrollment. In the case of comorbid diseases, ICD-10 code of principal and secondary diagnosis from January 1, 2013 to December 31, 2013 was extracted as the comorbid disease if there was a hospitalization or outpatient medical history. Comorbidities shown in Table 1 and Supplementary Table 1 (available online) included 17 conditions of Charlson comorbidity index (CCI) and a few more conditions (Supplementary Table 2, 3; available online). We calculated the CCI scores according to CCI standards (Supplementary Table 2).

The current study was performed in accordance with the Declaration of Helsinki 2013 and approved by the Institutional Review Board (IRB) of Ewha Womans University, Mokdong Hospital (No. EUMC 2018-12-25). As the study subjects were deidentified, the IRB waived the need for written consent from the patients.

**Definitions**

AF patients were identified as patients diagnosed with I48 according to ICD-10 code as a principle or as secondary disease among 10 coexisting diseases between January and December 2013. We also included subjects as AF patients who answered “yes” to the questionnaire for dialysis assessment asking if he/she used medication or kept a pacemaker because of AF.

All-cause mortality was regarded as death if a person was extracted from enrollment in the HIRA, and ‘hospitalization’ was considered when a patient had been hospitalized at least once during the follow-up period from January 1, 2014 to December 31, 2017. All-cause hospitalization was identified.

An ischemic stroke event was recognized when a subject was hospitalized with I63-, I65-, or I66- as a principal disease during the period from January 1, 2014 to December 31, 2017 or when diagnosed with these codes as coexisting disease during that period if there was no such illness in 2013. Up to 10 coexisting diseases were searched. Likewise, a hemorrhagic stroke event was identified when a patient had been hospitalized with I60.-, I61.- or I62.- during the same follow-up period or when diagnosed with a coexisting disease during that period, if there was no such disease in 2013.

Warfarin users were defined as those who had >90 days of cumulative prescriptions for warfarin in 2013. The drug ingredient codes were 249105ATB and 249103ATB. Additionally, comorbid diseases were identified from the list of ICD-10 codes if there was a hospitalization or outpatient history of the disease during the period of 2013.

**Outcomes**

Primary outcomes were determined as all-cause mortality, hospitalization, and stroke events that occurred from January 1, 2014 to December 31, 2017.

**Statistical analysis**

We first stratified the total enrolled HD patients into two groups based on the existence of AF (AF vs. non-AF) to investigate the impact of AF on clinical outcomes. Next, we classified AF patients into two groups based on the use of
Table 1. Baseline patient characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>All (n = 21,839)</th>
<th>Non-AF (n = 21,115)</th>
<th>AF (n = 724)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>59.3 ± 13.0</td>
<td>59.1 ± 13.0</td>
<td>64.0 ± 11.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male sex</td>
<td>12,766 (58.5)</td>
<td>12,304 (58.3)</td>
<td>462 (63.8)</td>
<td>0.003</td>
</tr>
<tr>
<td>Dialysis vintage (yr)</td>
<td>5.6 ± 5.1</td>
<td>5.6 ± 5.0</td>
<td>6.8 ± 6.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>22.2 ± 3.3</td>
<td>22.2 ± 3.3</td>
<td>22.1 ± 3.2</td>
<td>0.582</td>
</tr>
<tr>
<td>SBP, pre-HD (mmHg)</td>
<td>141.2 ± 15.9</td>
<td>141.3 ± 15.9</td>
<td>138.1 ± 15.4</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>DBP, pre-HD (mmHg)</td>
<td>78.8 ± 9.4</td>
<td>78.8 ± 9.4</td>
<td>76.9 ± 9.4</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Causes of ESRD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DM</td>
<td>8,831 (40.4)</td>
<td>8,579 (40.6)</td>
<td>252 (34.8)</td>
<td></td>
</tr>
<tr>
<td>HTN</td>
<td>5,906 (27.0)</td>
<td>5,656 (26.8)</td>
<td>250 (34.5)</td>
<td></td>
</tr>
<tr>
<td>CGN</td>
<td>2,603 (11.9)</td>
<td>2,535 (12.0)</td>
<td>68 (9.4)</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>1,859 (8.5)</td>
<td>1,799 (8.5)</td>
<td>60 (8.3)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>2,640 (12.1)</td>
<td>2,546 (12.1)</td>
<td>94 (13.0)</td>
<td></td>
</tr>
<tr>
<td>Laboratory data</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>10.6 ± 0.9</td>
<td>10.6 ± 0.9</td>
<td>10.7 ± 0.9</td>
<td>0.128</td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>4.0 ± 0.3</td>
<td>4.0 ± 0.3</td>
<td>3.9 ± 0.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>9.7 ± 2.8</td>
<td>9.7 ± 2.7</td>
<td>9.2 ± 2.6</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Total calcium (mg/dL)</td>
<td>9.0 ± 0.9</td>
<td>9.0 ± 0.9</td>
<td>9.0 ± 0.8</td>
<td>0.220</td>
</tr>
<tr>
<td>Phosphorus (mg/dL)</td>
<td>5.1 ± 1.4</td>
<td>5.1 ± 1.4</td>
<td>4.9 ± 1.3</td>
<td>0.001</td>
</tr>
<tr>
<td>Urea reduction ratio (%)</td>
<td>70.7 ± 6.0</td>
<td>70.8 ± 6.0</td>
<td>70.5 ± 5.7</td>
<td>0.200</td>
</tr>
<tr>
<td>Comorbidity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute MI</td>
<td>410 (1.9)</td>
<td>377 (1.8)</td>
<td>33 (4.6)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>CHF</td>
<td>995 (4.6)</td>
<td>886 (4.2)</td>
<td>109 (15.1)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>PVD</td>
<td>983 (4.5)</td>
<td>942 (4.5)</td>
<td>41 (5.7)</td>
<td>0.125</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>1,485 (6.8)</td>
<td>1,400 (6.6)</td>
<td>85 (11.7)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Dementia</td>
<td>649 (3.0)</td>
<td>627 (3.0)</td>
<td>22 (3.0)</td>
<td>0.914</td>
</tr>
<tr>
<td>Chronic pulmonary disease</td>
<td>1,414 (6.5)</td>
<td>1,354 (6.4)</td>
<td>60 (8.3)</td>
<td>0.044</td>
</tr>
<tr>
<td>Connective tissue disease</td>
<td>498 (2.3)</td>
<td>481 (2.3)</td>
<td>17 (2.4)</td>
<td>0.901</td>
</tr>
<tr>
<td>Peptic ulcer</td>
<td>2,425 (11.1)</td>
<td>2,321 (11.0)</td>
<td>104 (14.4)</td>
<td>0.005</td>
</tr>
<tr>
<td>Mild liver disease</td>
<td>1,169 (5.4)</td>
<td>1,134 (5.4)</td>
<td>35 (4.8)</td>
<td>0.528</td>
</tr>
<tr>
<td>Severe liver disease</td>
<td>362 (1.7)</td>
<td>342 (1.6)</td>
<td>20 (2.8)</td>
<td>0.018</td>
</tr>
<tr>
<td>DM without complication</td>
<td>5,232 (24.0)</td>
<td>5,042 (23.9)</td>
<td>190 (26.2)</td>
<td>0.143</td>
</tr>
<tr>
<td>DM with complication</td>
<td>7,690 (35.2)</td>
<td>7,442 (35.3)</td>
<td>248 (34.3)</td>
<td>0.583</td>
</tr>
<tr>
<td>Hemiparesis</td>
<td>163 (0.7)</td>
<td>155 (0.7)</td>
<td>8 (1.1)</td>
<td>0.254</td>
</tr>
<tr>
<td>Chronic renal disease</td>
<td>21,835 (100)</td>
<td>21,115 (100)</td>
<td>724 (100)</td>
<td>0.711</td>
</tr>
<tr>
<td>Cancer without metastasis</td>
<td>1,253 (5.7)</td>
<td>1,206 (5.7)</td>
<td>47 (6.5)</td>
<td>0.375</td>
</tr>
<tr>
<td>Cancer with metastasis</td>
<td>48 (0.2)</td>
<td>46 (0.2)</td>
<td>2 (0.3)</td>
<td>0.674</td>
</tr>
<tr>
<td>AIDS</td>
<td>1 (0.0)</td>
<td>1 (0.0)</td>
<td>0 (0)</td>
<td>0.999</td>
</tr>
<tr>
<td>HTN</td>
<td>11,594 (53.1)</td>
<td>11,142 (52.8)</td>
<td>452 (62.4)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>DM</td>
<td>9,649 (44.2)</td>
<td>9,329 (44.2)</td>
<td>320 (44.2)</td>
<td>0.993</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>3,163 (14.5)</td>
<td>2,922 (13.8)</td>
<td>241 (33.3)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Stroke</td>
<td>1,258 (5.8)</td>
<td>1,186 (5.6)</td>
<td>73 (10.1)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Cancer</td>
<td>1,257 (5.8)</td>
<td>1,210 (5.7)</td>
<td>47 (6.5)</td>
<td>0.387</td>
</tr>
<tr>
<td>AF</td>
<td>724 (3.3)</td>
<td>NA</td>
<td>NA</td>
<td></td>
</tr>
</tbody>
</table>

Data are expressed as mean ± standard deviation or number (%).
AF, atrial fibrillation and atrial flutter; AIDS, acquired immunodeficiency syndrome; CGN, chronic glomerulonephritis; CHF, congestive heart failure; DBP, diastolic blood pressure; DM, diabetes mellitus; ESRD, end-stage renal disease; HD, hemodialysis; HTN, hypertension; MI, myocardial infarction; NA, not available; PVD, peripheral vascular disease; SBP, systolic blood pressure.
warfarin (warfarin user vs. warfarin non-user) to examine the effect of warfarin use on clinical outcomes among AF patients undergoing HD.

To compare baseline characteristics, chi-square tests for categorical variables and unpaired t-tests for continuous variables were performed. Continuous variables were expressed as means and standard deviations, and categorical variables were described using frequencies and percentages. Cox proportional hazard modeling was used to explore the association between AF and the incidence of outcomes; all-cause mortality, hospitalization, and stroke events (ischemic or hemorrhagic). Moreover, as the CCI includes common comorbidities, we used it to adjust for potentially confounding variables. Additionally, Cox proportional hazard models were conducted to reveal the impact of warfarin on the occurrence of adverse clinical outcomes.

The cumulative event-free survival rates were estimated by Kaplan-Meier analysis and log-rank test. This was used to compare chronic HD patients with AF and without AF with respect to event rates of new ischemic stroke, hemorrhagic stroke, hospitalization, or all-cause mortality. Survival time was defined as the interval between time at the beginning of cohort and the onset of the endpoint of follow-up, whichever came first. Repeated events were not considered.

All statistical tests were evaluated using a two-tailed 95% confidence interval (CI) with hazard ratios (HRs). Age, sex, body mass index (BMI), systolic blood pressure (SBP), diastolic blood pressure (DBP), and CCI were used for the adjusted variables. All analyses were performed using SAS, version 9.4 (SAS Institute, Cary, NC, USA), and p < 0.05 was considered statistically significant.

### Results

**Baseline characteristics**

Table 1 shows the baseline characteristics among enrolled patients. In the total patient group (n = 21,839), the mean age was 59.3 ± 13.0 years; 12,766 patients (58.5%) were men; the mean dialysis vintage was 5.6 ± 5.1 years; the mean BMI was 22.2 ± 3.3 kg/m²; and the mean SBP and DBP were 141.2 ± 15.9 and 78.8 ± 15.9 mmHg, respectively. Among the total patients, 724 patients (3.3%) were identified with AF (Table 1).

The patients with AF were significantly older, more likely to be male, had been undergoing HD for longer, and had higher mean SBP and DBP than those without AF. There were also significantly more several comorbid diseases, such as acute myocardial infarction, congestive heart failure, cerebrovascular disease, chronic pulmonary disease, peptic ulcer, and hypertension, in the AF group compared with the non-AF group, while there was no significant difference in urea reduction ratio or the prevalence of diabetes mellitus (DM) between groups (Table 1).

### Effects of atrial fibrillation on hemodialysis patients: all-cause mortality, hospitalization, and stroke events

Multivariate Cox proportional regression analysis model 1 showed that AF was a significant risk factor for all-cause mortality (HR, 1.356; 95% CI, 1.222–1.506; p < 0.001), hospitalization (HR, 1.323; 95% CI, 1.225–1.430, p < 0.001), and hemorrhagic stroke (HR, 1.500; 95% CI, 1.050–2.141; p = 0.026), after adjusting for age, sex, BMI, SBP, DBP, and CCI. However, AF was not significantly associated with an increased risk of ischemic stroke (HR, 1.240; 95% CI, 0.961–1.601; p = 0.984) (Table 2). Multivariate Cox proportional regression analysis model 2, which was selectively adjusted with dialysis vintage, albumin, acute myocardial infarction, congestive heart failure, cerebrovascular disease, and hypertension, also showed that AF was a significant risk factor for all-cause mortality (HR, 1.294; 95% CI, 1.152–1.452, p < 0.001), hospitalization (HR, 1.276; 95% CI, 1.171–1.390, p < 0.001), and hemorrhagic stroke (HR, 1.766; 95% CI, 1.211–2.576; p = 0.003). In model 2, similar to model 1, AF was not significantly associated with an increased risk of ischemic stroke (HR, 1.182; 95% CI, 0.888–1.574; p = 0.251) (Table 3). The findings of univariate Cox proportional regression analyses are presented in Supplementary Table 4 (available online).

The mortality, hospitalization, cerebral infarction, and cerebral hemorrhage by absence vs. presence of AF were estimated through Kaplan-Meier curve analysis. The rates for all four outcomes were higher in the AF group; the differences were statistically significant, with a p-value less than 0.05 (Supplementary Fig. 1, available online).

### Effects of warfarin treatment on atrial fibrillation patients undergoing hemodialysis

We next explored the impact of warfarin use on clinical
Table 2. Multivariate Cox analysis model 1 for all-cause mortality, hospitalization, and stroke events

<table>
<thead>
<tr>
<th>Variable</th>
<th>All-cause mortality</th>
<th>Hospitalization</th>
<th>Ischemic stroke</th>
<th>Hemorrhagic stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>p-value</td>
<td>HR (95% CI)</td>
<td>p-value</td>
</tr>
<tr>
<td>Age</td>
<td>1.053 (1.051–1.056)</td>
<td>&lt;0.0001</td>
<td>1.013 (1.012–1.014)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Male, vs. female</td>
<td>1.186 (1.133–1.246)</td>
<td>&lt;0.0001</td>
<td>0.956 (0.928–0.985)</td>
<td>0.003</td>
</tr>
<tr>
<td>BMI</td>
<td>0.971 (0.963–0.978)</td>
<td>&lt;0.0001</td>
<td>1.000 (0.998–1.001)</td>
<td>0.438</td>
</tr>
<tr>
<td>SBP, pre-HD</td>
<td>1.005 (1.003–1.007)</td>
<td>&lt;0.0001</td>
<td>1.004 (1.002–1.005)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>DBP, pre-HD</td>
<td>1.000 (0.998–1.003)</td>
<td>0.734</td>
<td>0.997 (0.995–0.999)</td>
<td>0.005</td>
</tr>
<tr>
<td>CCI</td>
<td>1.127 (1.113–1.141)</td>
<td>&lt;0.0001</td>
<td>1.112 (1.102–1.122)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>AF, vs. non-AF</td>
<td>1.356 (1.222–1.506)</td>
<td>&lt;0.0001</td>
<td>1.323 (1.225–1.430)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Multivariate Cox analysis was conducted after being adjusted for age, sex, BMI, SBP, DBP, and CCI.

AF, atrial fibrillation and atrial flutter; BMI, body mass index; CCI, Charlson comorbidity index; CI, confidence interval; DBP, diastolic blood pressure; HD, hemodialysis; HR, hazard ratio; SBP, systolic blood pressure.

Table 3. Multivariate Cox analysis model 2 for all-cause mortality, hospitalization, and stroke events

<table>
<thead>
<tr>
<th>Variable</th>
<th>All-cause mortality</th>
<th>Hospitalization</th>
<th>Ischemic stroke</th>
<th>Hemorrhagic stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>p-value</td>
<td>HR (95% CI)</td>
<td>p-value</td>
</tr>
<tr>
<td>Age</td>
<td>1.050 (1.047–1.052)</td>
<td>&lt;0.001</td>
<td>1.013 (1.011–1.014)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Male, vs. female</td>
<td>1.234 (1.173–1.299)</td>
<td>&lt;0.0001</td>
<td>0.987 (0.956–1.019)</td>
<td>0.410</td>
</tr>
<tr>
<td>BMI</td>
<td>0.979 (0.971–0.987)</td>
<td>&lt;0.0001</td>
<td>1.000 (0.999–1.001)</td>
<td>0.459</td>
</tr>
<tr>
<td>Dialysis vintage</td>
<td>1.006 (1.000–1.011)</td>
<td>0.035</td>
<td>0.996 (0.993–0.999)</td>
<td>0.004</td>
</tr>
<tr>
<td>Albumin</td>
<td>0.581 (0.538–0.627)</td>
<td>&lt;0.0001</td>
<td>0.737 (0.702–0.774)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>AcuteMI</td>
<td>1.481 (1.286–1.707)</td>
<td>&lt;0.0001</td>
<td>1.259 (1.127–1.406)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>CHF</td>
<td>1.218 (1.096–1.354)</td>
<td>&lt;0.0001</td>
<td>1.169 (1.087–1.257)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Cerebrovasculardisease</td>
<td>1.340 (1.231–1.460)</td>
<td>&lt;0.0001</td>
<td>1.247 (1.169–1.329)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>HTN</td>
<td>0.967 (0.920–1.018)</td>
<td>0.202</td>
<td>1.050 (1.017–1.084)</td>
<td>0.003</td>
</tr>
<tr>
<td>AF, vs. non-AF</td>
<td>1.294 (1.152–1.452)</td>
<td>&lt;0.0001</td>
<td>1.276 (1.171–1.452)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Multivariate Cox analysis was conducted after being adjusted for age, sex, BMI, dialysis vintage, albumin, acute MI, CHF, cerebrovascular disease, and HTN.

AF, atrial fibrillation and atrial flutter; BMI, body mass index; CHF, congestive heart failure; CI, confidence interval; HR, hazard ratio; HTN, hypertension; MI, myocardial infarction; NA, not available.
outcomes (all-cause mortality, hospitalization, and ischemic or hemorrhagic stroke) among AF patients undergoing HD, and we investigated their baseline characteristics (Supplementary Table 1). Among the 724 AF patients, there were 177 warfarin users (24.4%). Comparisons between the two groups (warfarin users vs. warfarin non-users) showed that mean SBP (133.7 ± 14.6 mmHg vs. 139.4 ± 15.4 mmHg) and DBP (75.6 ± 10.2 mmHg vs. 77.4 ± 9.1 mmHg) were significantly lower among warfarin users than among non-users. Moreover, serum albumin and creatinine levels were also significantly lower among warfarin users compared with non-users. However, there were significantly more cases of congestive heart failure, cerebrovascular disease, DM, and stroke among warfarin users than among non-users (Supplementary Table 1).

We next performed multivariate Cox proportional regression analysis to investigate the impact of warfarin treatment. Use of warfarin was significantly associated with increased hemorrhagic stroke incidence (HR, 1.593; 95% CI, 1.075–2.360; p = 0.020) relative to non-use, while there was no significant association between warfarin treatment and all-cause mortality, hospitalization, and ischemic stroke (Table 4).

We next performed Kaplan-Meier curve analysis for both warfarin user and non-user groups within the AF group for death, hospitalization, cerebral infarction, and cerebral hemorrhage. No statistically significant differences were observed in the four curves (Supplementary Fig. 2, available online).

### Discussion

The prevalence of AF in Korea increased by 2.10-fold from 0.73% in 2006 to 1.53% in 2015. The annual trends of AF incidence were stable, with a 10-year overall incidence of 1.77 per 1,000 person-years [10]. Unfortunately, there has been no data on the prevalence and incidence of AF in Korean ESRD patients. However, we identified the prevalence in Korea as 3.3% in this study. This rate is lower than we expected. As shown in an international study called the Dialysis Outcomes and Practice Patterns Study in which 12 countries participated, among the cross-section of HD patients, 12.5% of patients (2,188 out of 17,513) had pre-existing AF at baseline, compared with 5.6% in Japan and 24.7% in Belgium. The incidence of newly diagnosed AF

### Table 4. Multivariate Cox analysis for effect of warfarin treatment in HD patients with atrial fibrillation

<table>
<thead>
<tr>
<th>Variable</th>
<th>All-cause mortality</th>
<th>Hospitalization</th>
<th>Ischemic stroke</th>
<th>Hemorrhagic stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>p-value</td>
<td>HR (95% CI)</td>
<td>p-value</td>
</tr>
<tr>
<td>Age</td>
<td>1.038 (1.031–1.045)</td>
<td>0.001</td>
<td>1.04 (1.031–1.045)</td>
<td>0.001</td>
</tr>
<tr>
<td>Male, vs. female</td>
<td>1.05 (0.999–1.013)</td>
<td>0.173</td>
<td>1.03 (0.999–1.013)</td>
<td>0.173</td>
</tr>
<tr>
<td>BMI</td>
<td>0.958 (0.922–0.998)</td>
<td>0.021</td>
<td>0.998 (0.974–1.021)</td>
<td>0.087</td>
</tr>
<tr>
<td>SBP, pre-HD</td>
<td>1.010 (1.000–1.021)</td>
<td>0.001</td>
<td>1.007 (1.000–1.012)</td>
<td>0.001</td>
</tr>
<tr>
<td>DBP, pre-HD</td>
<td>0.999 (0.993–1.006)</td>
<td>0.839</td>
<td>0.999 (0.992–1.004)</td>
<td>0.839</td>
</tr>
<tr>
<td>CCI</td>
<td>1.051 (1.042–1.061)</td>
<td>0.246</td>
<td>1.051 (1.042–1.061)</td>
<td>0.246</td>
</tr>
<tr>
<td>Warfarin user, vs. non-user</td>
<td>1.053 (1.038–1.069)</td>
<td>0.373</td>
<td>1.053 (1.038–1.069)</td>
<td>0.373</td>
</tr>
</tbody>
</table>

Multivariate Cox analysis was conducted after being adjusted for age, sex, BMI, SBP, DBP and CCI. BMI, body mass index; CCI, Charlson comorbidity index; CI, confidence interval; DBP, diastolic blood pressure; HD, hemodialysis; HR, hazard ratio; SBP, systolic blood pressure.
during the follow-up period was 1.0 per 100 patient-years, compared with 0.5 in Japan and 3.0 in Sweden [11]. Since the adequacy assessment excludes people admitted during the period, AF prevalence may have been underestimated in our data.

We investigated whether AF was associated with a worse prognosis among HD patients using a large-scale, nationwide, population-based database. We noted that AF patients undergoing HD had significantly greater all-cause mortality, hospitalization, and hemorrhagic stroke, but not ischemic stroke. Moreover, we found that hemorrhagic stroke was more likely to occur among warfarin users among the AF patients undergoing HD compared with non-users, whereas warfarin treatment did not reduce or increase the risk of all-cause mortality, hospitalization, or ischemic stroke. Therefore, future studies should be performed with larger number of subjects in the warfarin-related cohort.

Several previous studies have demonstrated that AF patients on maintenance dialysis have a poor prognosis. In the RAKUEN (registry of atrial fibrillation in chronic kidney disease under hemodialysis from Niigata) study, which was a single-center, retrospective, observational study over a mean period of 36 months, AF was independently associated with death from any cause (HR, 1.69; 95% CI, 1.04–2.74; p = 0.034), but not significantly associated with ischemic stroke or major bleeding events. Moreover, the findings suggested that AF had less impact on the risk of ischemic stroke in non-anticoagulated patients [12]. In a prospective study conducted by a Japanese group, the authors concluded that patients who had AF at the time of dialysis initiation showed high rates of mortality and cardiovascular or cerebrovascular disease [13]. The potential biologic mechanisms by which AF might cause death include thromboembolic events and worsening of heart failure (induced by tachycardia or possibly by beat-to-beat ventricular irregularity), although the absolute risk increase for heart failure was the highest among the outcomes, such as cardiovascular disease, renal disease, and stroke [14,15]. Data from a study conducted by Genovesi et al. [7] indicated that left atrial remodeling—because of the presence of heart diseases—is likely to be accelerated by dialytic therapy and has an independent role in increasing the mortality rate. Consistent with these studies, we found that AF was significantly associated with an increased risk of death from any cause. However, we also found increased rates of hospitalization and hemorrhagic stroke in the AF group compared with the non-AF group. We could not determine why hemorrhagic stroke occurred more frequently among AF patients than among patients without AF, which was in contrast to the RAKUEN study. Thus, we investigated whether warfarin use would have an effect on hemorrhagic stroke incidence.

We found that warfarin use was significantly associated with an increased risk of hemorrhagic stroke among AF patients undergoing HD. The use of anticoagulation therapy for HD patients with AF is still controversial. In a retrospective cohort study, Kai et al. [16] concluded that warfarin use was associated with lower all-cause mortality and ischemic stroke risk, without significantly increasing the risk of bleeding in HD patients with AF. However, another study demonstrated a significant association between warfarin use and decreased risk of ischemic stroke but no association between warfarin use and death, hemorrhagic stroke, or gastrointestinal bleeding in intention-to-treat analyses (HR, 0.68; 95% CI, 0.47–0.99). In contrast, in the as-treated analyses, warfarin use was associated with reduced mortality (HR, 0.84; 95% CI, 0.73–0.97) [17].

Some studies have reported findings that contrast with the above. In a prospective cohort study of Japanese HD patients with chronic sustained AF, warfarin use did not significantly reduce ischemic stroke events [18]. Moreover, in a meta-analysis performed by Lee et al. [19], which comprised eight studies with a total of 9,539 participants and 706 stroke events, warfarin use had a neutral effect on ischemic stroke or thromboembolism incidence among AF patients undergoing HD. The authors also indicated that warfarin use was associated with a higher risk of hemorrhagic stroke and bleeding and was associated with no effect on death.

The 2019 AHA/ACC/HRS guideline recommends that it might be reasonable to prescribe warfarin (international normalized ratio, 2.0–3.0) or apixaban for oral anticoagulation to patients with AF who have a CHA2DS2-VASc score of 2 or greater in men or 3 or greater in women and those who have end-stage chronic kidney disease (CKD; creatinine clearance of <15 mL/min) or are on dialysis (Class of Recommendation IIb, Level of Evidence B-NR) [8]. In a large United States claims database analysis evaluating patients with AF and stage 4 or 5 CKD or undergoing hemolysis, rivaroxaban was associated with less major bleeding compared with warfarin in patients with severe kidney dysfunction (HR, 0.68; 95% CI, 0.47–0.99) [20]. In 2018, Siontis et al. [21] published a
A study comparing apixaban to warfarin among patients with nonvalvular AF undergoing hemodialysis. No difference in the hazard of stroke or systemic embolism was revealed; however, apixaban was associated with a significantly lower risk of major bleeding (HR, 0.72; 95% CI, 0.59–0.84; p < 0.001). Non-vitamin K oral anticoagulant, so-called NOAC, could possibly replace warfarin to lower the risk of bleeding.

This study had some limitations. The percentage of AF patients in our cohort was only 3.3%. Under-diagnosis, missed diagnoses, and code input errors may have contributed to this low prevalence. In addition, all the diagnoses were based on ICD-10 codes, which do not differentiate between different types of AF (valvular vs. nonvalvular disease, chronic vs. paroxysmal, and fibrillation vs. flutter). Because the purpose of adequacy assessment is to qualify dialysis facilities themselves and acquire certification, there is some possibility of selection bias in favor of, for example, outpatients only or excluding patients with severe conditions. Furthermore, not all of the dialysis facilities in Korea were involved in the evaluation. As the national assessment for dialysis adequacy was undertaken from October to December 2013, its data collection period was three months which might reflect patient characteristics less well than one full year. Thus, the results should be interpreted with caution. The HAS-BLED score, which evaluates major bleeding risk among anticoagulation patients, was not collected or adjusted. Likewise, prescription of antiplatelet agents was not investigated. Since this study investigated the prescriptions of warfarin, the actual dose and adherence may differ among patients. Due to the limitations of detailed investigation in a retrospective study, it was difficult to clarify the successive relationship between warfarin and stroke.

Nevertheless, the strength of this study is that, as HIRA is a national system, our study included a large pool of subjects (a total of 21,839 patients). Furthermore, the follow-up duration was longer than in other previous studies. Additionally, as this study targeted only Korean patients, we generated novel data for this particular ethnic group, which can be compared with other groups.

In conclusion, our analysis showed that AF could be an independent risk factor for adverse clinical outcomes among HD patients. However, warfarin administration did not decrease the incidence of ischemic stroke, mortality, or hospitalization but was associated with an increased risk of hemorrhagic stroke among HD patients. Our study suggests that physicians should specifically assess for AF, and they should be more cautious with AF patients when they consider prescribing warfarin.

**Conflicts of interest**

All authors have no conflicts of interest to declare.

**Funding**

This work was supported by an Ewha Womans University Research Grant in 2018.

**Acknowledgments**

The authors participated in the Joint Project on Quality Assessment Research, and HIRA collected and provided the claims data and quality assessment data to the authors.

**Authors’ contributions**

Conceptualization: YK, HJO, DRR
Data curation: HYC, YEK, JHS, EMW, KHY
Formal analysis: YK, HJO, DRR
Investigation: DRR
Methodology: DRR
Project administration: HJO, DRR
Visualization: YK
Writing—original draft: YK, HJO
Writing—review & editing: All authors
All authors read and approved the final manuscript.

**ORCID**

Yeunmi Kang, https://orcid.org/0000-0002-8475-2255
Hyung Yun Choi, https://orcid.org/0000-0001-8496-6723
Young Eun Kwon, https://orcid.org/0000-0002-8370-1333
Ji Hyeon Shin, https://orcid.org/0000-0001-8915-6885
Eun Mi Won, https://orcid.org/0000-0001-6213-394X
Ki Hwa Yang, https://orcid.org/0000-0003-0134-3059
Hyung Jung Oh, https://orcid.org/0000-0002-4281-696X
Dong-Ryeol Ryu, https://orcid.org/0000-0002-5309-7606
References


Elevated levels of soluble ST2 but not galectin-3 are associated with increased risk of mortality in hemodialysis patients

Ae Jin Kim¹,², Han Ro¹,², Hyunsook Kim³, Kwang-Pil Ko⁴, Jae Hyun Chang¹,², Hyun Hee Lee¹,², Wookyung Chung¹,², Ji Yong Jung¹,²,³

¹Division of Nephrology, Department of Internal Medicine, Gachon University Gil Medical Center, Incheon, Republic of Korea
²Department of Internal Medicine, Gachon University College of Medicine, Incheon, Republic of Korea
³Department of Health Sciences and Technology, Gachon University, Incheon, Republic of Korea
⁴Department of Preventive Medicine, Gachon University College of Medicine, Incheon, Republic of Korea

Background: The soluble forms of suppression of tumorigenicity-2 (ST2) and galectin-3 have been proposed as novel biomarkers for cardiac fibrosis and heart failure, as well as predictors of cardiovascular events and mortality. However, there are limited data on the association between soluble ST2 and galectin-3 and clinical outcomes in patients with kidney failure on replacement therapy. To determine this, we examined the associations between soluble ST2 and galectin-3 and all-cause mortality and cardiovascular events in patients on hemodialysis.

Methods: This study included maintenance hemodialysis patients (over 18 years old) who consented to preserve their serum in the Biobank at our institution between March 2014 and March 2015. We used Cox proportional hazards regression analysis to evaluate the associations between soluble ST2, galectin-3 levels, and clinical outcomes. The primary outcome was all-cause mortality, the secondary outcome was cardiovascular disease, and patients were followed for both outcomes until March 2018.

Results: A total of 296 patients were analyzed in this study. The mean age was 57 ± 13 years, and 53.0% were male. Serum concentration of soluble ST2 was significantly associated with higher mortality, after adjustment for confounding factors, but was not associated with cardiovascular disease. Serum galectin-3 level was not independently associated with either outcome after adjustment.

Conclusion: Elevated soluble ST2 is independently associated with an increased risk of mortality, but not with cardiovascular disease, in patients on hemodialysis. Elevated galectin-3 was not associated with mortality or cardiovascular disease.

Keywords: Cardiovascular diseases, Galectin 3, Hemodialysis, Mortality, Soluble ST2
Introduction

The incidence and prevalence of kidney failure with replacement therapy (KFRT) are both on the increase, and this constitutes a major public health challenge worldwide [1–3]. Although the mortality rate of patients with KFRT has decreased over the past two decades, both morbidity and mortality remain high; the adjusted survival for incident hemodialysis (HD) patients three years after the onset of KFRT is 57% [1,2,4,5]. Cardiovascular disease (CVD) is common in these patients and contributes significantly to mortality, accounting for nearly 50% of all deaths [1]. These poor survival trends have led to the need for risk stratification and strategies to improve outcomes in patients with KFRT.

Soluble suppression of tumorigenicity-2 (sST2), a member of the interleukin (IL)-1 receptor family, is thought to be involved in inflammation, myocardial hypertrophy, and fibrosis by neutralizing the effect of IL-33 [6]. Galectin-3 is a β-galactoside-binding lectin that is thought to be involved in inflammation, the induction of cardiac fibrosis, and ventricular remodeling [7]. Recent studies have suggested sST2 and galectin-3 as novel biomarkers of heart failure (HF) [8] and independent predictors of CVD and mortality in the general population [6,9]. Both markers have been approved by the U.S. Food and Drug Administration for clinical use [8]. Some studies have reported that their levels are significantly associated with all-cause mortality in patients with chronic kidney disease (CKD) [10,11].

However, few studies have investigated these biomarkers in patients with KFRT, which has limited their prognostic value. Therefore, in this study, we aimed to investigate whether sST2 and galectin-3 predict adverse outcomes and provide additional prognostic value in maintenance HD patients.

Methods

Study population

This study involved participants from a prospective observational cohort of prevalent HD patients at Gachon University Gil Medical Center in Incheon, Republic of Korea. This cohort included patients who were >18 years of age and consented to preserve their serum in the Biobank at our institution. We excluded patients with insufficient clinical data, any physical, mental, or medical condition that prohibited the ability to provide informed consent, and those who withdrew consent before follow-up blood analysis, or who declined to store their blood samples. Under the Biobank study protocol, blood samples were collected from each patient at baseline and then yearly for up to 5 years. Predialysis blood samples were collected according to a standardized protocol. Specimens were processed on refrigerated packs on the day of collection and transported to the Biobank, where they were aliquoted and stored at -80°C. All patients were treated with a 4-hour HD session (5008S; Fresenius Medical Care, St. Wendel, Germany) twice (n = 5) or thrice (n = 291) per week using high-flux polysulfone membranes (FX CorDiax 60; Fresenius Medical Care). Patients were enrolled for one calendar year between March 2014 and March 2015 and were followed until March 2018. Patients were censored at the time of kidney transplantation (n = 20), transfer to other dialysis centers (n = 28), loss to follow-up (n = 15), or at the end of follow-up (March 27, 2018). This study adheres to the Declaration of Helsinki and was approved by the Institutional Review Board at the Gachon University Gil Medical Center (GBIRB2018-224). Written informed consent was obtained from all participants. Biospecimens were provided by Gachon University Gil Medical Center Biobank.

Parameters

All demographics, clinical data, comorbidities, laboratory values, and medications were collected at study enrollment from the participant’s medical record by a well-trained study coordinator. Baseline demographic and clinical characteristics were collected as follows: age, sex, body mass index (BMI), and pre- and postdialysis systolic blood pressure and diastolic blood pressure. We identified comorbidities, including hypertension, diabetes mellitus (DM), ischemic heart disease such as angina pectoris and myocardial infarction, HF, transient ischemic attack (TIA), and stroke. Angina pectoris and myocardial infarction were defined as the presence of coronary artery disease as documented by angiography, or an acute coronary syndrome or angina requiring percutaneous coronary intervention or coronary artery bypass grafting surgery. Stroke and TIA were defined as cases where magnetic
resonance imaging was performed in patients with suspected symptoms and diagnosed by a neurologist. Systolic HF was defined as left ventricular ejection fraction of <40% and diastolic HF was defined as E/a > 15. Laboratory data included hemoglobin (Hb), white blood cells, platelets, serum creatinine, blood urea nitrogen, albumin, protein, calcium, phosphorus, alkaline phosphatase, uric acid, total cholesterol, HbA1c, and high-sensitivity C-reactive protein (hs-CRP). Anemia was defined as Hb of <10 g/dL. Hypoalbuminemia was defined as serum albumin of <3.5 g/dL. Hypocalcemia was defined as serum total calcium of <8.2 mg/dL. Hyperphosphatemia was defined as serum phosphorus of >4.7 mg/dL. Medication data included the use of renin-angiotensin system (RAS) blockers, calcium channel blockers (CCB), β-blockers, diuretics, and antiplatelet agents.

Serum sST2 and galectin-3 levels (ng/mL) were measured using commercial quantitative enzyme-linked immunosorbent assay kits DST200 and DGAL30, respectively (QuantiKine, R&D Systems, Minneapolis, MN, USA).

Outcomes

The primary outcome was all-cause mortality. The secondary outcome was cardiovascular events (CVD), defined as unstable angina pectoris, acute myocardial infarction, TIA, stroke, and HF.

Statistical analyses

Continuous variables are presented as the mean ± standard deviation (SD) or median (interquartile range), as appropriate. Categorical data are presented as absolute values and percentage frequency. For continuous variables, between-group comparisons were performed using Student t tests; for categorical variables, chi-square tests were used. Receiver operating characteristic (ROC) curve analyses were performed to identify the optimal cut-off values for sST2 and galectin-3 with the highest sum of sensitivity and specificity for mortality. Logistic regression analysis was used to demonstrate the association between sST2, galectin-3, and underlying HF. The Cox proportional hazard regression model was used to investigate the prognostic utility of these two biomarkers for predicting mortality and CVD. For Cox analyses, log-transformed sST2 and galectin-3 were used and hazard ratio (HR) refers to a 1 SD rise in log-transformed units. Covariates were adjusted in four different models. The first model was adjusted for age and sex. The second was additionally adjusted for smoking status, HD duration, DM, hypertension, and underlying CVD, including angina pectoris, myocardial infarction, TIA, stroke, and HF. The third was then adjusted for medications (RAS blockers, CCB, β-blockers, diuretics, and antiplatelet agents), and the fourth model was further adjusted for laboratory variables (anemia, hypoalbuminemia, hypocalcemia, hyperphosphatemia, and hs-CRP). We further examined the interaction between sST2 and several risk factors (age, sex, DM, hypertension, previous CVD, anemia, hypoalbuminemia, and use of RAS blockers and β-blockers) by including interaction terms in the models. Interaction terms were created by multiplying each factor by sST2. The likelihood ratio test was used to test the significance of the interaction terms. We showed the effect modification of sST2 and galectin-3 for mortality and CVD in prespecified subgroups: age (<70 years vs. ≥70 years), sex (female vs. male), DM, hypertension, previous CVD, anemia (Hb of <10 g/dL vs. ≥10 g/dL), hypoalbuminemia (albumin of <3.5 g/dL vs. ≥3.5 g/dL), and use of RAS blockers and β-blockers. Statistical analyses were performed using IBM SPSS version 22.0 (IBM Corp., Armonk, NY, USA). All analyses were two-sided and p-values of <0.05 were considered statistically significant.

Results

Patient characteristics (baseline characteristics)

The baseline characteristics of the study population are presented in Table 1. A total of 296 patients enrolled in this study. The mean age was 57 ± 13 years and 53.0% were male. In this cohort, 45.6% of the patients were diabetic, 86.5% were hypertensive, 23.6% had ischemic heart disease, 10.8% had TIA or stroke, and 35.8% had HF. Survivors were younger, less likely to have DM or HF, more likely to take statins, and had higher creatinine, phosphorus, and albumin and lower sST2 and galectin-3 levels than non-survivors. The median serum sST2 and galectin-3 level were higher in non-survivors than in survivors: sST2, 21.190 ng/mL (interquartile range [IQR], 16.208–29.176) vs. 28.200 ng/mL (IQR, 20.851–37.763), p = 0.003 (Table 1); galectin-3, 34.957 ng/mL (IQR, 28.413–41.908) vs. 38.619 ng/mL (IQR, 31.013–
Table 1. Baseline characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total (n = 296)</th>
<th>Survivor (n = 260)</th>
<th>Non-survivor (n = 36)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>57 ± 13</td>
<td>56 ± 13</td>
<td>64 ± 13</td>
<td>0.001*</td>
</tr>
<tr>
<td>Male sex</td>
<td>157 (53.0)</td>
<td>138 (53.1)</td>
<td>19 (52.8)</td>
<td>0.973</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>22.5 ± 3.8</td>
<td>22.5 ± 3.9</td>
<td>21.9 ± 3.2</td>
<td>0.383</td>
</tr>
<tr>
<td>Pre-HD SBP (mmHg)</td>
<td>146 ± 26</td>
<td>147 ± 27</td>
<td>142 ± 22</td>
<td>0.249</td>
</tr>
<tr>
<td>Pre-HD DBP (mmHg)</td>
<td>70 ± 14</td>
<td>71 ± 14</td>
<td>62 ± 11</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Post-HD SBP (mmHg)</td>
<td>131 ± 24</td>
<td>131 ± 24</td>
<td>127 ± 23</td>
<td>0.353</td>
</tr>
<tr>
<td>Post-HD DBP (mmHg)</td>
<td>69 ± 41</td>
<td>68 ± 13</td>
<td>79 ± 113</td>
<td>0.584</td>
</tr>
<tr>
<td>HD duration (mo)</td>
<td>48.5 (18.0–75.8)</td>
<td>47.5 (17.0–74.8)</td>
<td>55.0 (33.5–102.0)</td>
<td>0.318</td>
</tr>
<tr>
<td>Comorbidity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>256 (86.5)</td>
<td>224 (86.2)</td>
<td>32 (88.9)</td>
<td>0.799</td>
</tr>
<tr>
<td>DM</td>
<td>135 (45.6)</td>
<td>113 (43.5)</td>
<td>22 (61.1)</td>
<td>0.046*</td>
</tr>
<tr>
<td>IHD</td>
<td>70 (23.6)</td>
<td>57 (21.9)</td>
<td>13 (36.1)</td>
<td>0.060</td>
</tr>
<tr>
<td>Stroke or TIA</td>
<td>32 (10.8)</td>
<td>25 (9.6)</td>
<td>7 (19.4)</td>
<td>0.086</td>
</tr>
<tr>
<td>Heart failure</td>
<td>106 (35.8)</td>
<td>87 (33.5)</td>
<td>19 (52.8)</td>
<td>0.023*</td>
</tr>
<tr>
<td>Laboratory</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>11.0 ± 5.6</td>
<td>11.1 ± 6.0</td>
<td>10.0 ± 1.4</td>
<td>0.295</td>
</tr>
<tr>
<td>WBC (×10³/mm)</td>
<td>5.82 ± 2.18</td>
<td>5.79 ± 2.13</td>
<td>6.03 ± 2.47</td>
<td>0.540</td>
</tr>
<tr>
<td>PLT (×10³/mm)</td>
<td>191 (150–232)</td>
<td>191 (154–234)</td>
<td>187 (112–228)</td>
<td>0.177</td>
</tr>
<tr>
<td>BUN (mg/dL)</td>
<td>55.1 ± 16.1</td>
<td>55.0 ± 15.7</td>
<td>55.5 ± 18.4</td>
<td>0.856</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>8.3 ± 2.3</td>
<td>8.5 ± 2.4</td>
<td>7.4 ± 1.9</td>
<td>0.012*</td>
</tr>
<tr>
<td>Calcium (mg/dL)</td>
<td>8.7 ± 0.6</td>
<td>8.7 ± 0.6</td>
<td>8.7 ± 0.8</td>
<td>0.926</td>
</tr>
<tr>
<td>Phosphorus (mg/dL)</td>
<td>4.6 ± 1.6</td>
<td>4.7±1.6</td>
<td>4.0 ± 1.5</td>
<td>0.024*</td>
</tr>
<tr>
<td>ALP (IU/mL)</td>
<td>83.0 (66.0–110.8)</td>
<td>82.0 (65.0–107.0)</td>
<td>93.5 (76.5–128.5)</td>
<td>0.323</td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>3.9 ± 0.4</td>
<td>3.9 ± 0.4</td>
<td>3.7 ± 0.4</td>
<td>0.003*</td>
</tr>
<tr>
<td>Protein (g/dL)</td>
<td>6.9 ± 0.5</td>
<td>6.9 ± 0.5</td>
<td>6.8 ± 0.6</td>
<td>0.127</td>
</tr>
<tr>
<td>Uric acid (mg/dL)</td>
<td>7.0 ± 1.4</td>
<td>7.1 ± 1.4</td>
<td>6.6 ± 1.4</td>
<td>0.054</td>
</tr>
<tr>
<td>TC (mg/dL)</td>
<td>137 ± 29</td>
<td>137 ± 29</td>
<td>139 ± 29</td>
<td>0.635</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>6.2 ± 4.2</td>
<td>6.2 ± 4.5</td>
<td>6.0 ± 1.7</td>
<td>0.797</td>
</tr>
<tr>
<td>hs-CRP (mg/dL)</td>
<td>0.13 (0.05–0.45)</td>
<td>0.12 (0.04–0.39)</td>
<td>0.24 (0.10–1.04)</td>
<td>0.628</td>
</tr>
<tr>
<td>sST2 (ng/mL)</td>
<td>22.074 (16.515–30.768)</td>
<td>21.190 (16.208–29.176)</td>
<td>28.200 (20.851–37.763)</td>
<td>0.003*</td>
</tr>
<tr>
<td>Galectin-3 (ng/mL)</td>
<td>35.609 (28.534–41.981)</td>
<td>34.957 (28.413–41.908)</td>
<td>38.619 (31.013–45.576)</td>
<td>0.044*</td>
</tr>
<tr>
<td>Medication</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RAS blockers</td>
<td>143 (48.3)</td>
<td>124 (47.7)</td>
<td>19 (52.8)</td>
<td>0.567</td>
</tr>
<tr>
<td>CCB</td>
<td>148 (50.0)</td>
<td>128 (49.2)</td>
<td>20 (55.6)</td>
<td>0.477</td>
</tr>
<tr>
<td>β-blockers</td>
<td>120 (40.5)</td>
<td>104 (40.0)</td>
<td>16 (44.4)</td>
<td>0.611</td>
</tr>
<tr>
<td>Diuretics</td>
<td>159 (53.7)</td>
<td>144 (55.4)</td>
<td>15 (41.7)</td>
<td>0.122</td>
</tr>
<tr>
<td>Anti-platelets</td>
<td>250 (84.5)</td>
<td>221 (85.0)</td>
<td>29 (80.6)</td>
<td>0.490</td>
</tr>
</tbody>
</table>

Data are expressed as the mean ± standard deviation, median (interquartile range), or number of patients (%).

ALP, alkaline phosphatase; BMI, body mass index; BUN, blood urea nitrogen; CCB, calcium channel blocker; DBP, diastolic blood pressure; DM, diabetes mellitus; HbA1c, hemoglobin A1c; HD, hemodialysis; hs-CRP, high-sensitivity C-reactive protein; IHD, ischemic heart disease; PLT, platelet; RAS, renin-angiotensin system; SBP, systolic blood pressure; sST2, soluble suppression of tumorigenicity-2; TC, total cholesterol; TIA, transient ischemic attack; WBC, white blood cell.

* p < 0.05.

There were no differences in the HD duration or use of RAS blockers, CCB, β-blockers, diuretics, and antiplatelet agents between survivors and non-survivors.

Serum soluble suppression of tumorigenicity-2 and galectin-3 levels as predictors of mortality

During a mean follow-up period of 37.8 ± 13.9 months, 36
patients (12.5%) died. The main cause of death was infection (9 patients). Other causes included cardiovascular (6), malignancy (4), bleeding (6), aspiration (1), and unknown (10). The predictive value of sST2 and galectin-3 for mortality was evaluated using ROC analysis (Fig. 1). The area under curve of sST2 and galectin-3 for mortality were 0.645 (p = 0.005) and 0.578 (p = 0.129), respectively. The calculated cut-off values of sST2 and galectin-3 for mortality were 22.07 ng/mL (sensitivity, 75.0%; specificity 53.5%) and 35.27 ng/mL (sensitivity, 66.7%; specificity, 51.2%), respectively. In the Cox proportional hazard analysis, serum sST2 was significantly associated with an increased risk of all-cause mortality (HR per 1 SD increase of log-transformed sST2, 1.811; 95% confidence interval [CI], 1.240–2.645; p = 0.002) (Crude in Table 2). After adjusting for covariates, serum sST2 level remained an independent predictor of all-cause mortality (HR, 1.589; 95% CI, 1.016–2.484; p = 0.042) (Model 4 in Table 2). Because of the significant interaction between sST2 and hypoalbuminemia for all-cause mortality in the multivariable Cox proportional hazard model, the interaction term (sST2*hypoalbuminemia) was included in the final multivariable analysis. Serum sST2 was still associated with all-cause mortality (HR, 2.100; 95% CI, 1.231–3.580; p = 0.006) (Model 5 in Table 2).

In contrast to sST2, serum galectin-3 level was not associated with all-cause mortality (HR per 1 SD increase of log-transformed galectin-3, 1.354; 95% CI, 0.931–1.971; p = 0.113) (Crude in Table 2). After adjustment for covariates, galectin-3 level was still not associated with all-cause mortality (HR per 1 SD increase, 1.450; 95% CI, 0.926–2.271; p = 0.105) (Model 4 in Table 2).

**Serum sST2 and galectin-3 levels as predictors of CVDs**

During the follow-up period, a total of 69 CVDs occurred; of these, 33 events were unstable angina pectoris/myocardial infarction, 35 were HF, and one was TIA/stroke. Using Cox proportional hazard analysis, serum sST2 level was not found to be associated with CVD (HR per 1 SD increase, 1.100; 95% CI, 0.855–1.414; p = 0.460) (Crude in Table 3),

![Figure 1](https://example.com/image.png)

**Figure 1.** Receiver operating characteristic curve for sST2 and galectin-3 to predict mortality.

AUC, area under curve; SD, standard deviation; sST2, soluble suppression of tumorigenicity-2.

<table>
<thead>
<tr>
<th>Adjust model</th>
<th>Log sST2</th>
<th>p-value</th>
<th>Log galectin-3</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crude</td>
<td>1.811 (1.240–2.645)</td>
<td>0.002*</td>
<td>1.354 (0.931–1.971)</td>
<td>0.113</td>
</tr>
<tr>
<td>Model 1</td>
<td>1.804 (1.203–2.707)</td>
<td>0.004*</td>
<td>1.279 (0.882–1.854)</td>
<td>0.194</td>
</tr>
<tr>
<td>Model 2</td>
<td>1.917 (1.247–2.947)</td>
<td>0.003*</td>
<td>1.244 (0.861–1.798)</td>
<td>0.246</td>
</tr>
<tr>
<td>Model 3</td>
<td>1.833 (1.192–2.819)</td>
<td>0.006*</td>
<td>1.337 (0.899–1.987)</td>
<td>0.152</td>
</tr>
<tr>
<td>Model 4</td>
<td>1.589 (1.016–2.484)</td>
<td>0.042*</td>
<td>1.450 (0.926–2.271)</td>
<td>0.105</td>
</tr>
<tr>
<td>Model 5</td>
<td>2.100 (1.231–3.580)</td>
<td>0.006*</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

Data are expressed as HR (95% CI); HRs are calculated based on per standard deviation increase in log-transformed biomarker level.

Model 1, adjusted for demographics (age and sex); model 2, adjusted for demographics, and comorbidities (model 1 + smoking status, hemodialysis duration, diabetes mellitus, hypertension, and cardiovascular disease); model 3, adjusted for demographics, comorbidities, and medications (model 2 + renin-angiotensin system blockades, calcium channel blockers, β-blockers, diuretics, and antiplatelet agents); model 4, adjusted for demographics, comorbidities, medications, and laboratory findings (model 3 + anemia, hypoalbuminemia, hypocalcemia, hyperphosphatemia, and high-sensitivity C-reactive protein); model 5, model 4 + interaction term sST2 × hypoalbuminemia.

CI, confidence interval; HR, hazard ratio; NA, not applicable; sST2, soluble suppression of tumorigenicity-2.

*p < 0.05.
Association of serum sST2 and galectin-3 with underlying HF

In a logistic regression analysis, underlying HF (composite of systolic HF and diastolic HF) was not significantly associated with serum sST2 (odds ratio [OR] per 1 SD increase of log-transformed sST2, 1.008; 95% CI, 0.794–1.278; p = 0.950) (Crude in Supplementary Table 1, available online), or galectin-3 levels (OR per 1 SD increase of log-transformed galectin-3, 0.843; 95% CI, 0.665–1.067; p = 0.156) (Crude in Supplementary Table 1). Serum sST2 and galectin-3 levels were still not associated with underlying HF after adjusting for covariates (sST2: OR, 0.987; 95% CI, 0.737–1.322; p = 0.929; galectin-3: OR, 0.806; 95% CI, 0.614–1.058; p = 0.120) (Model 4 in Supplementary Table 1).

Discussion

In this study, we investigated the association between two novel biomarkers and clinical outcomes in patients undergoing HD. We showed that the sST2 level was an independent predictor for survival in HD patients, unlike galectin-3. We also demonstrated that elevated sST2 and galectin-3 were not independently predictive of CVD in HD patients.

ST2, a member of the IL-1 receptor family, exists in two main isoforms: sST2 (soluble form) and ST2L (transmembrane form) [12]. The IL-33/ST2 pathway is associated with inflammation and the pathologic process of CVD. In cardiomyocytes and fibroblasts, it is upregulated in response to myocardial stress [13], and has a cardioprotective function, conferring anti-

Subgroup analyses

In subgroup analysis, we found that hypoalbuminemia modified the association between sST2 and mortality in patients undergoing HD (Fig. 2). When we analyzed the risk of all-cause mortality by Cox proportional hazard analyses of log sST2 per 1 SD increase, in those with hypoalbuminemia, the HR of sST2 was 0.887 (95% CI, 0.427–1.842; p = 0.748) while it was 2.011 (95% CI, 1.287–3.141; p = 0.002) in those without hypoalbuminemia (Fig. 2). The p-value for this interaction was 0.047.

The HRs of sST2 for CVD among those with age of <70 years and ≥70 years were 0.944 (95% CI, 0.717–1.243; p = 0.682) and 2.399 (95% CI, 1.205–4.773; p = 0.013) (Supplementary Fig. 1, available online). The p-value for this interaction was 0.010. The HRs of sST2 for CVD among those without β-blocker and with β-blocker were 1.429 (95% CI, 0.968–2.111; p = 0.073) and 0.827 (95% CI, 0.582–1.175; p = 0.289) (Supplementary Fig. 1). The p-value for interaction was 0.041. There were no significant interactions between galectin-3 and subgroups for all-cause mortality and CVD (Supplementary Fig. 2, 3; available online).

Table 3. Adjusted HR for incidence of cardiovascular disease based on levels of log sST2 and log galectin-3

<table>
<thead>
<tr>
<th>Adjust model</th>
<th>Log sST2</th>
<th>p-value</th>
<th>Log galectin-3</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crude</td>
<td>1.100 (0.855–1.414)</td>
<td>0.460</td>
<td>1.042 (0.820–1.325)</td>
<td>0.734</td>
</tr>
<tr>
<td>Model 1</td>
<td>1.055 (0.802–1.387)</td>
<td>0.703</td>
<td>0.999 (0.787–1.267)</td>
<td>0.991</td>
</tr>
<tr>
<td>Model 2</td>
<td>1.035 (0.784–1.367)</td>
<td>0.806</td>
<td>0.979 (0.768–1.248)</td>
<td>0.863</td>
</tr>
<tr>
<td>Model 3</td>
<td>1.008 (0.765–1.329)</td>
<td>0.954</td>
<td>0.984 (0.768–1.262)</td>
<td>0.901</td>
</tr>
<tr>
<td>Model 4</td>
<td>0.993 (0.748–1.318)</td>
<td>0.961</td>
<td>0.969 (0.753–1.247)</td>
<td>0.808</td>
</tr>
<tr>
<td>Model 5</td>
<td>0.427 (0.110–1.655)</td>
<td>0.218</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

Data are expressed as HR (95% CI); HRs are calculated based on per standard deviation increase in log-transformed biomarker level. Model 1, adjusted for demographics (age and sex); model 2, adjusted for demographics, and comorbidities (model 1 + smoking status, hemodialysis duration, diabetes mellitus, hypertension, and cardiovascular disease); model 3, adjusted for demographics, comorbidities, and medications (model 2 + renin-angiotensin system blockers, calcium channel blockers, β-blockers, diuretics, and antiplatelet agents); model 4, adjusted for demographics, comorbidities, medications, and laboratory findings (model 3 + anemia, hypoalbuminemia, hypocalcemia, hyperphosphatemia, and high-sensitivity C-reactive protein); model 5, model 4 + interaction term sST2 × age and sST2 × β-blockers. CI, confidence interval; HR, hazard ratio; NA, not applicable; sST2, soluble suppression of tumorigenicity-2.

Association of serum sST2 and galectin-3 with underlying HF

In a logistic regression analysis, underlying HF (composite of systolic HF and diastolic HF) was not significantly associated with serum sST2 (odds ratio [OR] per 1 SD increase of log-transformed sST2, 1.008; 95% CI, 0.794–1.278; p = 0.950) (Crude in Supplementary Table 1, available online), or galectin-3 levels (OR per 1 SD increase of log-transformed galectin-3, 0.843; 95% CI, 0.665–1.067; p = 0.156) (Crude in Supplementary Table 1). Serum sST2 and galectin-3 levels were still not associated with underlying HF after adjusting for covariates (sST2: OR, 0.987; 95% CI, 0.737–1.322; p = 0.929; galectin-3: OR, 0.806; 95% CI, 0.614–1.058; p = 0.120) (Model 4 in Supplementary Table 1).
fibrotic, anti-hypertrophic, and anti-apoptotic effects to volume-overloaded or injured myocardium [13]. However, sST2, a soluble, truncated form of ST2L, is secreted into the circulation and is believed to function as a decoy receptor for IL-33, inhibiting the effects of IL-33/ST2 signaling, and reducing its various activities, including cardioprotective effects [13]. Serum levels of sST2 are significantly increased in inflammatory diseases, cancer, liver, and cardiac diseases [6,14–16].

To date, the prognostic value of sST2 has been mainly studied in the general population and has been significantly associated with mortality and adverse outcomes in patients with HF [17] and coronary artery disease, including myocardial infarction [18]. Hitherto, studies that evaluated the association of sST2 with kidney function have shown conflicting results. An analysis of the Cardiovascular Health Study cohorts (a community-based multicenter cohort of older adults free of clinical HF) found that sST2 was not associated with kidney function decline or the development of incident estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m² [19]. Similarly, a study of participants of the Framingham Offspring Study cohort found no significant association between sST2 and risk for incident CKD [20]. However, sST2 was associated with incident albuminuria in a previous study [20], and with the risk of acute kidney injury in patients with ST-segment elevation myocardial infarction [21].

sST2 is a promising prognostic marker for patients with CKD. The recent Seattle Kidney Study (SKS) and Clinical Phenotyping and Resource Biobank Study (C-PROBE) cohort suggested that sST2 was also associated with all-cause mortality and a composite of hospitalization and atherosclerotic CVD events [10].

There are limited data on the prognostic value of sST2 in dialysis patients. In our study, elevated sST2 concentration was significantly associated with increased mortality in maintenance HD patients. In a previous study of 414 HD patients, elevated sST2 concentration was an independent predictor of all-cause and cardiovascular mortality [22]. Another recent observational study of 423 HD patients investigated the association of sST2 with all-cause mortality and the composite outcome of death and cerebrocardiovascular events [23]. It also suggested that sST2 had an independent and incremental prognostic value for both outcomes [23]. Our data support previous studies that demonstrated an association of sST2 and all-cause mortality. In this regard, sST2 may be used as a prognostic marker for survival in HD patients. In subgroup analysis, the association of sST2 with mortality disappeared in patients with hypoalbuminemia. Because hypoalbuminemia is a significant predictor of mortality in this population, it might attenuate the association between sST2 and mortality.

However, the risk of CVD was not associated with sST2 levels in our study. Recent studies on the general population showed an association of sST2 with CVD [24]. However, in a study of 883 CKD patients, sST2 concentration was not associated with atherosclerotic CVD [10]. There is no previous study showing an association of sST2 with solely CVD in HD patients. Patients with CKD have unique CVD risk factors, such as metabolic abnormalities, disordered mineral metabolism, and accumulation of uremic toxins, which may impact the association between sST2 and CVD. In addition, previous studies suggest that sST2 may reflect hemodynamic alterations and inflammatory status in the general population [25,26]; therefore, more complex underlying pathophysiology could also impact the relationship between sST2 and CVD in this population, including the larger hemodynamic burden and the increased inflammatory environment of HD patients. In subgroup analysis, sST2 was associated with the risk of CVD in older patients (aged ≥70 years). There were fewer patients in the older group, but the CVD event rate was high. This result could be attributable to the small size of this high-risk group. Further studies are needed to investigate associations with sST2 and CVD in this population.

Galectin-3 is a 29- to 35-kDa protein and belongs to the family of β-galactoside-binding lectins [27]. It plays a role in embryonic development and promotes fibrosis and inflammation [28]. Previous studies have shown that galectin-3 is associated with cardiac fibrosis, ventricular remodeling, and dysfunction [7,29]. In support of these mechanisms, many clinical studies have demonstrated that galectin-3 has a predictive value for the diagnosis and prognosis of acute and chronic HF [30]. Galectin-3 is also associated with CVD and all-cause mortality in the general population [31,32].

In the kidney, galectin-3 is also a profibrotic agent and could be considered as a marker of fibrosis [29]. Serum galectin-3 levels are inversely correlated with kidney function in the general population [33] and in patients with HF [34] or CKD [10]. Clinical studies have shown that
Elevated galectin-3 levels are associated with increased risk of rapid decline in eGFR \[35\] and incident CKD in the general population \[35,36\]. In patients with CKD, higher circulating galectin-3 concentration is significantly associated with greater mortality \[10,11\].

In our study, however, higher galectin-3 level was not significantly associated with all-cause mortality in HD patients. There are few studies to demonstrate the association of galectin-3 with risk for mortality in patients undergoing HD, and any such results are controversial \[11,23,37,38\]. In the analysis of the German Diabetes Dialysis Study (4D study), galectin-3 concentration was

---

**Figure 2. Association of log sST2 and mortality in subgroups of patients (per SD increase).**

CI, confidence interval; CVD, cardiovascular disease; DM, diabetes mellitus; Hb, hemoglobin; HF, heart failure; HR, hazard ratio; HTN, hypertension; RAS, renin-angiotensin system; SD, standard deviation; sST2, soluble suppression of tumorigenicity-2.

*p < 0.05.*
not associated with all-cause mortality after adjusting for confounders \[11\]. Even in the meta-analysis from four studies, there was no statistical difference between galectin-3 and the risk of all-cause mortality in HD patients \[37\]. However, Obokata et al. \[23\] reported galectin-3 as an independent predictor of all-cause death in patients receiving HD, and Hogas et al. \[38\] also found it to be an independent predictor of mortality.

Previous studies demonstrated that the concentration of galectin-3 was inversely correlated with eGFR and was further elevated in patients on dialysis \[10,11\]. In a 4D cohort of HD patients, the mean galectin-3 concentration was 54 ng/mL, compared to 11–14 ng/mL for the general population \[11\]. In our study of HD patients, the mean galectin-3 concentration was 35.5 ng/mL. Furthermore, in previous studies of congestive HF, adding kidney function to regression analysis substantially attenuated the prognostic power of galectin-3, suggesting that elevated levels of galectin-3 could compromise the prognostic value in this population.

In the present study, galectin-3 concentrations are not associated with CVD in HD patients. Previous studies associating galectin-3 with CVD are limited. In the German 4D study, galectin-3 concentration was a predictor of CVD in HD patients \[11\], and Obokata et al. \[23\] reported that galectin-3 was significantly associated with a composite of deaths and cerebrocardiovascular events. Further studies are needed to elucidate the relationship between galectin-3 and cardiovascular outcomes.

Our study has several limitations. First, we did not exclude patients with underlying HF, although our multivariable logistic regression analysis shows that there is no association between sST2 and galectin-3 concentration with underlying HF in patients undergoing HD. Second, we measured the sST2 and galectin-3 levels from frozen samples rather than fresh ones; bias from using frozen samples cannot be excluded. Third, it is possible that elevated galectin-3 and sST2 concentrations reflect decreased kidney function in this population, and we cannot determine mechanisms or causality of the association from this observational study. Fourth, there was no residual kidney function data and this could not be adjusted. Fifth, this study is a single-center study with a single ethnic group. Thus, further studies with other centers and ethnic groups are needed, to generalize our findings. Finally, despite considering multiple risk factors, it is possible that we may have omitted residual confounding from the analysis.

In conclusion, sST2 is a significant predictor of all-cause mortality in HD patients, but galectin-3 is not, and neither is associated with CVD. Our study highlights the need for more research to elucidate the mechanism causing the observed elevations in sST2, specifically in the vulnerable HD population. Further studies are also needed to validate the association of sST2 and galectin-3 with clinical outcomes.

Conflicts of interest

All authors have no conflicts of interest to declare.

Funding

This study was supported by the Young Investigator Research Grant from the Korean Society of Nephrology in 2018.

Acknowledgments

We appreciate the cooperation of Gachon University Gil Medical Center Biobank for giving us the biospecimens and the data of enrolled patients (No: GBB2014–04).

Authors’ contributions

Conceptualization: JYJ
Data curation: AJK, JYJ, HK
Formal analysis: AJK, JYJ, KPK
Funding acquisition: AJK
Investigation: AJK, HK
Methodology: JYJ
Writing–original draft: AJK, JYJ
Writing–review & editing: AJK, JYJ, HR, JHC, HHL, WC
All authors read and approved the final manuscript.

ORCID

Ae Jin Kim, https://orcid.org/0000-0001-5017-8649
Han Ro, https://orcid.org/0000-0001-7170-0571
Hyunsook Kim, https://orcid.org/0000-0002-0674-2713
Kwang-Pil Ko, https://orcid.org/0000-0002-7788-2887
Jae Hyun Chang, https://orcid.org/0000-0003-3947-0715
Hyun Hee Lee, https://orcid.org/0000-0003-2200-5948
References


Changes in plasma sclerostin level associated with use of a medium cut-off dialyzer in end-stage renal disease

Seon-Ho Ahn¹, Mi Mi Ko², Ju Hung Song¹, Jong Hwan Jung¹

¹Division of Nephrology, Department of Internal Medicine, Wonkwang University Hospital, Wonkwang University School of Medicine Hospital, Iksan, Republic of Korea
²KM Fundamental Research Division, Korea Institute of Oriental Medicine, Daejeon, Republic of Korea

Background: Larger middle molecules are important substances associated with cardiovascular complications in end-stage renal disease. Unfortunately, larger middle molecules are not reliably removed by a high-flux dialyzer. A medium cut-off (MCO) membrane could effectively remove larger middle molecules. This study aimed to identify the long-term effect of the MCO membrane for changes of larger middle molecules.

Methods: Thirty-four patients were prospectively analyzed for 12 months. The enrolled patients were divided into control and MCO groups. We measured the plasma levels of growth differentiation factor 15, sclerostin, and fibroblast growth factor 23 in larger middle molecules and those of biomarkers including small solutes. Single-pool Kt/V (spKt/V) and reduction ratios also were evaluated.

Results: Plasma sclerostin did not increase significantly in patients using the MCO dialyzer (135.3 [–637.7 to 908.3], p = 0.715). And there was a significant difference in change of plasma sclerostin level between the two groups (–1,646.9 [–3,015.2 to –278.7], p = 0.033). Furthermore, a negative association between calcium and sclerostin was not observed in the MCO group (r = –0.142, p = 0.587). Solute clearance of larger middle molecules in the MCO group was significantly higher. Moreover, spKt/V values for patients in the MCO group were significantly increased without albumin loss. Values are presented as mean (95% confidence interval [CI]) or adjusted mean (95% CI).

Conclusion: The MCO dialyzer can increase dialytic adequacy and suppress the increase in plasma sclerostin level without significant albumin loss in patients with end-stage renal disease.

Keywords: Dialysis, Membranes, Molecular weight, Renal insufficiency

Introduction

Uremic toxins with size greater than 500 Da or less than 60 kDa are classified as middle molecules. β2-Microglobulin (β2MG), with a molecular weight of approximately 11 kDa, is a surrogate marker for clearance of middle molecules in patients with end-stage renal disease (ESRD) [1,2]. Middle molecules are associated with development of uremic
symptoms and contribute to disease progression of chronic kidney disease (CKD) and development of cardiovascular complications in patients with ESRD. Practically, the strong association between plasma level of β2MG and renal function was confirmed, and strong associations between various larger middle molecules, such as tumor necrosis factor alpha (TNF-α) and interleukins (ILs), and unfavorable outcomes including cardiovascular complications were confirmed [2–4]. Introduction of a high-flux (HF) dialyzer and dialytic modality, such as hemodiafiltration (HDF), prominently increased the clearance of middle molecules such as β2MG. However, larger middle molecules with molecular weights greater than that of β2MG could not be easily removed through a conventional HF dialyzer or HDF [3]. Although the clinical effect of such molecules on uremic toxicity is not proven, larger middle molecules are important in development of cardiovascular complications, particularly in CKD patients [5,6]. In detail, middle molecules, including larger middle molecules, are associated with various pathological conditions such as endothelial dysfunction, oxidative stress, and inflammation. The probable association between middle molecules and pathological conditions has led to development of the innovative medium cut-off (MCO) membrane [6].

Compared to a conventional HF membrane, the MCO membrane is characterized by larger, more consistent pore size and a narrower inner diameter of hollow fibers. Theoretically, the innovative structure of the MCO membrane can remove larger middle molecules that cannot be easily removed using the HF dialyzer or HDF [6,7]. To date, several clinical studies regarding the MCO membrane have been conducted. However, there are few long-term studies regarding change in plasma levels of larger middle molecules using the MCO membrane. Moreover, most clinical studies have focused on the clinical effects of the MCO membrane for only larger middle molecules, such as proinflammatory cytokines (TNF-α and ILs) and kappa or lambda free light chains (κFLC or λFLC) [6–9]. Additionally, cardiovascular changes in patients with ESRD undergoing maintenance hemodialysis (HD) mainly present with fluid overload, uremic cardiomyopathy, and ischemic heart disease; these clinical changes are associated with secondary hyperparathyroidism, anemia, inter-dialytic weight gain, and uremic toxin accumulation. Generally, cardiovascular complications are common in ESRD, and a strong independent association between CKD and cardiovascular complications has been confirmed [10,11]. Specifically, sclerostin is secreted by osteocyte and reduces differentiation and activity of osteoblasts, and its presence is associated with cardiovascular calcifications regardless of CKD existence [12–14]. In addition, sclerostin level in CKD patients with vascular calcifications is higher than in patients with only vascular calcifications [15,16]. However, the function of the sclerostin association with vascular calcification remains unclear [17]. In this regard, it is clinically important to assess changes in plasma sclerostin level and associations between sclerostin and other parameters after long-term use of the MCO dialyzer in HD patients. And, the more definite function of the sclerostin associated with cardiovascular complications including vascular calcification in HD patients can suggest. Other than sclerostin, larger middle molecules such as growth differentiation factor 15 (GDF15, 16.7 kDa), leptin (16 kDa), and fibroblast growth factor 23 (FGF23, 22.5 kDa) are well-known independent cardiovascular risk factors in dialytic patients [18–20]. Thus, an analysis to quantify the plasma concentration changes of larger middle molecules, such as sclerostin, GDF15, leptin, and FGF23; small solutes; and various additional parameters in response to long-term application may identify the impact of HD using the MCO dialyzer on cardiovascular complications in dialytic patients.

Methods

Experimental design

This study was a prospective, observational study conducted over 12 months in Wonkwang University Hospital, Iksan, Republic of Korea, to investigate the efficacy of a new dialyzer for larger middle molecules such as GDF15, leptin, sclerostin, FGF23, retinol-binding protein 4 (RBP4), and β2MG in patients with ESRD. The study was conducted with approval of the Institutional Review Board of Wonkwang University Hospital (No. 2019-07-005-002) according to the Declaration of Helsinki guidelines. All participating patients provided written informed consent prior to the beginning of the study. First, the enrolled patients were divided into two groups (the Theranova group [the MCO membrane group] and the control group). Patients in the MCO group met all of the following conditions: sustained HD using the HF
membrane in the past 3 months, underwent maintenance HD 2 or 3 times per week, and 19 to 70 years old without cardiovascular complications including myocardial infarction, heart failure, arrhythmias, angina pectoris, and peripheral arterial diseases within the past 3 months. Additionally, patients in the MCO group met at least one of the following conditions: serum albumin ≥ 3.5 g/dL at baseline; uncontrolled serum phosphorus despite intensive use of phosphate-lowering agents during the past 3 months (serum calcium × phosphate > 55); uncontrolled secondary hyperparathyroidism despite intensive use of vitamin D analogs or calcimimetics (serum parathyroid hormone (PTH) > 300 pg/mL on two consecutive examinations with a 3-month interval while using vitamin D analogs or calcimimetics); and severe pruritus despite intensive medical therapy. Additionally, patients in the control group were randomly selected from patients who met the first three criteria. The exclusion criteria for this study population were CKD patients undergoing HD and who had psychiatric disorder or severe chronic disease such as advanced chronic obstructive pulmonary disease requiring home oxygen, severe heart failure, uncontrolled diabetes, or advanced liver cirrhosis.

**Use of phosphate-lowering agents and PTH-lowering agents**

The enrolled patients received phosphate-lowering agents or PTH-lowering agents according to levels of serum phosphate, calcium, and PTH at a 1-month (serum phosphate and calcium) or 3-month interval (serum PTH). We mainly used medications of calcium acetate (710 mg, tablet), sevelamer carbonate (800 mg, tablet), calcitriol (0.25 μg, capsule), and cinacalcet (25 mg, tablet). We increased dosage or changed medications according to levels of serum phosphate, calcium, and PTH. If the dialytic patients showed hyperphosphatemia (>4.5 mg/dL), we initially prescribed 2 to 3 calcium acetate tablets per day. If serum calcium × phosphate > 55 or hypocalcemia was persistent despite increased dose (up to six tablets per day) of calcium acetate, we administered sevelamer carbonate. Furthermore, when serum PTH level was >300 pg/mL, we prescribed 1 to 2 capsules of calcitriol per day. If serum PTH level remained >300 pg/mL despite use of calcitriol, we added cinacalcet (1 tablet per day) and changed the dosage according to serum calcium and PTH levels at a 3-week interval.

**Dialyzers and techniques**

HD in the control group was performed using the HF membrane (Polyflux 140H; Baxter, Deerfield, IL, USA), whereas HD in the MCO group was performed using the MCO membrane (Theranova 400; Baxter). All enrolled patients underwent HD using the HF membrane (Polyflux 140H) before beginning this study. The manufacturer specifications of the above dialyzers are as follows: Theranova 400 (MCO membrane, polyarylethersulfone-polyvinylpyrrolidone; inner diameter: 180 μm, wall thickness: 35 μm, and effective membrane area: 1.7 m²) and Polyflux 140H (HF membrane, polyarylethersulfone; inner diameter: 200 μm, wall thickness: 50 μm, and effective membrane area: 1.4 m²).

**Measurement of serological biomarkers**

In this study, blood samples were collected at 3-month or 6-month intervals. For measurement of plasma levels of GDF15 (16.7 kDa), leptin (16 kDa), sclerostin (22.5 kDa), FGF23 (22.5 kDa), RBP4 (21 kDa), and β2MG (11 kDa), blood samples of enrolled patients were drawn prior to each dialysis session at 6-month intervals, centrifuged according to standard guidelines, and stored at –80°C until final analysis. Other serological markers including hemoglobin (Hb), total protein, albumin, calcium, phosphate, C-reactive protein (CRP, 23 kDa), and PTH were measured by standard laboratory techniques prior to dialysis at 3-month intervals. Moreover, blood samples were drawn just before and after the midweek dialysis session at 12 months to evaluate the reduction ratio (RR) per dialytic session for the biomarkers GDF15, leptin, sclerostin, FGF23, RBP4, β2MG, calcium, phosphate, and CRP. Furthermore, the blood samples were centrifuged according to standard guidelines and stored at –80°C until their final analysis. The plasma levels of GDF15, leptin, sclerostin, FGF23, RBP4, β2MG, calcium, phosphate, and CRP were measured by the Luminex 200 System (Luminex, Austin, TX, USA) using the Human Magnetic Luminex Assay Kit (R&D Systems, Minneapolis, MN, USA).
Calculation of reduction ratios

We collected blood samples prior to and after one HD session 12 months after application of MCO or HF dialyzer to calculate the RR of several biomarkers. The RRs of small molecules and middle molecules including larger middle molecules were calculated using the following formula:

\[
RR(\%) = \{1 - (C_{\text{post}}/C_{\text{pre}})\} \times 100,
\]

where the predialysis concentration \( C_{\text{pre}} \) and postdialysis concentration \( C_{\text{post}} \) are measured plasma concentrations of the small and middle molecules prior to and after one HD session, respectively. Specifically, to compensate the hemoconcentration after one session of dialysis, the values of \( C_{\text{post}} \) for all molecules were corrected using a single-compartment kinetic model using the following formula:

\[
\text{corrected } C_{\text{post}} = C_{\text{post}} / \{1 + (BW_{\text{pre}} - BW_{\text{post}})/0.2 \times BW_{\text{post}}\},
\]

where \( BW_{\text{pre}} \) and \( BW_{\text{post}} \) are body weight prior to and after one HD session, respectively \[21]\.

Measurement of body composition index and dialysis adequacy

Body composition monitoring in dialytic patients was performed using multi-frequency electrical bio-impedance (Body Composition Monitor, Fresenius Medical Care, Bad Homburg, Germany). The lean tissue index (LTI), fat tissue index (FTI), and relative overhydration (OH\%) were measured at 3-month intervals prior to dialysis sessions for all enrolled patients. The values of single-pool Kt/V (spKt/V) were calculated at 3-month intervals to determine dialysis adequacy. The spKt/V values were calculated using the following formula, which is described and modified by Daugirdas:

\[
\text{spKt/V} = -\ln (R - 0.008 \times t) + (4 - 3.5 \times R) \times UF/W,
\]

where \( t \) is the session length (in hours), \( R \) is the ratio of postdialysis to predialysis serum urea nitrogen, \( UF \) is the volume of fluid removed during dialysis (in liters), \( V \) is the postdialysis urea distribution volume (in liters), and \( W \) is the postdialysis body weight \[22]\.

Calculations of normalized protein catabolic rate

We calculated the normalized protein catabolic rate (nPCR) in all patients at 3, 6, 9, and 12 months after dialysis. The nPCR values are presented as grams of protein per kilogram of body weight per day (g/kg per day) and estimated using the following formula:

\[
nPCR = (0.0136 \times \text{Kt/V} \times (\text{[pre-blood urea nitrogen (BUN) + post-BUN]/2})) + 0.251
\]

(BUN, midweek averaged BUN) \[23]\]. Generally, the nPCR is used as a method to evaluate protein intake in dialytic patients \[24,25]\. The levels of serum albumin and LTI can be influenced by daily protein intake and nutritional status, particularly in dialytic patients. Thus, we calculated the nPCR at 3, 6, 9, and 12 months to perform precise evaluation of the effect of the MCO membrane on serum albumin loss or change in LTI value.

Statistical analysis

The level of significance was set to 0.05, and two-tailed comparisons were performed. The differences in baseline characteristics between the two groups were evaluated using independent two-sample t tests or Wilcoxon rank sum tests for continuous variables and chi-square tests or Fisher exact tests for categorical variables. Analysis of covariance was employed to evaluate the differences in outcome measures between the groups. Paired-sample t tests or Wilcoxon signed-rank tests were conducted to analyze changes in outcome within each group at each visit compared to baseline. Additionally, we performed Pearson correlation analysis to identify the association between changes of large middle molecules and changes of other molecules or index. Fisher exact tests were used for a comparative analysis of incidence of cardiovascular adverse events and mortality during the study period between the two groups. Statistical analyses were performed using R statistical software version 3.5.2 (R Foundation for Statistical Computing, Vienna, Austria; http://www.r-project.org).

Results

Characteristics at baseline

A total of 34 patients was divided into two groups in this study: the control group comprising 18 patients who underwent maintenance dialysis using the HF dialyzer and the MCO group comprising 16 patients who underwent maintenance dialysis using the MCO dialyzer. Three patients in the MCO group initially showed clinical features of tertiary hyperparathyroidism. This is possibly because patients who had poorly controlled serum phosphorus or secondary hyperparathyroidism were categorized into the
MCO group at initial enrollment. We performed basal and follow-up analyses for several biomarkers in 16 patients who did not show tertiary hyperparathyroidism. The baseline characteristics of the 34 patients are shown in Table 1. The mean ± standard deviation (SD) age of patients in the MCO group was 47.88 ± 12.03 years, significantly lower than that of the control group. The values of serum albumin and phosphorus in the MCO group also were significantly higher than those of the control group (serum phosphate: 4.82 ± 1.46 vs. 6.31 ± 2.20, p = 0.030 and serum albumin: 3.80 ± 0.22 vs. 4.07 ± 0.28, p = 0.004). The values of OH% in the MCO group were significantly lower than those of the control group.

### Table 1. Baseline characteristics of all enrolled patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Control group</th>
<th>MCO group</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>18</td>
<td>16</td>
<td>-</td>
</tr>
<tr>
<td>Sex, male:female</td>
<td>13:5</td>
<td>9:7</td>
<td>0.180</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>55.00 ± 7.57</td>
<td>47.88 ± 12.03</td>
<td>0.043*</td>
</tr>
<tr>
<td>HD duration (mo)</td>
<td>35.00 (12.00–66.25)</td>
<td>36.00 (27.00–65.50)</td>
<td>0.557*</td>
</tr>
<tr>
<td>Frequency/wk</td>
<td>2</td>
<td>1 (5.6)</td>
<td>0.999b</td>
</tr>
<tr>
<td>Hypertension</td>
<td>17 (94.4)</td>
<td>14 (87.5)</td>
<td>0.591b</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>13 (72.2)</td>
<td>9 (56.3)</td>
<td>0.331</td>
</tr>
<tr>
<td>Cv Cx</td>
<td>4 (22.2)</td>
<td>3 (18.8)</td>
<td>&gt;0.999b</td>
</tr>
<tr>
<td>Cause</td>
<td>DMN</td>
<td>13</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>HN</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>CGN</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>PCKD</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Lab parameter</td>
<td>PTH (pg/mL)</td>
<td>120.80 (68.46–255.30)</td>
<td>153.45 (102.20–317.95)</td>
</tr>
<tr>
<td></td>
<td>CRP (mg/L)</td>
<td>2.03 (0.87–3.57)</td>
<td>1.22 (0.64–10.28)</td>
</tr>
<tr>
<td></td>
<td>Albumin (g/dL)</td>
<td>3.80 ± 0.22</td>
<td>4.07 ± 0.28</td>
</tr>
<tr>
<td></td>
<td>Total protein (g/dL)</td>
<td>6.51 ± 0.44</td>
<td>6.80 ± 0.42</td>
</tr>
<tr>
<td></td>
<td>Hemoglobin (g/dL)</td>
<td>10.31 ± 0.83</td>
<td>10.94 ± 1.73</td>
</tr>
<tr>
<td></td>
<td>Calcium (mg/dL)</td>
<td>9.22 ± 0.64</td>
<td>9.21 ± 0.64</td>
</tr>
<tr>
<td></td>
<td>Phosphate (mg/dL)</td>
<td>4.82 ± 1.46</td>
<td>6.31 ± 2.20</td>
</tr>
<tr>
<td></td>
<td>spKt/V</td>
<td>1.46 ± 0.18</td>
<td>1.47 ± 0.27</td>
</tr>
<tr>
<td></td>
<td>FTT (kg/m^2)</td>
<td>9.14 ± 4.75</td>
<td>9.92 ± 3.48</td>
</tr>
<tr>
<td></td>
<td>LTI (kg/m^2)</td>
<td>14.05 ± 2.47</td>
<td>14.56 ± 2.78</td>
</tr>
<tr>
<td></td>
<td>OH (%ECW)</td>
<td>17.63 ± 9.21</td>
<td>10.26 ± 11.22</td>
</tr>
<tr>
<td></td>
<td>GDF15 (pg/mL)</td>
<td>8,043.43 ± 3,491.54</td>
<td>5,245.67 ± 1,426.06</td>
</tr>
<tr>
<td></td>
<td>Leptin (pg/mL)</td>
<td>21,172.57 ± 25,480.09</td>
<td>18,146.72 ± 28,050.34</td>
</tr>
<tr>
<td></td>
<td>Sclerostin (pg/mL)</td>
<td>9,606.6 ± 2,998.6</td>
<td>8,227.2 ± 3,082.9</td>
</tr>
<tr>
<td></td>
<td>FGF23 (pg/mL)</td>
<td>597.40 ± 405.35</td>
<td>1,294.05 ± 906.97</td>
</tr>
<tr>
<td></td>
<td>RBP4 (ng/mL)</td>
<td>66,522.00 ± 10,296.59</td>
<td>63,412.12 ± 13,115.55</td>
</tr>
<tr>
<td></td>
<td>β2MG (ng/mL)</td>
<td>75,787.14 ± 32,591.76</td>
<td>97,553.53 ± 70,029.65</td>
</tr>
</tbody>
</table>

Data are expressed as number only, mean ± standard deviation, median (interquartile range), or number (%). HD, hemodialysis; CGN, chronic glomerulonephropathy; CRP, C-reactive protein; Cv Cx, cardiovascular complications; DMN, diabetic nephropathy; ECW, extracellular water; FGF23, fibroblast growth factor 23; FTT, fat tissue index; GDF15, growth differentiation factor 15; HN, hypertensive nephropathy; LTI, lean tissue index; MCO, medium cut-off; PCKD, polycystic kidney disease; PTH, parathyroid hormone; RBP4, retinol-binding protein 4; spKt/V, single-pool Kt/V; β2MG, beta-2 microglobulin.

*Statistical significant (p < 0.05).
group (10.26 ± 11.22 vs. 17.63 ± 9.21, p = 0.030). Males were predominant in both groups. HD vintage, dialytic frequency, prevalence of diabetes mellitus, and hypertension did not show a significant difference between the two groups. Moreover, body composition indexes of FTI, LTI, Hb, total protein, spKt/V, CRP, and PTH levels did not differ between the two groups. The plasma levels of larger middle molecules and β2MG at baseline were not significantly different between the two groups (Table 1).

Changes of several biomarkers including small solutes and serum albumin during 12-month treatments

Values are presented as mean changes [95% confidence intervals] and p-values, if otherwise specified. There were no significant changes in serological biomarkers such as Hb and serum phosphorus throughout 12 months of dialysis in both groups. However, total calcium level showed significant change during 12 months of dialysis in the control and MCO groups (−0.547 [−0.854 to −0.241], p = 0.001 vs. −0.594 [−0.929 to −0.258], p = 0.002). Serum PTH level did not show significant change during 12 months of dialysis in the MCO group compared to the control group (control group: 124.428 [6.765 to 242.093], p = 0.001 vs. MCO group: 163.216 [33.050 to 359.481], p = 0.097, respectively). Moreover, the MCO group showed a significant change in total protein during 12 months of dialysis (control group vs. MCO group: −0.111 [−0.297 to 0.077], p = 0.231 vs. −0.288 [−0.506 to −0.069], p = 0.013). The LTI values in both groups showed decreasing tendency, but there was no statistical significance (control group vs. MCO group: −0.650 [−1.360 to 0.060], p = 0.07 vs. −0.744 [−1.492 to 0.005], p = 0.066) (Table 2, Fig. 1). In addition, there were non-significant differences in nPCR values (mean ± SD) at 3, 6, 9, and 12 months of dialysis, associated with serum albumin, nutritional status, or daily protein intake in dialytic patients, between control and MCO groups (3 months: 1.164 ± 0.148 g/kg/day vs. 1.258 ± 0.273 g/kg/day, p = 0.233; 6 months: 1.204 ± 0.185 g/kg/day vs. 1.231 ± 0.296 g/kg/day, p = 0.750; 9 months: 1.175 ± 0.195 g/kg/day vs. 1.185 ± 0.203 g/kg/day, p = 0.889; 12 months: 1.195 ± 0.214 g/kg/day vs. 1.221 ± 0.272 g/kg/day, p = 0.758) (Fig. 2) [24]. Moreover, compared to the changes of total protein levels, serum albumin level in the MCO group did not show a significant decreasing tendency during 12 months of treatment (−0.138 [−0.295 to 0.002], p = 0.083) (Table 2). Additionally,
<table>
<thead>
<tr>
<th>Variable</th>
<th>Control group</th>
<th>MCO group</th>
<th>p-value within control</th>
<th>p-value within MCO</th>
<th>Adjusted mean difference between the groups (95% CI)</th>
<th>p-value between groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albumin (g/dL)</td>
<td>3</td>
<td>-0.090 (-0.248 to 0.069)</td>
<td>-0.313 (-0.431 to -0.194)</td>
<td>0.250</td>
<td>&lt;0.001*</td>
<td>-0.102 (-0.318 to 0.115)</td>
</tr>
<tr>
<td>LTI (kg/m²)</td>
<td>3</td>
<td>-0.032 (-0.590 0.527)</td>
<td>-0.475 (-1.317 to 0.367)</td>
<td>0.907</td>
<td>0.248</td>
<td>-0.162 (-1.134 to 0.810)</td>
</tr>
<tr>
<td>FTI (kg/m²)</td>
<td>3</td>
<td>38.316 (-41.659 to 118.291)</td>
<td>0.294 (-0.525 to 1.112)</td>
<td>0.334</td>
<td>0.456</td>
<td>-39.005 (-135.068 to 75.057)</td>
</tr>
<tr>
<td>OH (%ECW)</td>
<td>3</td>
<td>1.668 (-0.788 to 4.125)</td>
<td>1.319 (-3.362 to 5.999)</td>
<td>0.171</td>
<td>0.557</td>
<td>-2.424 (-7.076 to 2.229)</td>
</tr>
<tr>
<td>spKt/V</td>
<td>3</td>
<td>0.022 (-0.057 to 0.102)</td>
<td>0.092 (0.001 to 0.183)</td>
<td>0.567</td>
<td>0.048*</td>
<td>0.022 (-0.097 to 0.140)</td>
</tr>
<tr>
<td>PTH (pg/mL)</td>
<td>3</td>
<td>36.647 (-11.606 to 84.901)</td>
<td>102.893 (-17.732 to 223.519)</td>
<td>0.016</td>
<td>0.039</td>
<td>166.153 (84.901)</td>
</tr>
<tr>
<td>CRP (mg/L)</td>
<td>3</td>
<td>-1.479 (-2.872 to 0.086)</td>
<td>1.503 (-4.874 to 7.880)</td>
<td>0.039</td>
<td>0.569</td>
<td>3.530 (-2.683 to 9.744)</td>
</tr>
</tbody>
</table>

CI, confidence interval; CRP, Creactive protein; ECW, extracellular water; FTI, fat tissue index; LTI, lean tissue index; MCO, medium cut-off; OH, overhydration; PTH, parathyroid hormone; spKt/V, single-pool Kt/V.

*Paired t test, Wilcoxon signed-rank test. **Adjustment for mean difference between the groups (MCO vs. control). Analyis of covariance (adjusted by baseline value and age). Statistical significant (p < 0.05).
spKt/V values increased during the 12-month dialysis period in the MCO group only (control group vs. MCO group: -0.015 [-0.081 to 0.052], \( p = 0.041 \) (Table 2).

**Changes in plasma levels of larger middle molecules and middle molecules during the 12-month treatment period**

This study also showed 12-month outcomes regarding changes of larger middle molecules, such as GDF15, leptin, sclerostin, FGF23, RBP4, and CRP, and the middle molecule, such as \( \beta \)2MG, in patients using the MCO membrane. The plasma levels of RBP4 and \( \beta \)2MG after 12 months significantly decreased in both groups (RBP4: control group, -17,337.286 [-32,002.551 to -2,672.020], \( p = 0.028 \) vs. MCO group, -14,794.667 [-21,606.880 to -7,982.453], \( p = 0.006 \); \( \beta \)2MG: control group, -35,975.571 [-67,157.403 to -4,793.740], \( p = 0.030 \) vs. MCO group, -61,236.067 [-95,247.526 to -27,224.607], \( p = 0.001 \)). However, compared with the control group, change of plasma sclerostin in the MCOa group was not significant (control group: 1,865.143 [875.649 to 2,854.637], \( p = 0.004 \) vs. MCO group: 135.294 [–637.726 to 908.314], \( p = 0.715 \)). There was no a significant increase in levels of plasma sclerostin in the MCO group compared with those in the control group throughout 12 months. There was also a significant difference between the two groups in change of plasma sclerostin over 12 months (adjusted mean difference between the groups [95% CI], -1,646.916 [-3,015.150 to -278.682], \( p = 0.021 \) (Table 3, Fig. 3). Also, while the control group showed a negative association between changes in total calcium and plasma sclerostin levels, the MCO group did not show this negative association (control group vs. MCO group: \( r = -0.758, p = 0.048 \) vs. MCO group: \( r = -0.142, p = 0.587 \)). Moreover, the changes of other biomarkers, such as serum phosphorus, CRP, albumin, and total protein, did not show a significant association with change of plasma sclerostin level in either group (Table 4).

**Solute clearance of several biomarkers including larger middle molecules during a single dialytic session after 12 months**

We calculated the RR at 12 months after application of MCO or HF dialyzer to identify the removal of several solutes including small molecules and larger middle molecules during a single session of HD. Values are presented as means ± SDs and \( p \)-values. The RR per dialytic session of larger middle molecules except leptin and CRP was significantly higher in the MCO group than in the control group (control group vs. MCO group: GDF15, 35.67 ± 7.03 vs. 62.60 ± 10.47, \( p < 0.001 \); leptin, 36.87 ± 6.43 vs. 35.09 ± 7.40, \( p = 0.588 \); sclerostin, 31.62 ± 6.98 vs. 52.65 ± 9.92, \( p < 0.001 \); FGF23, 18.89 ± 17.34 vs. 47.82 ± 17.72, \( p = 0.005 \); RBP4, 7.17 ± 8.76
Figure 2. The distribution of normalized protein catabolic rates (nPCR) in the groups at 3, 6, 9, and 12 months. MCO, medium cut-off.

vs. 24.40 ± 13.42, p = 0.005; CRP, 7.57 ± 12.66 vs. 5.35 ± 24.67, 
p = 0.729) (Fig. 4). However, the RRs of small or middle 
molecules of serum phosphorus, total calcium, and β2MG 
did not show a significant difference between the two groups 
(control group vs. MCO group: serum phosphorus, 52.43 ± 
12.95 vs. 53.81 ± 23.05, p = 0.821; total calcium, –22.81 ± 15.70 
vs. –23.95 ± 16.15, p = 0.827; β2MG, 82.73 ± 5.74 vs. 88.01 ± 
12.07, p = 0.286) (Fig. 5). In our study, the solute clearance 
of the MCO dialyzer is superior to that of the HF dialyzer in 
removal of larger middle molecules in dialytic patients.

Discussion

The MCO dialyzer is an emerging technology characterized 
by narrow inner diameters of hollow fibers and large-
sized pores with uniform distribution. These physical 
characteristics resulted in increased internal filtration 
within the membrane. Moreover, advanced sieving profiles 
and increased internal filtration easily enabled convective 
movement of large uremic solutes, even in conventional HD 
that requires no replacement fluids [26]. In most studies, 
the MCO dialyzer has shown excellent solute clearance 
of larger middle molecules in the clinical setting [1,7,27]. 
However, a recent study reported that the plasma levels of κFLC and λFLC during the first 2 weeks after application 
of the MCO dialyzer sharply decreased and remained 
low for another 2 weeks [28]. Factors such as increased 
production rate of uremic toxins, limited time for removal 
of uremic toxins, and redistribution from sequestrated 
tissue during the inter-dialytic period would halve the effect 
of high RRs when using the MCO dialyzer [6,9,29]. In our 
study, the plasma levels of β2MG and RBP4 significantly
Table 3. The changes of larger middle molecules and β2MG over 12 months

<table>
<thead>
<tr>
<th>Variable</th>
<th>Time (mo)</th>
<th>Mean change (95% CI)</th>
<th>p-value within control</th>
<th>p-value within MCO</th>
<th>Adjusted mean difference between the groups (95% CI)</th>
<th>p-value between groups</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Control group</td>
<td>MCO group</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GDF15</td>
<td>6–baseline</td>
<td>-956.429 (-3,232.594 to 1,519.736)</td>
<td>254.667 (-3,232.594 to 1,519.736)</td>
<td>0.612</td>
<td>0.508</td>
<td>138.773 (-1,785.977 to 2,063.524)</td>
</tr>
<tr>
<td></td>
<td>12–baseline</td>
<td>-889.286 (-3,222.725 to 1,444.153)</td>
<td>-118.111 (-3,222.725 to 1,444.153)</td>
<td>0.387</td>
<td>0.719</td>
<td>-593.600 (-2,126.963 to 939.764)</td>
</tr>
<tr>
<td></td>
<td>12–6</td>
<td>-32.857 (-1,200.064 to 1,134.350)</td>
<td>-118.111 (-1,200.064 to 1,134.350)</td>
<td>0.947</td>
<td>0.353</td>
<td>-1,063.359 (-2,296.294 to 169.575)</td>
</tr>
<tr>
<td>Leptin</td>
<td>6–baseline</td>
<td>829.714 (-7,823.227 to 9,482.656)</td>
<td>-933.239 (-7,823.227 to 9,482.656)</td>
<td>0.822</td>
<td>0.948</td>
<td>-2,229.025 (-11,295.350 to 6,837.299)</td>
</tr>
<tr>
<td></td>
<td>12–baseline</td>
<td>1,051.286 (-8,557.041 to 10,659.612)</td>
<td>966.063 (-8,557.041 to 10,659.612)</td>
<td>0.798</td>
<td>0.267</td>
<td>-1,144.737 (-14,473.017 to 12,183.543)</td>
</tr>
<tr>
<td></td>
<td>12–6</td>
<td>221.571 (-8,112.530 to 11,955.673)</td>
<td>1,899.303 (-8,112.530 to 11,955.673)</td>
<td>0.965</td>
<td>0.199</td>
<td>562.211 (-10,874.046 to 11,998.468)</td>
</tr>
<tr>
<td>Sclerostin</td>
<td>6–baseline</td>
<td>1,437.1 (795.7 to 2,078.6)</td>
<td>-188.9 (-662.4 to 284.6)</td>
<td>0.018*</td>
<td>0.412</td>
<td>-1,616.7 (-2,477.5 to -755.9)</td>
</tr>
<tr>
<td></td>
<td>12–baseline</td>
<td>1,865.1 (875.7 to 2,854.6)</td>
<td>135.3 (-637.7 to 908.3)</td>
<td>0.004*</td>
<td>0.715</td>
<td>-1,646.9 (-3,015.2 to -278.7)</td>
</tr>
<tr>
<td></td>
<td>12–6</td>
<td>428.0 (-464.7 to 1,320.7)</td>
<td>282.3 (-247.7 to 812.4)</td>
<td>0.285</td>
<td>0.276</td>
<td>-35.9 (-1,098.2 to 1,026.3)</td>
</tr>
<tr>
<td>FGF23</td>
<td>6–baseline</td>
<td>-73.721 (-336.639 to 189.196)</td>
<td>14.018 (-189.842 to 217.879)</td>
<td>0.518</td>
<td>0.723</td>
<td>66.108 (-321.391 to 453.607)</td>
</tr>
<tr>
<td></td>
<td>12–baseline</td>
<td>-145.654 (-174.767 to 466.075)</td>
<td>71.120 (-202.381 to 344.621)</td>
<td>0.309</td>
<td>0.590</td>
<td>25.928 (-474.577 to 526.433)</td>
</tr>
<tr>
<td></td>
<td>12–6</td>
<td>219.376 (-48.828 to 487.580)</td>
<td>57.102 (-237.351 to 351.554)</td>
<td>0.092</td>
<td>0.688</td>
<td>25.075 (-466.596 to 516.745)</td>
</tr>
<tr>
<td>RBP4</td>
<td>6–baseline</td>
<td>-583.714 (-12,401.678 to 11,234.249)</td>
<td>-2,303.688 (-12,401.678 to 11,234.249)</td>
<td>0.908</td>
<td>0.419</td>
<td>-2,229.925 (-12,792.592 to 8,332.742)</td>
</tr>
<tr>
<td></td>
<td>12–baseline</td>
<td>-17,337.286 (-32,002.551 to -2,672.020)</td>
<td>-14,794.667 (-32,002.551 to -2,672.020)</td>
<td>0.028*</td>
<td>0.006**</td>
<td>538.200 (-10,878.671 to 11,955.072)</td>
</tr>
<tr>
<td></td>
<td>12–6</td>
<td>-16,753.571 (-27,344.178 to -6,162.965)</td>
<td>-12,334.400 (-27,344.178 to -6,162.965)</td>
<td>0.008*</td>
<td>0.012*</td>
<td>597.652 (-11,102.058 to 12,297.362)</td>
</tr>
<tr>
<td>β2MG</td>
<td>6–baseline</td>
<td>-7,101.714 (-23,190.394 to 8,986.965)</td>
<td>-3,628.000 (-23,190.394 to 8,986.965)</td>
<td>0.322</td>
<td>0.803</td>
<td>17,504.945 (-15,241.088 to 50,250.979)</td>
</tr>
<tr>
<td></td>
<td>12–baseline</td>
<td>-35,975.571 (-67,157.403 to -4,793.740)</td>
<td>-61,236.067 (-67,157.403 to -4,793.740)</td>
<td>0.030*</td>
<td>0.001**</td>
<td>1,085.527 (-13,305.429 to 15,476.482)</td>
</tr>
<tr>
<td></td>
<td>12–6</td>
<td>-28,873.857 (-605,21.140 to 2,773.426)</td>
<td>-51,036.667 (-605,21.140 to 2,773.426)</td>
<td>0.067</td>
<td>&lt;0.001*</td>
<td>1,083.954 (-14,389.169 to 16,557.078)</td>
</tr>
</tbody>
</table>

CI, confidence interval; GDF15, growth differentiation factor 15; FGF23, fibroblast growth factor 23; MCO, medium cut-off; RBP4, retinol-binding protein 4; β2MG, beta-2 microglobulin.

*Paired t test, Wilcoxon signed-rank test. *Adjustment for mean difference between the groups (MCO vs. control). **Analysis of covariance (adjusted by baseline value and age).

*Statistical significant (p < 0.05).
decreased in both groups, but the plasma levels of other larger middle molecules did not. Plasma sclerostin, GDF15, and FGF23, compared to plasma β2MG and RBP4, are significantly associated with parameters such as serum phosphorus, calcium, PTH, and vitamin D. Thus, we should consider the relationships between various parameters, such as phosphorus, calcium, PTH, and vitamin D, and larger middle molecules including sclerostin to identify their changes. The association between the above solutes would influence predialytic concentration over a relatively long period. Generally, serum sclerostin level is inversely associated with serum PTH level, and intermittent infusion of PTH can inhibit the production of sclerostin in osteocytes. Moreover, persistently increased sclerostin level can lead to a low-turnover bone disorder in HD patients. Thus, a high level of sclerostin may be a good biomarker for mineral bone

Figure 3. The changes in predialytic levels of larger middle molecules over 12 months. Data are presented as geometric mean, and error bars represent 95% confidence interval. Each graph presents growth differentiation factor 15 (GDF15), leptin, sclerostin, fibroblast growth factor 23 (FGF23), beta-2 microglobulin (β2MG), and retinol-binding protein 4 (RBP4), respectively. MCO, medium cut-off.
*p < 0.05; **p < 0.01; ***p < 0.05 of adjusted mean difference between control and MCO groups.
**Table 4.** The correlation between changes of larger middle molecules and other molecules in the two groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>ΔSclerostin</th>
<th>Total</th>
<th>Control group</th>
<th>MCO group</th>
</tr>
</thead>
<tbody>
<tr>
<td>ΔP</td>
<td>r</td>
<td>0.064</td>
<td>0.143</td>
<td>-0.229</td>
</tr>
<tr>
<td></td>
<td>p</td>
<td>0.767</td>
<td>0.760</td>
<td>0.376</td>
</tr>
<tr>
<td></td>
<td>n</td>
<td>34</td>
<td>18</td>
<td>16</td>
</tr>
<tr>
<td>ΔTotal protein</td>
<td>r</td>
<td>-0.006</td>
<td>0.242</td>
<td>-0.107</td>
</tr>
<tr>
<td></td>
<td>p</td>
<td>0.978</td>
<td>0.601</td>
<td>0.682</td>
</tr>
<tr>
<td></td>
<td>n</td>
<td>34</td>
<td>18</td>
<td>16</td>
</tr>
<tr>
<td>ΔAlbumin</td>
<td>r</td>
<td>0.109</td>
<td>-0.424</td>
<td>-0.039</td>
</tr>
<tr>
<td></td>
<td>p</td>
<td>0.613</td>
<td>0.343</td>
<td>0.883</td>
</tr>
<tr>
<td></td>
<td>n</td>
<td>34</td>
<td>18</td>
<td>16</td>
</tr>
<tr>
<td>ΔCa</td>
<td>r</td>
<td>0.074</td>
<td>-0.758*</td>
<td>-0.142</td>
</tr>
<tr>
<td></td>
<td>p</td>
<td>0.730</td>
<td>0.048*</td>
<td>0.587</td>
</tr>
<tr>
<td></td>
<td>n</td>
<td>34</td>
<td>18</td>
<td>16</td>
</tr>
<tr>
<td>ΔCRP</td>
<td>r</td>
<td>-0.177</td>
<td>-0.234</td>
<td>-0.208</td>
</tr>
<tr>
<td></td>
<td>p</td>
<td>0.4080</td>
<td>0.613</td>
<td>0.423</td>
</tr>
<tr>
<td></td>
<td>n</td>
<td>34</td>
<td>18</td>
<td>16</td>
</tr>
</tbody>
</table>

Ca, serum total calcium; CRP, C-reactive protein; MCO, medium cut-off; n, numbers in each group; P, serum phosphorus; p, p-value; r, Pearson correlation coefficient; Δ, change of parameter between 12 months and baseline.

*Statistical significant (p < 0.05).

Ahn, et al. Biomarkers and a medium cut-off membrane disorder in HD patients [30,31]. In the present study, plasma sclerostin level tended to increase in the control group but not in the MCO group. Furthermore, there was no significant association between changes in total calcium and sclerostin levels in the MCO group compared to the control group. Although the association between the other parameters and sclerostin level in HD patients is unclear [15,30], the present results suggest that the long-term use of the MCO dialyzer can suppress the characteristic increase of plasma sclerostin level in HD patients. In present study, MCO dialyzer compared to HF dialyzer showed a significantly higher RR for plasma sclerostin. Although plasma sclerostin level may rebound for interdialytic period, a repetitive application of MCO dialyzer during relatively long period may temporarily reduce the increase of predialytic sclerostin level regardless of the changes in serological parameters. If several cardiac markers, including parameters related to vascular calcification and echocardiographic parameters, were simultaneously analyzed in present study, the observed significant change in predialytic sclerostin level

**Figure 4.** The reduction ratios (RR) of larger middle molecules per session of hemodialysis at 12 months. In the box-and-whisker plots, the whiskers represent the range, and boxes represent median 25th and 75th percentile values. Connecting lines represent significant differences between mean values of the control (C) and MCO (T) groups.

CRP, C-reactive protein; GDF15, growth differentiation factor 15; FGF23, fibroblast growth factor 23; MCO, medium cut-off; RBP4, retinol-binding protein 4.

* **p < 0.001, *p < 0.01.
after application of MCO membrane during a relatively long period could provide more clinical significance.

Theoretically, one of the important concerns surrounding long-term use of the MCO dialyzer is the modest reduction of serum albumin level. However, there was no reduction in serum albumin level during use of the MCO dialyzer over 12 months in this study. The decreasing tendency of serum albumin was no longer observed after 9 months in the MCO group (Fig. 1). Compared to serum albumin level, total protein levels tended to decrease in the MCO group, but nPCR values, which indicate nutritional status or daily protein intake, in HD patients at 3, 6, 9, and 12 months did not show a significant difference between the two groups. In addition, LTI level after 12 months did not decrease significantly in the MCO group. Although additional long-term studies with larger scale are required, these results suggest that use of the MCO dialyzer is not inferior to that of the HF dialyzer in terms of albumin loss over a 12-month period. Interestingly, our results also showed that dialysis adequacy (spKt/V) was significantly higher in the MCO group than in the control group. In our opinion, the increased dialysis adequacy after 12 months in the MCO group may result from the impact of increased internal filtration in the MCO membrane and larger dialyzer surface area (Polyflux 140H, 1.4 m² vs. Theranova 400, 1.7 m²). These results suggest that clinical use of the MCO membrane is not inferior to that of the HF membrane, particularly in terms of changes of serum albumin, nPCR, LTI values, small solutes, and spKt/V over a 12-month period.

In addition, there were no deaths in either group during the study, and the incidence of cardiovascular adverse events did not show significant difference between the two groups. To be specific, acute myocardial infarction developed 6 months after enrollment for one patient in the MCO group, and nonfatal stroke developed 12 months after enrollment for one patient in the control group.

This study has several limitations. First, we utilized frozen, stored blood samples for this study; indicating use of degraded samples. We did not consider residual renal function in enrolled patients. Moreover, this study has a small sample size. Additionally, because significant albumin loss due to chronic use of the MCO membrane has been reported, younger and relatively healthier patients were primarily enrolled into the MCO group at baseline [1,32]. Thus, baseline serum phosphorus and albumin levels were higher and OH% values were lower in the MCO group. This study is not a randomized controlled trial but an observational cohort study. Categorization of patients who showed uncontrolled hyperphosphatemia, secondary hyperparathyroidism, and well-nutritional status into the MCO group could lead to selection bias. Furthermore, quantification of mortality and morbidity differences between two groups was difficult due to the short study duration and small sample size. Despite these, our study has several strengths. First, only one type of dialytic machine was used in both groups. Second, changes in larger middle molecules associated with cardiovascular risk factors or vascular calcification were analyzed during a relatively long-term period (12 months). Third, we analyzed other biomarkers such as dialysis adequacy (spKt/V) and body composition index with short-term intervals during the 12-month period.

Conclusively, this study showed the 12-month outcome in changes of larger middle molecules in HD patients using the MCO dialyzer. Among these molecules, plasma sclerostin did not increase significantly in the MCO group. The RRs...
of larger middle molecules by a single dialytic session were prominently higher in the MCO group. In addition, long-term use, over 12 months, of the MCO dialyzer increased spKt/V without modest albumin loss or significant adverse effect. Therefore, if longer-term and more frequent use of the MCO dialyzer is possible, HD using the MCO dialyzer may be an option for reduction of larger middle molecules.

Conflicts of interest

All authors have no conflicts of interest to declare.

Funding

This study was supported by the Young Investigator Research Grant from the Korean Nephrology Research Foundation (2019).

Acknowledgments

The bio-specimens and data used in this study were provided by the Biobank of Wonkwang University Hospital, a member of the Korea Biobank Network, which is supported by the Ministry of Health, Welfare, and Family Affairs. All samples derived from the Korea Biobank Network were obtained with informed consent under Institutional Review Board-approved protocols.

Authors’ contributions

Conceptualization: JHJ, SHA
Data curation: JHJ
Formal analysis: JHJ, MMK, SHA
Funding acquisition: JHJ
Investigation: JHJ, SHA, JHS
Methodology: JHJ, SHA
Project administration: JHJ, SHA, JHS
Visualization: JHJ, MMK, SHA
Writing-original draft: JHJ, SHA
Writing-review & editing: JHJ, SHA, MMK, JHS
All authors read and approved the final manuscript.

ORCID

Seon-Ho Ahn, https://orcid.org/0000-0002-3482-1056
Mi Mi Ko, https://orcid.org/0000-0002-5758-4655
Ju Hung Song, https://orcid.org/0000-0002-8149-2195
Jong Hwan Jung, https://orcid.org/0000-0002-1252-9679

References


Changes in extracellular water and left ventricular mass in peritoneal dialysis patients

Theerasak Tangwonglert¹, Andrew Davenport²

¹Nephrology Division, Department of Medicine, Phramongkutklao Hospital, Bangkok, Thailand
²UCL Department of Nephrology, Royal Free Hospital, University College London Medical School, London, United Kingdom

**Background:** Increasing number of peritoneal dialysis (PD) patients are reported to have increased left ventricular hypertrophy (LVH), a major risk factor for cardiovascular mortality. We wished to determine which factors were most associated with changes in left ventricular mass index (LVMI).

**Methods:** We reviewed patient and treatment factors in prevalent PD patients with repeat echocardiograms 18 to 24 months apart, with corresponding bioimpedance measurements of extracellular water (ECW) and serum N-terminal pro-brain natriuretic peptide (NT-proBNP).

**Results:** We studied 60 patients (34 males, 35 with diabetes) who were treated with PD for a median of 14 months (2.5–26.3 months). All but one had LVH; on repeat echocardiography, there was no overall change in LVMI (106 [84–127] g/m² vs. 108 [91–122] g/m²) despite a loss of residual renal function. Left ventricular mass increased in 34 (56.7%), and the percent change in LVMI was associated with percent change in NT-proBNP (r = 0.51, p = 0.017) and ECW/height (r = 0.32, p = 0.029), but not with ECW/total body water or changes in systolic or mean arterial pressure, urine output, 24-hour PD ultrafiltration, or net sodium balance. Only ECW/height remained independently associated with the percent change in LVMI in a multivariable model (odds ratio, 1.25; 95% confidence interval, 1.08–1.36; p = 0.007).

**Conclusion:** In this observational longitudinal report, a reduction in ECW/height was associated with regression of LVMI, whereas an increased ECW/height was associated with increased LVMI. As there was no corresponding association with systolic or mean arterial pressure, then volume expansion would appear to be a more significant factor in determining LVH than blood pressure.

**Keywords:** Hypertension, Hypertrophy, N-terminal pro-brain natriuretic peptide (1-76), Peritoneal dialysis; Water

**Introduction**

Although peritoneal dialysis (PD) does not lead to the repeated weekly volume and blood pressure changes associated with hemodialysis, cardiovascular mortality remains the most common cause of death [1]. A number of...
studies have observed that the majority of patients starting both hemodialysis and PD have left ventricular hypertrophy (LVH) \[2,3\]. Patients with chronic kidney disease have a number of potential risk factors for LVH, as they are more likely to have hypertension, extracellular water (ECW) expansion, and anemia.

Previous observational cross-sectional studies have reported an association between LVH and increased mortality among PD patients \[4\]. Although many studies have reported on the results of a single echocardiogram in PD patients, very few studies have reviewed serial echocardiograms. Serial echocardiogram studies have reported varying results, with progression of LVH in one study of 12 patients, no change in a Chinese study of 40 patients, and a reduction in left ventricular mass (LVM) in a larger Korean study \[3,5,6\]. These studies were unable to address whether changes in LVM were related to changes in ECW, as LVM was reported to decrease even in patients who were persistently over-hydrated \[6\].

To determine whether LVM changes with ECW or other factors, we reviewed the results of prevalent PD patients with repeat echocardiograms and corresponding measurements of ECW, dialysis adequacy, and residual renal function.

**Methods**

We retrospectively reviewed data on adult PD patients who had visited a predialysis specialized chronic kidney disease clinic and then electively started PD and who had repeat outpatient echocardiograms 18 to 24 months after their first two-dimensional M mode transthoracic echocardiogram (Philips IE33; Philips Medical Systems, Eindhoven, the Netherlands). No patients had acute heart failure, acute coronary syndrome, or other acute cardiologic dysfunction at the time of imaging. Images were taken from the parasternal view with patients in the left decubitus position by trained and certified cardiology echocardiography technicians. LVM was calculated from the left ventricular posterior wall thickness, interventricular septal thickness, and left ventricular end-diastolic diameter using the Devereux formula \[7\]. To compare patients, LVH was adjusted for body size and then categorized by an LVM index (LVMI) of >52 g/m\(^2\) for males and >47 g/m\(^2\) for females, as recommended by the 2013 guidelines of the European Society of Hypertension (ESH) and the European Society of Cardiology (ESC) \[8\]. Using the American Society of Echocardiography (ASE) recommendations to determine relative wall thickness (RWT), we then calculated the ratio of the intraventricular and posterior wall thickness to the left ventricular end-diastolic diameter, where ratios of ≤0.42 and >0.42 describe eccentric and concentric LVH, respectively \[9\].

PD adequacy was calculated using standard methods from 24-hour urinary collections and samples taken from all spent dialysate bags and normalized protein nitrogen appearance was estimated using standard equations \[10–12\]. Blood glucose, glycated hemoglobin, C-reactive protein (CRP), N-terminal pro-brain natriuretic peptide (NT-proBNP), and dialysate glucose were measured by standard methods (Roche Modular P analyzer; Roche Diagnostics Ltd., Burgess Hill, UK) \[13\]. Peritoneal membrane transport was calculated from a 4-hour peritoneal dialysate dwell and plasma creatinine concentrations using a standard 2.0-L 22.7 g/L glucose peritoneal dialysate (Baxter Health Care, Deerfield, MA, USA), with creatinine measured enzymatically (Roche Modular P analyzer) \[14\]. Patients were assigned as slow, medium, or fast transporter status according to European Dialysis and Transplant Best Practice guidelines \[10\].

To estimate combined peritoneal and urinary sodium losses, we used the inflow and drained volumes recorded by the automated PD (APD) cycler (Baxter Health Care), and measured sodium in the spent dialysate and 24-hour urine. For patients treated by continuous ambulatory PD (CAPD), patients and staff were instructed to allow 15 seconds for the flush-before-fill CAPD technique, and the median volume measured was 90 mL, as such sodium in the spent CAPD dialysates were adjusted from an initial volume of 2.15 L in a fresh 2.0-L dialysate bag \[15\]. The amount of PD sodium removed was calculated as the difference between the amount of sodium instilled into the peritoneal cavity in 24 hours and that measured in the 24-hour drained effluent.

ECW, intracellular (ICW), and total body water (TBW) were measured using multifrequency bioelectrical impedance using a standardized protocol (InBody 720; InBody, Seoul, Korea), with peritoneal dialysate drained out and after voiding \[16,17\]. To make comparisons between patients, ECW was adjusted as ECW/TBW \[18\] and by height \[19\].

The Stoke-Davies grading system was used for patient
comorbidity [20]. Other relevant information, including prescription of antihypertensive medications, was obtained from computerized hospital medical records.

Ethics

Our retrospective audit complied with the United Kingdom National Health Service Health Research Authority guidelines for clinical audit and service development (https://www.hra.nhs.uk) and was registered with the UCL Department of Nephrology Royal Free Hospital. All patient data were anonymized in keeping with the Helsinki accord.

Statistical analysis

Statistical analysis was performed by using D’Agostino Pearson testing for analysis of normality and groups were compared using t tests and Mann-Whitney U tests, chi-square tests, and paired t tests, Wilcoxon rank-sum pair testing with appropriate correction for multiple testing by Bonferroni and Tukey post hoc testing, and for small numbers. We used Spearman univariate correlation and standard statistical programs (IBM SPSS, version 24.0; IBM, Armonk, NY, USA and GraphPad Prism, version 9.0; GraphPad Software, San Diego, USA). A step-backward multivariable logistic regression model was created comparing patients who had an increase in LVM compared to those with a fall in LVM, using all variables with a univariate association of p < 0.1, and were then eliminated if not statistically significant or did not improve the model fit. Data are presented as either the mean ± standard deviation, median (interquartile range), mean with 95% confidence interval of agreement, or as a percentage.

Results

We reviewed the records of 60 prevalent PD patients who had repeat echocardiograms 18 to 24 months apart, 34 (56.7%) were males and 35 (58.3%) had diabetes (Table 1). Nine patients (15.0%) had a prior medical history of an acute coronary syndrome, nine (15.0%) with coronary artery stenting, and four (6.7%) had undergone coronary artery bypass surgery. All male patients (100%) had LVH on both echocardiograms, 98.3% of the female patients had LVH at the time of the first echocardiogram, and 100% of the

<p>| Table 1. Patient demographics at the time of the first and second echocardiogram |</p>
<table>
<thead>
<tr>
<th>Variable</th>
<th>Echocardiogram</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>First</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>65.2 ± 13.9</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>69.8 ± 14.0</td>
</tr>
<tr>
<td>Comorbidity gradea</td>
<td>I (0–II)</td>
</tr>
<tr>
<td>CAPD</td>
<td>22 (36.7)</td>
</tr>
<tr>
<td>APD</td>
<td>7 (11.7)</td>
</tr>
<tr>
<td>CCPD</td>
<td>30 (50.0)</td>
</tr>
<tr>
<td>Using icodextrin</td>
<td>43 (71.7)</td>
</tr>
<tr>
<td>Using 22.7 g/L glucose</td>
<td>31 (51.7)</td>
</tr>
<tr>
<td>Weekly Kt/V</td>
<td></td>
</tr>
<tr>
<td>For urine</td>
<td>0.99 (0.54–0.78)</td>
</tr>
<tr>
<td>For peritoneal dialysis</td>
<td>1.54 (1.38–1.94)</td>
</tr>
<tr>
<td>For total</td>
<td>2.31 (1.75–3.03)</td>
</tr>
<tr>
<td>Peritoneal ultrafiltration (ml/day)</td>
<td>594 (252–881)</td>
</tr>
<tr>
<td>nPNA (g/kg/day)</td>
<td>0.88 (0.75–1.09)</td>
</tr>
<tr>
<td>Sodium balanceb (mmol/day)</td>
<td>–119 (-159 to –68)</td>
</tr>
<tr>
<td>4-hr dialysate/plasma creatinine</td>
<td>0.69 ± 0.15</td>
</tr>
<tr>
<td>LV mass index (kg/m²)</td>
<td>106 (84–127)</td>
</tr>
<tr>
<td>LV ejection fraction (%)</td>
<td>57 (47–59)</td>
</tr>
<tr>
<td>Relative wall thickness ratio</td>
<td>0.48 ± 0.11</td>
</tr>
<tr>
<td>NT-proBNP (pmol/L)</td>
<td>2,216 (732–8,926)</td>
</tr>
<tr>
<td>ECW/TBW</td>
<td>0.395 ± 0.013</td>
</tr>
<tr>
<td>ECW/height (L/m)</td>
<td>8.71 ± 1.66</td>
</tr>
<tr>
<td>Hemoglobin (g/L)</td>
<td>94.2 ± 12.7</td>
</tr>
<tr>
<td>Albumin (g/L)</td>
<td>39.1 ± 3.4</td>
</tr>
<tr>
<td>C-reactive protein (mg/L)</td>
<td>3.0 (1.0–7.5)</td>
</tr>
<tr>
<td>Blood pressure (mmHg)</td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>139.3 ± 28.5</td>
</tr>
<tr>
<td>Diastolic</td>
<td>79.1 ± 16.7</td>
</tr>
<tr>
<td>Antihypertensive medicationc</td>
<td>1 (0–2)</td>
</tr>
</tbody>
</table>

Data are expressed as mean ± standard deviation, median (interquartile range), or number (%).

*APD, automated peritoneal dialysis; CAPD, continuous ambulatory peritoneal dialysis; CCPD, continuous cycling peritoneal dialysis; ECW, extracellular water; LV, left ventricular; nPNA, normalized protein nitrogen appearance; NT-proBNP, N-terminal pro-brain natriuretic peptide; TBW, total body water.

According to Stoke-Davies classification. *Net difference between peritoneal and urinary sodium loss. **Number of different classes of antihypertensive medications.

*p < 0.05, **p < 0.01, and ***p < 0.001 vs. first echocardiogram.
females had LVH on the repeat echocardiogram. Volume overload is thought to be major factor in the development of eccentric LVH, and blood pressure the major factor for concentric hypertrophy. Although there is some debate as to the cut-off defining eccentric and concentric hypertrophy, use of the ASE recommendations revealed that 55.0% of the patients had concentric LVH [9].

Although there was no overall change in LVM or LVMI for the cohort, LVM increased in 34 patients (56.7%) and fell in 26 (43.3%). As such, we compared the characteristics of these two groups (Table 2). The median time between the bioimpedance and the first echocardiogram and was 1 month (1-3 months), and for the second echocardiogram was 2 months (1–2.3 months). There were no differences in age, comorbidity, or months of PD treatment at the time of the initial or follow-up echocardiogram between the groups (increased LVM vs. decreased LVM: acute coronary artery, syndrome 20.6% vs. 6.9%; coronary artery stenting, 17.7% vs. 13.8%; coronary artery bypass grafting, 5.9% vs. 6.9%; all p > 0.05). Left ventricular ejection fractions did not differ, and the percentage of patients with concentric hypertrophy was marginally but not significantly greater for those patients with a fall in LVM (88.5% vs. 73.6%). Similarly, there were no differences in PD adequacy, ultrafiltration, or net peritoneal sodium balance. However, no patients in the group with a fall in LVMI were initially treated by APD. Although ECW/TBW, ECW/height, and NT-proBNP at the time of the first echocardiogram were similar, those patients who had a subsequent decrease in LVMI initially had a greater LVMI (Fig. 1), despite similar clinical blood pressure recordings and prescription of antihypertensive medications. Initially, 18 patients were taking β-blockers, 16 were taking calcium channel blockers/α-blockers, nine were taking renin-angiotensin blockers/receptor blockers, and 41 were taking

### Table 2. Patient demographics and peritoneal dialysis prescriptions according to change in LV mass

<table>
<thead>
<tr>
<th>Variable</th>
<th>Decreased, first Echo</th>
<th>LV mass, second Echo</th>
<th>Increased, first Echo</th>
<th>LV mass, second Echo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>66.0 ± 12.0</td>
<td>68.2 ± 11.9</td>
<td>64.1 ± 15.3</td>
<td>66.0 ± 14.5</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>70.3 ± 12.8</td>
<td>68.0 ± 10.2</td>
<td>69.4 ± 15.0</td>
<td>69.4 ± 15.2</td>
</tr>
<tr>
<td>Peritoneal dialysis (mo)</td>
<td>13.5 (1–24)</td>
<td>30.0 (20–44)</td>
<td>18.0 (2–27)</td>
<td>33.5 (23–52)</td>
</tr>
<tr>
<td>CAPD/APD/CCPD</td>
<td>34.6/0/65.3*</td>
<td>38.2/20.6/38.2</td>
<td>34.6/3.8/61.5</td>
<td>35.3/14.7/50.0</td>
</tr>
<tr>
<td>Weekly Kt/V</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>For urine</td>
<td>0.86 (0.40–1.75)</td>
<td>0.32 (0–1.20)</td>
<td>1.28 (0.95–1.51)</td>
<td>0.23 (0.05–0.86)</td>
</tr>
<tr>
<td>For peritoneal dialysis</td>
<td>1.47 (1.01–1.65)</td>
<td>1.43 (1.21–1.75)</td>
<td>1.28 (0.95–1.51)</td>
<td>1.37 (0.97–1.79)</td>
</tr>
<tr>
<td>Peritoneal ultrafiltration (mL/day)</td>
<td>534 (221–900)</td>
<td>977 (412–1200)</td>
<td>565 (352–866)</td>
<td>722 (546–1384)</td>
</tr>
<tr>
<td>Sodium balance* (mmol/day)</td>
<td>−107 (−160 to −65)</td>
<td>−107 (−175 to −82)</td>
<td>−127 (−155 to −84)</td>
<td>−105 (−154 to −78)</td>
</tr>
<tr>
<td>nPNA (g/kg/day)</td>
<td>0.94 ± 0.28</td>
<td>0.84 ± 0.26</td>
<td>0.95 ± 0.22</td>
<td>0.86 ± 0.19</td>
</tr>
<tr>
<td>4-hr dialysate/plasma creatinine</td>
<td>0.72 ± 0.14</td>
<td>0.68 ± 0.20</td>
<td>0.64 ± 0.14</td>
<td>0.71 ± 0.14</td>
</tr>
<tr>
<td>Albumin (g/L)</td>
<td>37.9 ± 3.4*</td>
<td>36.7 ± 4.0</td>
<td>40.1 ± 3.1</td>
<td>36.9 ± 4.7</td>
</tr>
<tr>
<td>C-reactive protein (mg/L)</td>
<td>4.0 (2.0–12.0)*</td>
<td>6.5 (2.0–11.0)</td>
<td>2.0 (0.5–11.0)</td>
<td>3.5 (2.0–8.0)</td>
</tr>
<tr>
<td>NT-proBNP (pmol/L)</td>
<td>3,814 (1,624–14,470)</td>
<td>2,134 (1,446–7,298)</td>
<td>1,395 (516–6,106)*</td>
<td>7,265 (2,263–22,411)</td>
</tr>
<tr>
<td>ECW/TBW</td>
<td>0.394 ± 0.013</td>
<td>0.397 ± 0.009</td>
<td>0.396 ± 0.013</td>
<td>0.397 ± 0.013</td>
</tr>
<tr>
<td>ECW/height (L/m)</td>
<td>8.7 (7.4–9.3)</td>
<td>7.7 (7.0–8.7)</td>
<td>8.6 (7.4–9.8)</td>
<td>8.2 (7.4–9.1)</td>
</tr>
<tr>
<td>Blood pressure (mmHg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>144 ± 30</td>
<td>141 ± 27</td>
<td>136 ± 28</td>
<td>146 ± 28</td>
</tr>
<tr>
<td>Diastolic</td>
<td>82 ± 19</td>
<td>79 ± 15</td>
<td>77 ± 15</td>
<td>81 ± 17</td>
</tr>
<tr>
<td>Antihypertensive medication*b</td>
<td>1 (0–1)</td>
<td>1 (0–1)</td>
<td>1 (0–2)</td>
<td>1 (0–2)</td>
</tr>
<tr>
<td>LV ejection fraction (%)</td>
<td>57 (52–58)</td>
<td>58 (48–58)</td>
<td>57 (47–60)</td>
<td>57 (47–60)</td>
</tr>
<tr>
<td>Relative wall thickness ratio</td>
<td>0.50 ± 0.12</td>
<td>0.53 ± 0.14</td>
<td>0.48 ± 0.11</td>
<td>0.48 ± 0.09</td>
</tr>
</tbody>
</table>

Data are expressed as mean ± standard deviation, median (interquartile range), or number (%).

APD, automated peritoneal dialysis; CAPD, continuous ambulatory peritoneal dialysis; CCPD, continuous cycling peritoneal dialysis; Echo, echocardiogram; ECW, extracellular water; LV, left ventricular; nPNA, normalized protein nitrogen appearance; NT-proBNP, N-terminal pro-brain natriuretic peptide; TBW, total body water.

*p < 0.05 vs. increased LV mass group.

*Net difference between peritoneal and urinary sodium loss. **Number of different classes of antihypertensive medications prescribed.
loop diuretics. At the time of the second echocardiogram, 23 patients were on β-blockers, 16 were on calcium channel blockers/α-blockers, 12 were on renin-angiotensin blockers/receptor blockers, and 43 were on loop diuretics. There were no differences between the groups in terms of the proportion of prescribed renin-angiotensin inhibitors/receptor blockers, or β- or calcium channel blockers.

At the time of the repeat echocardiogram, NT-proBNP was greater in the group that had an increase in LVM (Table 2), as were the changes in NT-proBNP and ECW/height (Table 3). The changes in systolic blood pressure and mean arterial pressure were greater for the group with an increase in LVM, but after adjusting for multiple statistical testing, the difference was no longer statistically significant. There was no statistical difference in the changes made in the prescription of antihypertensive medications. Although patients who had a reduction in LVM had lost weight (unadjusted p = 0.025) (Table 2), there were no significant changes in body weights between the groups (Table 3).

On univariate analysis, the percent change in LVM was associated with the percent change in NT-proBNP (r = 0.51, p = 0.017) and percent change in ECW/height (r = 0.32, p = 0.029), but not with ECW/TBW or changes in systolic or mean arterial pressure, urine output, 24-hour ultrafiltration, weight, or net sodium balance. As the change in LVMI was nonparametric, with both positive and negative values, we

![Figure 1. Left ventricular mass index (LVMI) obtained by transthoracic two-dimensional echocardiography (Echo). Medians, interquartile ranges, and 90% confidence intervals are indicated. **p < 0.01 and ***p < 0.001 vs. the group with increased LVM.](image)

<table>
<thead>
<tr>
<th>Change</th>
<th>Decreased LVM</th>
<th>Increased LVM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (kg)</td>
<td>-1.8 (-5.4 to 1.1)</td>
<td>-0.6 (-3.9 to 2.8)</td>
</tr>
<tr>
<td>Reduction in urine Kt/V</td>
<td>0.29 (0.0–0.59)</td>
<td>0.36 (0–0.88)</td>
</tr>
<tr>
<td>Weekly PD Kt/V</td>
<td>0.21 (-0.05 to 3.40)</td>
<td>0.07 (-0.11 to 0.42)</td>
</tr>
<tr>
<td>Reduction in total Kt/V</td>
<td>0.19 (-0.03 to 0.48)</td>
<td>0.32 (-0.83 to 0.08)</td>
</tr>
<tr>
<td>Peritoneal ultrafiltration (mL/day)</td>
<td>484 (0–635)</td>
<td>130 (0–320)</td>
</tr>
<tr>
<td>Reduction in nPNA (g/kg/day)</td>
<td>0.05 (-0.19 to 0.02)</td>
<td>0.08 (-0.16 to 0.01)</td>
</tr>
<tr>
<td>Sodium balance^a (mmol/day)</td>
<td>4.4 (-3.0 to 57.0)</td>
<td>12.7 (-46.0 to 48.0)</td>
</tr>
<tr>
<td>4-hr dialysate/plasma creatinine</td>
<td>0.03 (0.07–0.1)</td>
<td>0.04 (-0.1–0)</td>
</tr>
<tr>
<td>NT-proBNP (pmol/L)</td>
<td>-8.5 (-4,739 to 440)</td>
<td>206 (-560 to 13,641)**</td>
</tr>
<tr>
<td>ECW/TBW</td>
<td>0.004 (-0.002 to 0.008)</td>
<td>0.006 (-0.001 to 0.009)</td>
</tr>
<tr>
<td>ECW/height (L/m)</td>
<td>-0.50 (-0.74 to 0.12)</td>
<td>0.21 (-0.10 to 0.50)^*</td>
</tr>
<tr>
<td>Albumin (g/L)</td>
<td>0 (0–1.0)</td>
<td>0 (0–0)</td>
</tr>
<tr>
<td>C-reactive protein (mg/L)</td>
<td>0 (-5.0 to 2.0)</td>
<td>3.0 (-3.0 to 0)</td>
</tr>
<tr>
<td>Blood pressure (mmHg)</td>
<td>-5.0 (-19.0 to 8.0)</td>
<td>9.0 (-10.0 to 36.0)^*</td>
</tr>
<tr>
<td>Systolic</td>
<td>-1.5 (-16.0 to 5.0)</td>
<td>3.0 (-8.5 to 17.0)</td>
</tr>
<tr>
<td>Diastolic</td>
<td>-3.5 (-17.0 to 5.7)</td>
<td>6.3 (-6.3 to 20.3)^*</td>
</tr>
<tr>
<td>Antihypertensive medication^b (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increase</td>
<td>6 (23.1)</td>
<td>7 (20.6)</td>
</tr>
<tr>
<td>Reduction</td>
<td>2 (7.7)</td>
<td>9 (26.5)</td>
</tr>
</tbody>
</table>

Data are expressed as median (interquartile range) or number (%).

LVM, left ventricular mass; PD, peritoneal dialysis; nPNA, normalized protein nitrogen appearance; ECW, extracellular water; NT-proBNP, N-terminal pro-brain natriuretic peptide; TBW, total body water.

^aNet difference between peritoneal and urinary sodium loss. ^bNumber of different classes of antihypertensive medications prescribed.

*p < 0.05 and **p < 0.01 vs. the decreased LVM group.
constructed a binary logistic step-backward multivariable model, including all variables with $p < 0.1$ (22.7 g/L dialysate, total weekly $Kt/V$, 24-hour PD ultrafiltration volume, percent change ECW/height, percent change in NT-proBNP, serum albumin, and serum CRP). Only ECW/height remained independently associated with the percent change in LVM (odds ratio, 1.25; 95% confidence interval, 1.08–1.36; $p = 0.007$, Nagelkerke $R^2 = 0.54$).

**Discussion**

Several observational studies found that the majority of PD patients have increased ECW, yet without overt clinical signs of volume overload \[21, 22\]. Interventional studies in hemodialysis patients, driven by bioimpedance to reduce ECW, have reported a reduction in both blood pressure and LVM \[23\], but similar studies in PD patients have failed to demonstrate a major change in blood pressure control \[6, 24\]. This may be due to the more regular assessment of hemodialysis patient target weights, the effect of residual renal function in PD patients, and differences in sodium removal between the two therapies.

To reduce the confounding effects of predialysis care, we reviewed echocardiograms in prevalent PD patients who had electively started PD following clinical care in a specialized chronic kidney disease clinic designed to prepare patients for dialysis. Despite specialized care, all but one patient had LVH by echocardiographic criteria \[8\], consistent with previous reports of an increased prevalence of LVH in PD patients \[3–5\].

We noted that, whereas there was no overall change in blood pressure control or LVM, LVM increased in the majority of our patients. To determine which factors contributed to changes in LVM, we compared changes in PD prescriptions, PD adequacy, blood pressure measurements, and assessment of volume status in patients who underwent repeat outpatient echocardiogram 18 to 24 months after the first echocardiogram. As expected with time, residual renal function declined, leading to a fall in total weekly $Kt/V$. To compensate for the loss in residual renal function, 24-hour PD ultrafiltration volumes increased, along with an increase in the prescription of icodextrin dialysates. In terms of ECW volume, whereas there were no changes in ECW/TBW ratios, ECW/height declined overall, with a greater change in patients with a reduction in LVM. The ratio of ECW/TBW not only reflects ECW but is also influenced by loss of ICW \[18\], so it can be affected by changes in body composition and inflammation \[25\]. NT-proBNP concentrations increased over time, and although often used as a biomarker of intravascular volume \[26\], NT-proBNP can increase with a fall in residual renal function, valvular heart disease, cardiac arrhythmias, and inflammation \[13, 27\]. However, brain natriuretic peptide has not been shown to be affected by LVH in patients with essential hypertension \[28\]. We observed that NT-proBNP increased in patients who had an increase in LVM, but not in patients who had a fall in LVM.

Comparing patients who had an increase or decrease in LVM over time, we found no differences in residual renal function, PD adequacy, PD ultrafiltration volumes, peritoneal transporter status, use of icodextrin, or hypertonic glucose dialysates. Although the change in weight between groups was not significant, there was an overall fall in body weight for patients with a reduction in LVM, and there was no correlation between weight loss and change in LVM. More patients with an increase in LVM were initially treated by APD cyclers, which have been reported to result in lower PD sodium removal compared to CAPD and continuous cycling peritoneal dialysis \[15\]. However, we found no difference in combined urinary and peritoneal sodium removal, but this estimation of sodium balance excludes dietary sodium, as we were unable to accurately record dietary sodium intake over time. Although absolute systolic and mean arterial pressures were not different, the change in blood pressure was greater in the group with an increase in LVM, as were the changes in NT-proBNP and ECW adjusted for height \[19\], and both were associated with the change in LVM. However, on multivariable testing, only the ratio of ECW/height remained independently associated with the change in LVM, suggesting that volume status, in particular ECW excess, is associated with increasing LVM. Our data is supported in reverse by one previous study which reported that a reduction in ECW was associated with a reduction in LVM, but equally LVM was also reduced in their cohort of patients who remained volume overloaded \[6\].

Longitudinal studies in PD patients have several confounders, due to patient drop-out, failure to follow techniques, peritonitis, transplantation, and mortality. As such, the number of patients with repeated measurements generally leads to reports from small observational studies. Thus, we report on a small cohort of 60 PD patients studied
in a single center, but this compares favorably to two earlier studies of 12 and 40 patients, respectively [3,5]. There has been debate regarding how to best adjust LVM to compare differences between patients [29]. We compared changes in LVM and LVMI in paired echocardiograms as advised by the European Society of Cardiology [8]. As remodeling of the left ventricle takes many months, we chose to compare echocardiograms 18 to 24 months apart, and as such accepted a short interval between echocardiograms and bioimpedance measurements. The majority of our patients had concentric LVH based on RWT criteria, and although there has been debate as to what RWT cut-off point should be used to categorize patients as having concentric and eccentric LVH, specifically 0.42 or 0.45, the percentage of patients with concentric hypertrophy only changed from 56.7% to 55% [9]. The greater concern is whether a single cut-off point can reliably separate concentric and eccentric LVH. We used bioimpedance to assess ECW, and as some studies have suggested that measurement of ECW can be affected by the presence of peritoneal dialysate, we took measurements after dialysate had been drained [17].

In hemodialysis, volume excess is a major risk factor for death, and in particular cardiovascular death. Reports in hemodialysis patients have linked ECW excess with LVH [1]. Although observational studies in PD patients have reported a high prevalence of LVH in PD patients [21], with an associated increased risk of cardiovascular mortality [2], these cross-sectional, single time point observational studies have been unable to establish the major causes of LVH. As residual renal function is important for PD patients, there have been concerns as to whether reducing ECW may lead to a premature loss of residual renal function, although studies have not supported this [30]. Our longitudinal observational work suggests a role for ECW excess as a driving force for increasing LVM, rather than blood pressure control.

Although there remains debate about the importance of ECW overload in PD patients, with meta-analyses failing to demonstrate a definitive association between PD technique failure and mortality [31], our study would suggest that greater attention to ECW could potentially prevent progression of LVM in PD patients.

Conflicts of interest

All authors have no conflicts of interest to declare.

Authors’ contributions

Conceptualization, Project administration, Visualization: AD
Data curation, Formal analysis, Investigation, Methodology: TW
Writing–original draft: AD
Writing–review & editing: TW, AD
All authors read and approved the final manuscript.

ORCID

Theerasak Tangwonglert, https://orcid.org/0000-0001-6475-0407
Andrew Davenport, https://orcid.org/0000-0002-4467-6833

References

task force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *J Hypertens* 2013;31:1281–1357.


Are there any further modalities for prediction of subclinical volume overload in advanced stages of chronic kidney disease?

Aber Halim Baki¹, Cherry Reda Kamel¹, Hazem Mansour²

¹Department of Internal Medicine and Nephrology, Faculty of Medicine, Ain Shams University, Cairo, Egypt
²Department of Cardiology, Faculty of Medicine, Ain Shams University, Cairo, Egypt

**Background:** Subclinical volume overload in chronic kidney disease (CKD) patient represents a debatable issue. Although many tools were used to detect volume overload in such patients, many non-specific results were due to presence of comorbidities. Bioimpedance spectroscopy is an objective fluid status assessment method, which is shown superior to classical methods in many studies. Combining some of these tools may improve their accuracy and specificity. Inferior vena cava collapsibility index (IVCCI) with brain natriuretic peptide (BNP) can be combined for more specific volume assessment. This study was performed to assess the usage of combined IVCCI and BNP levels in CKD patients to predict subclinical volume overload.

**Methods:** One hundred and ten patients with CKD (stages 4 and 5) not on dialysis and having normal left ventricular systolic function were included in this study. Exclusion criteria were: (1) patients with other causes of raised BNP than volume overload and (2) patients on diuretics. A complete medical history was obtained, and thorough examination and laboratory tests were performed for all included patients. IVCCI and BNP serum levels were evaluated. The patients who exhibited an overhydration (OH)/extracellular water (ECW) ratio of >15% were considered to have volume overload.

**Results:** Twenty-six patients (23.6%) had subclinical hypervolemia as diagnosed by OH/ECW ratio of >15%. IVCCI ≤ 38% had higher diagnostic performance than BNP ≥ 24 pg/mL. Combining both IVCCI ≤ 38% and BNP ≥ 24 pg/mL increased the specificity and positive predictive value for detection of subclinical hypervolemia.

**Conclusion:** Combined elevated BNP level and decreased IVCCI are more precise tools for subclinical volume overload detection in CKD patients.

**Keywords:** B-type natriuretic peptide, Bioelectric impedance, Chronic kidney disease, Echocardiography, Fluid overload, Inferior vena cava collapsibility index
Introduction

Volume overload is an essential prognostic parameter associated with compromised oxygenation, end-organ damage, prolonged hospital stays, morbidity, and mortality in chronic kidney disease (CKD) and end-stage renal disease (ESRD) patients. Volume overload manifests as left ventricular (LV) hypertrophy, hypertension, fluid shift into the third space, and increased arterial stiffness [1–6].

The use of bioimpedance spectroscopy (BIS) to detect volume overload is a novel tool that has been increasingly used due to its being simple, inexpensive, and noninvasive [7–9]. BIS is thought to be an objective fluid status assessment method more sensitive and accurate than classical methods such as BP and weight monitoring [10,11]. Whole-body BIS has now been widely used in clinical settings for the management of ESRD patients [12–14]. New research should critically evaluate the benefit of these BIS approaches in CKD patient care.

However, BIS is expensive—125 US dollars per test. This dollar value is based on the 2017 Medicare reimbursement amount [15]. Also, BIS devices are not widely available in most hemodialysis units and nephrology clinics in Egypt and other developing countries for financial reasons. Therefore, the need for the use of readily available laboratory or radiological markers to assess fluid overload (FO) in CKD patients exists.

Natriuretic peptides have been used for volume overload detection even in the absence of clinically diagnosed heart failure. Brain natriuretic peptide (BNP) levels are increased in patients with renal insufficiency [16–19]. In volume overload patients, an increase in natriuretic peptide levels was suggested to be a result of either volume expansion or LV hypertrophy or failure [20]. Although the use of natriuretic peptides for fluid status assessment is a subject of debate [16,20], numerous studies have shown a direct association between these biomarkers and hypervolemia [21,22].

Echocardiography, a widely available bedside test, is essential for assessing cardiac function in CKD patients. The inferior vena cava (IVC) acts as a reservoir for blood within the venous system, and changes in IVC collapsibility or distensibility correlate with the body’s fluid status. IVC collapsibility index (IVCCI) is the proportion of IVC collapse occurring with respiration and can be calculated by IVCCI = (IVCmax − IVCmin)/IVCmax [23]. Recent studies have demonstrated the high sensitivity and specificity of ultrasonographic evaluation of IVC collapse, and further investigations are indicated for determining the effectiveness of ultrasonography. Although many factors may affect IVC collapse measurement, ultrasonography can be used for the assessment of fluid responsiveness when bioimpedance is not available [24].

Therefore, use of the combination of IVCCI and BNP, rather than depending on a single method, is important for proper assessment of the fluid status in CKD, especially when BIS is not available or too costly. The aim of this work was to assess the combined usage of IVCCI and BNP levels as markers for concealed volume overload in patients with advanced CKD and normal LV systolic function.

Methods

A cross-sectional study was performed using data from 110 patients collected from January 2019 to October 2019 from multicenter outpatient clinics (OPCs): OPCs of Ain Shams University, Cairo Specialized Hospital, and Ain Shams University Specialized Hospital in Cairo, Egypt. The study is exempt from ethical committee approval as the authors provided full funding of the project that included only noninvasive procedures.

Inclusion criteria

Patients with CKD (stages 4 and 5) not on dialysis and having normal LV systolic function ejection fraction (> 55%) were included.

Exclusion criteria

(a) Patients with congestive heart failure (CHF) or clinical evidence of volume overload
(b) Patients with pulmonary hypertension
(c) Patients with significant structural valve lesions
(d) Patients on diuretics, angiotensin converting enzyme inhibitors, and angiotensin-receptor blockers

We collected demographic and clinical data. These data included age, sex, height, weight, body mass index (BMI), blood pressure, presence of diabetes, antihypertensive medication use, and laboratory investigations. These
Laboratory investigations included complete blood test; serum creatinine level; urea and uric acid level; albumin level; serum K, sodium (Na), and calcium levels; and serum BNP level.

Body composition monitor (BCM; Fresenius Medical Care D GmbH, Homburg, Germany) performed BIS for this study. BIS precisely measured the fluid status and body composition (extracellular water [ECW], overhydration [OH], fat tissue mass, and lean tissue mass [LTM]). We equated fluid to OH/ECW ratio and used this ratio to define subclinical volume overload. The patients who exhibited an OH/ECW ratio > 15% were considered to be hypervolemic [25,26].

Echocardiography

We measured LV dimensions and function and IVCCI and identified any valvular abnormalities. IVC was assessed through the subcostal window; the transducer was placed just inferior to the xiphoid process along the midline to obtain a long axis image of the IVC. The IVCCI is expressed as the difference between IVC maximum diameter (on expiration) and IVC minimum diameter (on inspiration) divided by the IVC maximum diameter; \((\text{IVC}_{\text{max}} - \text{IVC}_{\text{min}})/\text{IVC}_{\text{max}} \times 100\).

Statistical methods

Sample size justification

We used the results of Baki et al. [27] who demonstrated that the sensitivity and specificity of BNP were 71.0% and 77.8%, respectively, and the frequency of hypervolemia was 77.5%. We assumed the null hypothesis for sensitivity and specificity as 50.0% each, a power = 0.80 and an \(\alpha = 0.05\). We used Power Analysis and Sample Size (PASS) system, 11th version (Hintze [28]) to determine that the minimum sample size for a cross-sectional study using these parameters is 101 cases. We included 110 cases for better precision.

The collected data was coded, tabulated, and statistically analyzed using Microsoft Excel 2007 (Microsoft, Redmond, WA, USA) and IBM SPSS version 22.0 (IBM Corp., Armonk, NY, USA).

Descriptive statistics were performed on quantitative data and included range minimum and maximum and mean ± standard deviation for quantitative normally distributed data. Number and percentage are provided for qualitative data.

Inferential analyses were conducted on quantitative variables using the Shapiro-Wilk test for normality testing; an independent t test was conducted in cases of two independent groups with normally distributed data. For qualitative data, inferential analyses for independent variables was performed using the chi-square test for differences between proportions. Correlations were obtained using Pearson correlation for numerical normally distributed data. Receiver operating characteristic curve was used to evaluate the performance of different tests that differentiated between certain groups. A linear regression model was used to discover independent factors involving OH/ECW ratio. A p-value of <0.050 was considered to be significant.

Diagnostic characteristics were calculated as:

- Sensitivity = \((\text{true positive test/total positive golden}) \times 100\)
- Specificity = \((\text{true negative test/total negative golden}) \times 100\)
- Diagnostic accuracy = \(\left(\frac{\text{true positive test + true negative test}}{\text{total cases}}\right) \times 100\)
- Youden’s index = sensitivity + specificity – 1
- Predictive positive value = \((\text{true positive test/total positive test}) \times 100\)
- Predictive negative value = \((\text{true negative test/total negative test}) \times 100\)
- \(\text{LR}^+ = \text{sensitivity}/(1 – \text{specificity})\)
- \(\text{LR}^- = (1 - \text{sensitivity}/\text{specificity})\)
- \(\text{LR} = \text{LR}^+ / \text{LR}^-\)

Results

The mean age of the study group was 40.2 ± 9.7 years (Table 1). The study group’s mean BMI was 24.5 ± 2.5 kg/m². Forty-two patients (38.2%) were diabetics and 51 (46.4%) were hypertensive. Thirty-eight patients (34.5%) were smokers. The study group’s mean glomerular filtration rate (GFR) was 23.4 ± 5.6 mL/min/1.73 m² and mean serum creatinine level was 4.1 ± 0.8 mg/dL.

Patients with hypervolemia had significantly higher BMI, serum Na, and BNP level as well as highly significantly lower IVCCI. However, there was no significant difference between hypervolemic and normovolemic patients regarding other demographic and laboratory findings in the study population (Table 1).
There were significant positive correlations between FO (OH/ECW ratio) and BMI, serum Na, BNP, systolic blood pressure, diastolic blood pressure, and mean blood pressure as well as a significant negative correlation with IVCCI. Furthermore, no significant correlations were established between OH/ECW ratio and GFR, creatinine, urea, uric acid, albumin, calcium, and potassium (Table 2).

The linear regression model for diagnostic factors for FO showed that, among the studied variables, only lower IVCCI and higher BNP were significantly associated with higher OH/ECW ratio (Table 3). Multivariable linear regression analysis confirmed the significant correlations between FO and both BNP and IVCCI after adjustment for confounding variables (Table 4).

Our data showed that, regarding diagnosis of hypervolemia, BNP (≥24 pg/mL) had a significantly low diagnostic performance while IVCCI (≤38%) had a significantly moderate diagnostic performance. Despite the correlation between fluid

<table>
<thead>
<tr>
<th>Variable</th>
<th>All cases</th>
<th>Hypervolemia</th>
<th>Normovolemia</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>110</td>
<td>26</td>
<td>84</td>
<td>0.793*</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>40.2 ± 9.7</td>
<td>39.8 ± 9.3</td>
<td>40.4 ± 9.8</td>
<td>0.832*</td>
</tr>
<tr>
<td>Sex Male</td>
<td>70 (63.6)</td>
<td>17 (65.4)</td>
<td>53 (63.1)</td>
<td>0.631*</td>
</tr>
<tr>
<td>Female</td>
<td>40 (36.4)</td>
<td>9 (34.6)</td>
<td>31 (36.9)</td>
<td></td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>24.5 ± 2.5</td>
<td>25.5 ± 2.7</td>
<td>24.2 ± 2.4</td>
<td>0.019**</td>
</tr>
<tr>
<td>Duration of renal disease (yr)</td>
<td>6.9 ± 2.3</td>
<td>6.2 ± 1.9</td>
<td>7.1 ± 2.4</td>
<td>0.087*</td>
</tr>
<tr>
<td>Hypertension</td>
<td>38 (34.5)</td>
<td>12 (46.2)</td>
<td>26 (31.0)</td>
<td>0.154*</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>29 (26.4)</td>
<td>9 (34.6)</td>
<td>20 (23.8)</td>
<td>0.274*</td>
</tr>
<tr>
<td>Smoking</td>
<td>38 (34.5)</td>
<td>10 (38.5)</td>
<td>28 (33.3)</td>
<td></td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>4.1 ± 0.8</td>
<td>4.3 ± 0.8</td>
<td>4.1 ± 0.8</td>
<td>0.248*</td>
</tr>
<tr>
<td>Urea (mg/dL)</td>
<td>94.6 ± 19.7</td>
<td>95.9 ± 22.1</td>
<td>94.2 ± 19.0</td>
<td>0.698*</td>
</tr>
<tr>
<td>Uric acid (mg/mL)</td>
<td>4.4 ± 1.5</td>
<td>4.4 ± 1.6</td>
<td>4.5 ± 1.5</td>
<td>0.765*</td>
</tr>
<tr>
<td>Albmin (g/dL)</td>
<td>3.9 ± 0.3</td>
<td>3.8 ± 0.3</td>
<td>3.9 ± 0.3</td>
<td>0.079*</td>
</tr>
<tr>
<td>sNa (mmol/L)</td>
<td>144.5 ± 8.1</td>
<td>147.5 ± 6.0</td>
<td>143.5 ± 8.5</td>
<td>0.031**</td>
</tr>
<tr>
<td>Calcium (mg/dL)</td>
<td>7.6 ± 0.6</td>
<td>7.6 ± 0.6</td>
<td>7.5 ± 0.6</td>
<td>0.383*</td>
</tr>
<tr>
<td>sK (mmol/L)</td>
<td>4.8 ± 0.5</td>
<td>4.9 ± 0.5</td>
<td>4.8 ± 0.5</td>
<td>0.278*</td>
</tr>
<tr>
<td>BNP (pg/mL)</td>
<td>25.3 ± 9.4</td>
<td>30.2 ± 11.6</td>
<td>23.7 ± 8.1</td>
<td>0.002**</td>
</tr>
<tr>
<td>IVCCI (%)</td>
<td>37.4 ± 11.6</td>
<td>26.3 ± 7.2</td>
<td>40.9 ± 10.5</td>
<td>&lt;0.001**</td>
</tr>
<tr>
<td>OH/ECW ratio</td>
<td>10.2 ± 6.5</td>
<td>19.4 ± 3.1</td>
<td>7.3 ± 4.3</td>
<td>&lt;0.001**</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>143.7 ± 3.2</td>
<td>144.7 ± 3.0</td>
<td>143.4 ± 3.3</td>
<td>0.090</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>81.1 ± 2.0</td>
<td>81.7 ± 1.8</td>
<td>80.9 ± 2.0</td>
<td>0.092</td>
</tr>
<tr>
<td>MBP (mmHg)</td>
<td>102.0 ± 2.3</td>
<td>102.7 ± 2.2</td>
<td>101.8 ± 2.3</td>
<td>0.078</td>
</tr>
</tbody>
</table>

Data are expressed as number only, mean ± standard deviation, or number (%). BNP, brain natriuretic peptide; DBP, diastolic blood pressure; ECW, extracellular water ratio; IVCCI, inferior vena cava compressibility index; MBP, mean blood pressure; OH, overhydration; SBP, systolic blood pressure; sK, serum potassium; sNa, serum sodium.

*p < 0.050.

<table>
<thead>
<tr>
<th>Factor</th>
<th>r</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.006</td>
<td>0.954</td>
</tr>
<tr>
<td>Body mass index</td>
<td>0.205</td>
<td>0.032*</td>
</tr>
<tr>
<td>Duration</td>
<td>-0.124</td>
<td>0.195</td>
</tr>
<tr>
<td>Creatinine</td>
<td>0.063</td>
<td>0.513</td>
</tr>
<tr>
<td>Urea</td>
<td>0.010</td>
<td>0.915</td>
</tr>
<tr>
<td>Uric acid</td>
<td>-0.004</td>
<td>0.970</td>
</tr>
<tr>
<td>Albumin</td>
<td>-0.168</td>
<td>0.079</td>
</tr>
<tr>
<td>sNa</td>
<td>0.214</td>
<td>0.024*</td>
</tr>
<tr>
<td>Calcium</td>
<td>0.064</td>
<td>0.508</td>
</tr>
<tr>
<td>sK</td>
<td>0.078</td>
<td>0.416</td>
</tr>
<tr>
<td>BNP</td>
<td>0.262</td>
<td>0.006*</td>
</tr>
<tr>
<td>IVCCI</td>
<td>-0.434</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>SBP</td>
<td>0.264</td>
<td>0.005*</td>
</tr>
<tr>
<td>DBP</td>
<td>0.240</td>
<td>0.011*</td>
</tr>
<tr>
<td>MBP</td>
<td>0.261</td>
<td>0.006*</td>
</tr>
</tbody>
</table>

BNP, brain natriuretic peptide; DBP, diastolic blood pressure; IVCCI, inferior vena cava compressibility index; MBP, mean blood pressure; SBP, systolic blood pressure; sK, serum potassium; sNa, serum sodium.

*p < 0.050.
volume (OH/ECW ratio) and both BMI and Na, neither had a significant diagnostic performance for volume overload (Table 5, Fig. 1).

BNP had a sensitivity of 76.9% and a specificity of 58.3%; those values for IVCCI were 96.2% and 63.1%, respectively (Table 6). However, if the patient had both IVCCI ≤ 38% and BNP ≥ 24 pg/mL concurrently, the specificity and positive predictive value increased to 86.9% and 63.3%, respectively, while the sensitivity and negative predictive value decreased to 73.1% and 91.3%, respectively. If the patient had either IVCCI ≤ 38% or BNP ≥ 24 pg/mL, perfect sensitivity and negative predictive value (100%) were achieved at the expense of decreased specificity and positive predictive value (Table 6).

**Discussion**

Routine evaluation of hydration includes monitoring of

<table>
<thead>
<tr>
<th>Table 3. Linear regression analysis between fluid overload (OH/ECW ratio) and IVCCI and BNP</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Factor</strong></td>
</tr>
<tr>
<td>Constant</td>
</tr>
<tr>
<td>IVCCI</td>
</tr>
<tr>
<td>BNP</td>
</tr>
</tbody>
</table>

β, regression coefficient; BNP, brain natriuretic peptide; CI, confidence interval; ECW, extracellular water ratio; IVCCI, inferior vena cava collapsibility index; OH, overhydration; R², coefficient of determination; SE, standard error.

* p < 0.050.

<table>
<thead>
<tr>
<th>Table 4. Multivariable linear regression analysis for different predictors of fluid overload after adjustment for different confounders</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Factor</strong></td>
</tr>
<tr>
<td>Constant</td>
</tr>
<tr>
<td>BMI</td>
</tr>
<tr>
<td>sNa</td>
</tr>
<tr>
<td>BNP</td>
</tr>
<tr>
<td>IVCCI</td>
</tr>
<tr>
<td>SBP</td>
</tr>
<tr>
<td>DBP</td>
</tr>
<tr>
<td>MBP</td>
</tr>
</tbody>
</table>

β, regression coefficient; BMI, body mass index; BNP, brain natriuretic peptide; CI, confidence interval; DBP, diastolic blood pressure; IVCCI, inferior vena cava collapsibility index; MBP, mean blood pressure; R², coefficient of determination; SBP, systolic blood pressure; SE, standard error; sNa, serum sodium.

* p < 0.050.

<table>
<thead>
<tr>
<th>Table 5. Performance of BMI, sNa, BNP, and IVCCI in diagnosing hypervolemia</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Factor</strong></td>
</tr>
<tr>
<td>BMI</td>
</tr>
<tr>
<td>sNa</td>
</tr>
<tr>
<td>BNP</td>
</tr>
<tr>
<td>IVCCI</td>
</tr>
</tbody>
</table>

AUC, area under curve; BMI, body mass index; BNP, brain natriuretic peptide; CI, confidence interval; IVCCI, inferior vena cava collapsibility index; SE, standard error; sNa, serum sodium.

* p < 0.050.

**Figure 1.** Receiver operating characteristics curves for BMI, sNa, BNP, and IVCCI in diagnosing hypervolemia.

BMI, body mass index; sNa, serum sodium; BNP, brain natriuretic peptide; IVCCI, inferior vena cava collapsibility index.

body weight and blood pressure changes that are not reliably determined by fluid volume. Edema is not usually detectable until interstitial fluid volume increases 30% over normal levels (4–5 kg gain in body weight), and severe dehydration can occur before appearance of clinical signs. Thus, traditional indicators of over- and under-hydration in patients with renal disease are insensitive and inadequate [15].

Volume status assessment of advanced CKD (stages 4 and 5) patients not on dialysis is crucial. Clinical sign assessments are also essential even though a significant number of patients have subclinical volume overload with no evident clinical signs. For example, dependent edema is occasionally challenging to identify, especially in nonambulatory patients. Other physical measurements,
such as changes in body weight or blood pressure, are influenced by many issues other than volume load status. Early detection of this problem can prevent deleterious sequelae [24].

BIS is one of the modifications of bioimpedance analysis. Chamney et al. [29] developed a “three-compartment body model”, which differentiates between normally hydrated LTM, adipose tissue mass, and a virtual OH compartment. This model assumes a fixed hydration of LTM and adipose tissue mass that results in the calculation of a “normohydration weight.” The OH compartment is calculated as the difference between the measured and the expected ECW. “Expected” is the difference found in the normally functioning population; the 10th to 90th percentile (–1.1 L and +1.1 L) of the normal population is considered to represent a normovolemic situation. Literature definitions of FO vary between a value of >1.1 L and 2.5 L (or an OH/ECW ratio above 7% or 15%). Fluid depletion is defined as an FO level below –1.1 L [30].

The BIS method relies on the assumption that low-frequency current flows through the extracellular fluid (ECF) and high-frequency current penetrates ECF and intracellular fluid. These assumptions are open to criticism largely because of their derivation from in vitro studies of cells suspended in fluid; cell-cell interfaces that occur in tissues are ignored. These calculations are performed with software provided by the manufacturers of the different BIS instruments and are subject to change. Significant errors can occur in the estimation of total body water (TBW, 2 L) and ECW (~1 L) in individuals with increased adiposity. A proposed remedy to this limitation is the use of BMI as a proxy for adiposity. A limitation of the use of BMI as a surrogate for body fat content is the lack of sensitivity of BMI to reliably differentiate the body composition (body fat and muscle mass) of an individual, healthy or ill. A consistent observation is the wide limits of agreement between the impedance and reference methods that cautions against the use of these methods for individual assessment of fluid volumes [31].

Using BNP level to assess volume overload is relatively inexpensive; however, due to relatively low specificity, more studies are needed to clarify the effectiveness of BNP level in assessing volume overload in CKD patients [27].

IVCCI is the proportion that the IVC collapses with respiration and can be calculated by IVCCI = (IVC max – IVC min)/IVC max [23]. Changes in collapsibility or distensibility correlate with the body’s fluid status. However, IVCCI’s validity is questionable since IVC diameter does not only depend on volume status and may be affected by respiration, right heart function, and intraabdominal or intrathoracic pressure changes. Also, IVC imaging can be challenging especially in patients with large body habitus, excessive bowel gas, or large amounts of intrathoracic air [32,33]. A recent study showed that, after a certain threshold, IVCCI is considerably specific and sensitive for observing volume expansion [32].

Therefore, the combination of IVCCI and BNP, rather than depending on a single method, is important for proper assessment of the fluid status in CKD. This combination improves the specificity of the individual tests and may provide a guide to optimize medical management, especially when BIS is not available or too costly. Combining these tools

Table 6. Diagnostic characteristics of BNP and IVCCI cutoff points in hypervolemia

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>BNP ≥ 24.0 pg/mL</th>
<th>IVCCI ≤ 38.0%</th>
<th>BNP ≥ 24.0 pg/mL and IVCCI ≤ 38.0%</th>
<th>BNP ≥ 24.0 pg/mL or IVCCI ≤ 38.0%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity (%)</td>
<td>76.9</td>
<td>96.2</td>
<td>73.1</td>
<td>100</td>
</tr>
<tr>
<td>Specificity (%)</td>
<td>58.3</td>
<td>63.1</td>
<td>86.9</td>
<td>34.5</td>
</tr>
<tr>
<td>Diagnostic accuracy (%)</td>
<td>62.7</td>
<td>70.9</td>
<td>83.6</td>
<td>50.0</td>
</tr>
<tr>
<td>Youden’s index (%)</td>
<td>35.3</td>
<td>59.2</td>
<td>60.0</td>
<td>34.5</td>
</tr>
<tr>
<td>Positive predictive value (%)</td>
<td>36.4</td>
<td>44.6</td>
<td>63.3</td>
<td>32.1</td>
</tr>
<tr>
<td>Negative predictive value (%)</td>
<td>89.1</td>
<td>98.1</td>
<td>91.3</td>
<td>100</td>
</tr>
<tr>
<td>Positive likelihood ratio</td>
<td>1.85</td>
<td>2.61</td>
<td>5.58</td>
<td>1.53</td>
</tr>
<tr>
<td>Negative likelihood ratio</td>
<td>0.40</td>
<td>0.06</td>
<td>0.31</td>
<td>0</td>
</tr>
<tr>
<td>Diagnostic odds ratio</td>
<td>4.67</td>
<td>42.74</td>
<td>18.01</td>
<td>Infinity</td>
</tr>
</tbody>
</table>

BNP, brain natriuretic peptide; IVCCI, inferior vena cava collapsibility index.
may improve the accuracy and specificity of both and justifies using both rather than each one individually. Therefore, in this current study we evaluated the combination of these two easy and readily accessible tools. Our study population consisted of 110 patients with CKD in whom we detected volume overload before being evident clinically by measuring both IVCCI and BNP levels.

We assessed volume overload in the 110 cases by measuring OH/ECW ratio that equated to FO. We found that 26 patients (23.6%) had subclinical hypervolemia (OH/ECW > 15%). Data on subclinical volume overload in CKD patients is scarce. A few studies evaluated subclinical volume overload only in dialysis patients. Although there was paucity of data about the percentage of subclinical volume overload in CKD patients, few studies evaluated this issue; however, they included only patients on dialysis. One study of them which evaluated 100 hemodialysis patients, showed close results to ours; with the percentage of FO (29%) using BIS despite being clinically euvolemic. FO was defined by a relative tissue hydration, i.e., OH/ECW > 15%, which was the similar parameter used in our study to define hypervolemia [25].

Concerning the demographic and laboratory data, we found no significant differences between hypervolemic and euvolemic patients regarding age, sex, and presence of hypertension or diabetes. These results agreed with Antlanger et al. [34] who reported no significant sex and age differences in cases of FO.

Hung et al’s study [35] findings of data from 338 patients partially disagreed with our results. That group demonstrated a significant correlation between hypervolemia and diabetes mellitus. These conflicting results may be attributed to the larger sample size and a higher percentage of diabetics in that study. However, normo- and hypervolemic groups demonstrated significant differences; higher BMI, serum Na, BNP level, and lower IVCCI were present in the hypervolemic group.

Hypernatremia in subclinical hypervolemic CKD patients, although not commonly seen in patients with clinical volume overload, can be explained. Some patients, particularly those in late stages of CKD were prescribed sodium bicarbonate for treatment of metabolic acidosis leading to hypernatremia. This resulted from osmotic diuresis caused by elevated serum urea, impaired renal concentrating capacity, or nephron loss. Impaired angiotensin II production, which may contribute directly to the impaired thirst mechanism, or excessive water restriction may also be involved [36–38].

Another mechanism may be the use of loop diuretics that interfere with medullary hypertonicity with resultant electrolyte-free water loss from collecting ducts, but the use of diuretics was one of our exclusion criteria.

Similar to the Hung et al’s study [35], we demonstrated significant correlations between hypervolemia and serum Na and BNP levels. As expected, in our study hypervolemia had an important correlation with BMI since excessive body fluids accumulate in the extracellular compartment. A study conducted by Kwan et al. [39] had results consistent with ours. In that study, BMI had a significant correlation with OH (r = 0.376, p < 0.001).

Our data showed a highly significant negative correlation between hypervolemia and IVCCI (p < 0.001). Barbier et al. [32] showed that, after a certain threshold, IVCCI was highly specific and sensitive for demonstrating volume expansion. Some other studies evaluated this and determined that its accuracy is unproven as IVC diameter is affected by factors other than volume status [33–40].

Allinovi et al. [41] performed fluid assessments on 13 children on dialysis (eight on peritoneal dialysis and five on hemodialysis) with a median age of 4.0 years (range, 0.8–14.0 years). Their results disagreed with our data. The negative correlation between IVCCI and FO was not significant in their study. These conflicting results may be related to many factors; their study consisted of a small number of young patients and had a single-center design that lacked a robust gold standard measurement of FO.

Regarding BNP as a tool for volume overload detection, our study showed that there was a significant correlation between BNP level and hypervolemia (p = 0.002). BNP is useful for the evaluation of ventricular dysfunction in patients with various cardiac diseases. However, its diagnostic value has been considered to be limited in patients with chronic renal failure (CRF) not on dialysis. Also, a high BNP level (≥150 pg/mL) may have powerful predictive potential for heart failure in these patients. These results also agreed with those of Bongartz et al. [43] who reported that high plasma BNP concentrations were associated with volume overload in CKD patients.

Our results demonstrated a cutoff value for BNP’s
usefulness in diagnosing FO (≥24 pg/mL). However, no data for determination of a BNP level cutoff point for detecting subclinical volume overload in CKD patients not undergoing dialysis are available. Further studies are required to resolve this important issue. However, a study on 40 chronic dialysis patients suggested that a BNP level cutoff value of 17.65 pg/mL can be used to diagnose volume overload [31]. A cohort study of 348 consecutive patients evaluated the role of B-type natriuretic peptide in diagnosing acute decompensated heart failure in CKD patients. In the patients with heart failure and preserved left ventricular ejection fraction in CKD stages 3 and 4, BNP < 155 pg/mL was sufficient to rule out acute decompensated heart failure [44].

Our results showed an IVCCI ratio cutoff value of ≤38% for diagnosing FO in CKD patients. However, there were no previous data determining the cutoff value of IVCCI, IVCCI sensitivity, and IVCCI specificity to assess concealed volume overload in CKD patients. Some studies did evaluate IVCCI values in hemodialysis patients. In a study with 22 patients in whom dry weight was determined on clinical grounds, only six had a correct dry weight according to IVC indices [44]. Another study on 40 patients on dialysis to assess volume overload in CRF determined that volume status was categorized as either hypervolemia if IVCCI was <40% or hypovolemia if IVCCI >75% [45].

Our study found a sensitivity of 76.9% and a specificity of 58.3% for BNP and values of 96.2% and 63.1%, respectively, for IVCCI in the diagnosis of OH in CKD. In a 2013 prospective study, Anderson et al. [46] explored the accuracy of IVCCI, which was more specific than sensitive in diagnosing CHF; and BNP, which was highly specific. Concerning the concept of the study that combined two modalities to detect subclinical volume overload in CKD patients, there was no previous data for comparison. Our results showed that, for diagnosing hypervolemia, BNP (≥24 pg/mL) had a significantly low diagnostic performance, and IVCCI (≤38%) had a significantly moderate diagnostic performance. Moreover, the specificity and positive predictive value increased, but the sensitivity and negative predictive value decreased, with the concurrent use of IVCCI and BNP. However, if the case had any IVCCI or BNP, perfect sensitivity and negative predictive value were achieved but at the expense of decreased specificity and positive predictive value.

One of the limitations of this study is that we used only OH /ECW as the reference value for volume overload; comparisons of BNP and IVCCI using multiple reference values including ECW/ICW and ECW/TBW may have been more informative.

While IVCCI showed high sensitivity and specificity, measuring BIS with devices such as BCM is easier for assessing FO. This is due to the limited availability of expert echocardiologists in dialysis centers.

Using BIS as reference, we proved that combining IVCCI with a cutoff value of ≤38% and BNP with cutoff value of ≥24 pg/mL provides an accurate alternative to BIS for detection of subclinical volume overload in predialysis CKD patients. Further studies with a larger sample size are needed to evaluate the clinical impact of these findings on patient outcomes and mortality.

Conflicts of interest
All authors have no conflicts of interest to declare.

Acknowledgments
We acknowledge Dr. Hazem Elhariry for his statistical analysis, and Dr. Bishoy Tanagho for his help in paper submission.

Authors’ contributions
Conceptualization: AHB
Data curation: AHB, HM
Formal analysis: CRK
Investigation: AHB, HM
Methodology: AHB, HM
Project administration: AHB
Visualization: AHB
Writing–original draft: AHB, HM
Writing–review & editing: AHB, CRK
All authors read and approved the final manuscript.

ORCID
Aber Halim Baki, https://orcid.org/0000-0002-2374-8412
Cherry Reda Kamel, https://orcid.org/0000-0001-9698-0303
Hazem Mansour, https://orcid.org/0000-0002-5366-3698
References


Peripherally inserted central catheter procedure at the bedside by a nephrologist is safe and successful

Seong Cho

Division of Nephrology, Department of Internal Medicine, Samsung Changwon Hospital, Sungkyunkwan University School of Medicine, Changwon, Republic of Korea

Background: Peripherally inserted central catheter (PICC) use among critically ill patients with or without acute kidney injury (AKI) has gradually increased. Ultrasound-guided bedside PICC insertion in intensive care units (ICU) has been reported to be safe and effective. Reports of PICC insertion by a nephrologist without fluoroscopy, however, are relatively rare.

Methods: This retrospective study included patients (n = 224) who had a PICC inserted by a single nephrologist at Samsung Changwon Hospital from January 2019 to June 2020. Group 1 patients (n = 98) had PICCs inserted under ultrasound guidance, while group 2 patients (n = 126) had PICCs inserted under fluoroscopic guidance. Success rates, multiple puncture rates, and malposition rates were compared between the two groups.

Results: Underlying comorbidities (sepsis, AKI, ventilator use, and shock) were more common in group 1 than in group 2. Success rates were comparable between the two groups (93.9% vs. 97.6%, p = 0.171). Multiple puncture rate among successful cases (4.1% vs. 0.0%, p = 0.035) was higher in group 1 than group 2. Excluding central vein occlusion cases, malposition occurred only one in group 1.

Conclusion: Bedside PICC insertion by a nephrologist is easy and safe to perform in comorbid patients who are difficult to move to the angiography room. The success rate of ultrasound-guided PICC insertions was comparable to that of PICC insertion performed under fluoroscopic guidance. In the life-threatening ICU setting, PICCs can be successfully placed by the interventional nephrologists.

Keywords: Peripheral catheterization, Critical illness, Intensive care unit, Peripherally inserted central catheter

Introduction

A peripherally inserted central catheter (PICC) is essential for prolonged chemotherapy, nutritional support, and antibiotic injections [1,2]. The number of elderly and longer term comorbid patients who require PICC insertion by a nephrologist to achieve adequate blood access is gradually increasing [3]. PICC insertion is commonly conducted with fluoroscopic procedures in the angiography room. However, patients with poor medical conditions such as ventilator dependency...
or shock and patients who were required continuous renal replacement therapy (CRRT) or extracorporeal membrane oxygenation (ECMO) were needed to perform PICC insertion at bedside [4–6]. Lack of angiography room availability may also result in the need for bedside PICC insertion. Compared to fluoroscopy-guided insertion, bedside insertion using ultrasound guidance has several disadvantages such as dislocation of the catheter tip to the jugular vein or other inadequate locations and lack of adequate visualization to determine the cause of guidewire passage failures such as vein stenosis or kinking. Nevertheless, many intensivists have reported high bedside PICC insertion success rates [4–6]. However, reports comparing PICC bedside insertion to fluoroscopic insertion success rates and nephrologist experiences within a single practice are rare. Therefore, this study compared success rates between bedside PICC insertion and insertion conducted under fluoroscopic guidance by a single nephrologist.

**Methods**

This study retrospectively analyzed patients who had a PICC inserted by a nephrologist of Department of Nephrology, Samsung Changwon Hospital in Changwon, Korea from January 2019 to June 2020. In general, PICC insertion was conducted in the angiography room; these patients were assigned to group 2. PICC insertion among patients who were difficult to transfer to the angiography room due to comorbidities was performed at the bedside and these patients were classified as group 1 patients. Patient characteristics including age, sex, serum creatinine, estimated glomerular filtration rate (eGFR), septic condition, shock state, presence of artificial respiration, severe heart failure, acute kidney injury (AKI), postoperative surgery, and gastrointestinal bleeding were considered. Information about the side of the body where the PICC was inserted was recorded. PICC insertion was considered appropriate only when the scheduled duration of use was longer than 6 days or non-peripherally compatible infusions were needed. In patients with chronic kidney disease (CKD) stage 3b to 5, possible access creation needs were considered and PICC insertion was avoided if possible; therefore, these patients were excluded in this study.

The patient was placed in a supine position by abduction, and, when determining the arm to be treated, the side without any suspicion of proximal vein stenosis (previous catheter insertion site) was considered first. To prevent blood infection, the procedure was performed using sterile methods. A 5-French (Fr) dual-lumen catheter was used, and 2% chlorhexidine was used to prevent catheter-related infections. In both methods, an appropriate vein (more superficial, larger, or more distant from an artery) was selected using ultrasound (Supplementary Fig. 1, available online). Then, a 0.018-inch guidewire was inserted after puncture of the vein using a micro-puncture needle (Fig. 1A-C). After inserting the 5-Fr sheath in group 2 patients, a long guidewire was introduced, and the guidewire tip was positioned between the superior vena cava (SVC) and midportion of the right atrium (RA). Next, the operator measured the length from the sheath to a 60-cm marker at the guidewire surface, and catheter length was calculated as 60 cm minus the measured length. The operator trimmed the catheter to the desired length and inserted the catheter over the guidewire to a location between the SVC and midportion of the RA (Fig. 2). Group 1 patients had a 5-Fr sheath introduced using ultrasound as in group 2 patients (Fig. 1D). After sheath insertion, the operator calculated catheter length by summing the straight-line distance from the sheath insertion site to the mid-clavicular line (Fig. 1E) and the straight-line distance from the mid-clavicular line to the third intercostal space in the right parasternal area (Fig. 1F) [7]. The operator trimmed catheters according to the calculated length (Fig. 1G). While passing through the guidewire, a neck sonogram (Supplementary Fig. 2 and 3, available online) was used to observe the internal jugular vein to confirm that the guidewire had not been misdirected to the neck. When the guidewire could be advanced without resistance, a trimmed catheter was inserted along the guidewire (Fig. 1H). After the procedure, the location of the catheter was confirmed by simple chest anteroposterior imaging. Heparin flush, 100 units/mL, was injected as a single dose into the PICC line using a volume of solution equivalent to that of the indwelling catheter for thrombosis prevention.

Criteria for success were based on functional status (good inflow/outflow) and chest posteroanterior findings (catheter tip located between SVC and midportion of the RA; Fig. 2). Failure refers to functional status (substandard inflow/outflow) or catheter tip malposition. Failure can be due to one of three issues: 1) puncture failure, 2) catheter or
guidewire passage failure, and 3) malposition of the catheter tip to another site. Major malposition refers to a catheter tip located in the internal jugular (Fig. 3A) or subclavian vein (Fig. 3B). Minor malposition refers to a catheter tip 1 to 2 cm above the SVC (Fig. 3C) or deep portion of the RA (Fig. 3D).

First-puncture success refers to one-site puncture without interruption. Multiple-puncture success refers to insert PICC but with an additional puncture site on the ipsilateral or contralateral limb. Shock was diagnosed when the systolic arterial blood pressure was less than 90 mmHg or a vasopressor was administered. Sepsis was defined according to the new Sepsis-3 definitions [8]. AKI was indicated by an elevation of serum creatinine to 1.5 times greater than baseline or a urine output of less than 0.5 mL/kg/hr for 6 to 12 hours (Kidney Disease: Improving Global Outcomes (KDIGO) 2012 AKI clinical practice guideline) [9].

Figure 1. Implementation process. (A–C) The patient was fixed in a supine position by abduction, an appropriate vein was selected using ultrasound, and then a 0.018-inch guidewire was inserted after puncture of the vein using a micro-puncture needle. (D) A 5-French sheath was introduced. (E) After sheath insertion, catheter length was calculated by summing the straight-line distance from the sheath insertion site to the mid-clavicular line and (F) the straight-line distance from the mid-clavicular line to the third intercostal space in the right parasternal area. (G) The operator trimmed catheters according to calculated length. (H) When the guidewire proceeded without resistance, a trimmed catheter was inserted along the guidewire.

Figure 2. Catheter tip located between the superior vena cava and midportion of the right atrium.
serum creatinine and eGFR values were from laboratory findings of a previous stable period or periods after recovery from AKI.

Statistical analysis

Data were analyzed using SPSS ver. 12.0 program (SPSS Inc., Chicago, IL, USA). A p-value less than 0.05 was considered significant. This study was conducted at Samsung Changwon Hospital, Sungkyunkwan University School of Medicine and was approved by the Institutional Review Board (No. 2020-07-004).

Results

Demographic and clinical information

From January 2019 to June 2020, 224 PICC insertions were performed by one nephrologist. Group 1 patients (n = 98) had PICCs inserted using an ultrasound-guided method in the ICU (89.8%) or ward treatment rooms (10.2%). Group 2 patients (n = 126) had PICCs inserted under fluoroscopic guidance in the angiography room (100%). Demographic and clinical information were compared between groups (Table 1). Mean age (71.26 ± 13.30 vs. 75.32 ± 11.47 years, p = 0.007) was lower in group 1 patients than group 2 patients. Sex ratio (female, 43.9% vs. 51.6%, p = 0.282), implementation site (right, 40.8% vs. 53.2%, p = 0.080), access vein (basilic vein/brachial vein/cephalic vein, 54.1%/42.9%/3.0% vs. 54.8%/40.4%/4.8%, p = 0.788), prevalence of diabetes mellitus (43.9% vs. 34.9%, p = 0.345), and prevalence of hypertension (38.8% vs. 47.6%, p = 0.365) were not significantly different between groups. Serum creatinine (1.56 ± 1.45 vs. 1.52 ± 1.01 mg/dL, p = 0.825) and eGFR (72.32 ± 43.47 vs. 57.57 ± 34.13 mL/min/1.73 m², p = 0.094) levels at the time of a stable condition were similar in the two groups. Serum creatinine (2.24 ± 2.02 vs. 2.31 ± 1.94 mg/dL, p = 0.788), eGFR (60.81 ± 50.71 vs. 56.83 ± 62.88 mL/min/1.73 m², p = 0.610), hemoglobin (9.67 ± 1.40 vs. 10.42 ± 1.82 g/dL, p = 0.128), platelet count (128.75 ± 75.00 vs. 221.80 ± 64.50 × 10³/mm³, p = 0.148), prothrombin time (15.26 ± 6.50 vs. 15.30 ± 6.66 seconds, p = 0.993), activated partial thromboplastin time (33.84 ± 6.19 vs. 35.53 ± 8.03 seconds, p = 0.715), and serum albumin level (2.78 ± 0.70 vs. 2.82 ± 0.66 g/dL, p = 0.993) at the time of catheter insertion were also not different between the two groups. Underlying comorbidities were more common in group 1 than group 2. Sepsis (62.2% vs. 30.2%, p < 0.001), shock (52.0% vs. 4.8%, p < 0.001), AKI (70.4% vs. 47.6%, p = 0.001), ventilator use (62.2% vs. 0.0%, p < 0.001), and postoperative state rates (8.2% vs. 0.8%, p = 0.011) were more common in group 1 than group 2. In-hospital mortality (44.9% vs. 20.6%, p < 0.001) was also higher in group 1 than group 2.

Success and complication rates

Success and complication rates were compared between groups (Table 2). Median duration (IQR) of PICC catheter insertion (26 days [10–35 days] vs. 20 days [15–30 days], p = 0.597) was not different between the groups. Insertion success rate was high, with no significant difference between the two groups (93.9% vs. 97.6%, p = 0.171). In group 1, a total of six insertions were failures. No puncture failure cases occurred. Two cases failed due to guidewire passage disturbance, and a PICC was successfully inserted in one of these cases by changing to the fluoroscopic method. The cause of guidewire passage disturbance was the angle of the cephalic arch that blocked smooth passage of the
Table 1. Patient characteristics (n = 224)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group 1 (n = 98)</th>
<th>Group 2 (n = 126)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>71.26 ± 13.30</td>
<td>75.32 ± 11.47</td>
<td>0.007</td>
</tr>
<tr>
<td>Female sex</td>
<td>43 (43.9)</td>
<td>65 (51.6)</td>
<td>0.282</td>
</tr>
<tr>
<td>Comorbidity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>43 (43.9)</td>
<td>44 (34.9)</td>
<td>0.345</td>
</tr>
<tr>
<td>Hypertension</td>
<td>38 (38.8)</td>
<td>60 (47.6)</td>
<td>0.365</td>
</tr>
<tr>
<td>ICU length of stay (day)</td>
<td>88 (89.8)</td>
<td>12 (9.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sepsis</td>
<td>61 (62.2)</td>
<td>38 (30.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Shock</td>
<td>51 (52.0)</td>
<td>6 (4.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Acute kidney injury</td>
<td>69 (70.4)</td>
<td>60 (47.6)</td>
<td>0.001</td>
</tr>
<tr>
<td>Ventilator use</td>
<td>61 (62.2)</td>
<td>0 (0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>12 (12.2)</td>
<td>7 (5.6)</td>
<td>0.092</td>
</tr>
<tr>
<td>Postoperation</td>
<td>8 (8.2)</td>
<td>1 (0.8)</td>
<td>0.011</td>
</tr>
<tr>
<td>Gastrointestinal bleeding</td>
<td>2 (2.0)</td>
<td>0 (0)</td>
<td>0.190</td>
</tr>
<tr>
<td>Mortality</td>
<td>44 (44.9)</td>
<td>26 (20.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Baseline laboratory finding</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum creatinine (mg/dL)</td>
<td>1.56 ± 1.45</td>
<td>1.52 ± 1.01</td>
<td>0.825</td>
</tr>
<tr>
<td>eGFR (mL/min/1.73 m²)</td>
<td>72.32 ± 43.47</td>
<td>57.57 ± 34.13</td>
<td>0.094</td>
</tr>
<tr>
<td>Laboratory finding at catheter insertion</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum creatinine (mg/dL)</td>
<td>2.24 ± 2.02</td>
<td>2.31 ± 1.94</td>
<td>0.788</td>
</tr>
<tr>
<td>eGFR (mL/min/1.73 m²)</td>
<td>60.81 ± 50.71</td>
<td>56.83 ± 62.88</td>
<td>0.610</td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>9.67 ± 1.40</td>
<td>10.42 ± 1.82</td>
<td>0.128</td>
</tr>
<tr>
<td>Platelet (&gt;10⁹/mm³)</td>
<td>128.75 ± 75.00</td>
<td>221.80 ± 64.50</td>
<td>0.148</td>
</tr>
<tr>
<td>Prothrombin time (sec)</td>
<td>15.26 ± 6.50</td>
<td>15.30 ± 6.66</td>
<td>0.993</td>
</tr>
<tr>
<td>Activated partial thromboplastin time (sec)</td>
<td>33.84 ± 6.19</td>
<td>35.53 ± 8.03</td>
<td>0.715</td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>2.78 ± 0.70</td>
<td>2.82 ± 0.66</td>
<td>0.993</td>
</tr>
<tr>
<td>Information on catheter insertion</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right side Insertion</td>
<td>40 (40.8)</td>
<td>67 (53.2)</td>
<td>0.080</td>
</tr>
<tr>
<td>Access vein</td>
<td></td>
<td></td>
<td>0.788</td>
</tr>
<tr>
<td>Basilic vein</td>
<td>53 (54.1)</td>
<td>69 (54.8)</td>
<td></td>
</tr>
<tr>
<td>Brachial vein</td>
<td>42 (42.9)</td>
<td>51 (40.4)</td>
<td></td>
</tr>
<tr>
<td>Cephalic vein</td>
<td>3 (3.0)</td>
<td>6 (4.8)</td>
<td></td>
</tr>
</tbody>
</table>

Data are presented as mean ± standard deviation or number (%).

eGFR, estimated glomerular filtration rate; ICU, intensive care unit.

guidewire, as detected by venogram (Supplementary Fig. 4, available online). The other example of guidewire passage disturbance occurred after successful puncture; the method was changed to fluoroscopy but failed due to multiple venous stenoses. Major malposition, wherein the catheter tip was placed in the right jugular vein, occurred in one case. Three minor malpositions occurred in group 1. In two cases, the catheter tip was located in an innominate vein above the SVC; in the third case, the catheter tip was located at the deep RA. For these minor malpositions, catheter function was good and the catheter was used without exchange. Malpositions developed in three among 42 brachial vein access cases, one of 53 basilic vein access cases, and none of three cephalic vein access cases in group 1.

Three cases in group 2 failed. No puncture failures occurred. In one case, guidewire passage disturbance occurred due to venous stenosis. There were two major malposition cases of central vein stenosis where the catheter tip was located in the subclavian vein (Fig. 3B). There were no minor malpositions in group 2 because catheter length measurements were stricter. In group 2, all malposition cases were confirmed to have central vein stenosis.

Multiple-puncture rates among successful cases (4.1% vs. 0.0%, p = 0.035) were higher in group 1 than group 2.
Insertion site bleeding (5.1% vs. 6.3%, p = 0.779) was the most common complication in both groups. Thrombosis incidence (1.0% vs. 1.6%, p = 0.714) was low and was not different between the two groups. Insertion site exit infections (2.0% vs. 0.8%, p = 0.582) and systemic infections (2.0% vs. 3.2%, p = 0.698) were rare in both groups.

### Discussion

An increasing number of elderly patients and those who have hemodynamic instability, are in a state of shock, or are ventilator-dependent are admitted to the nephrology department or receive consultations from this department [3]. These patients need external support such as proper intravenous therapy due to long-term hospitalization, requirement for intravenous antibiotics, and nutritional therapy. However, lack of blood vessel access in this patient population can hinder proper treatment. To treat these patients in the ICU, a central catheter needs to be inserted. Considering the higher incidence of CKD development in AKI patients, a centrally inserted central catheter (CICC) may be better in patients with AKI as indicated by a serum creatinine level greater than 2.0 or 3.0 mg/dL for vascular protection. However, if clinical necessity is considered more significant than future access creation, a PICC may be a useful alternative. Traditionally, a CICC is inserted through a subclavian vein or the internal jugular vein. In recent years, PICCs have increasingly been used in critical care settings because of their benefits over CICCs [10]. First, their insertion is easy and safe, simply involving puncture and cannulation of a peripheral vein of the arm. PICC insertion and United States guidance negate the risk of hemothorax and pneumothorax, and the possibility of primary malposition is very low [11, 12]. Furthermore, PICC placement is appropriate in patients with coagulative disorders who need central vein access to avoid post-procedural hemorrhage [11, 13]. PICCs also have a low catheter-related blood flow infection rate [14]. At present, PICCs are highly recommended in the following clinical conditions; major anatomic abnormalities of the chest and neck that may lead to difficulties in the placement and dressing of CICCs, tracheostomy, and decreased platelet count or coagulation abnormalities [11]. PICC use has also been recommended in critically ill patients with severe cardiopulmonary problems, severe malnutrition, or obesity [12].

However, the increased use of PICCs has increased the

### Table 2. Results of PICC procedures between the two groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group 1 (n = 98)</th>
<th>Group 2 (n = 126)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of PICC insertion (day)</td>
<td>26 (10-35)</td>
<td>20 (15-30)</td>
<td>0.597</td>
</tr>
<tr>
<td>Successful cases</td>
<td>92 (93.9)</td>
<td>123 (97.6)</td>
<td>0.171</td>
</tr>
<tr>
<td>Failure cases</td>
<td>6 (6.1)</td>
<td>3 (2.4)</td>
<td>0.216</td>
</tr>
<tr>
<td>Cause of failure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Puncture failure</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>&gt;0.999</td>
</tr>
<tr>
<td>Guidewire passage</td>
<td>2 (2.0)</td>
<td>1 (0.8)</td>
<td>0.505</td>
</tr>
<tr>
<td>Malposition</td>
<td>4 (4.1)</td>
<td>2 (1.6)</td>
<td>0.568</td>
</tr>
<tr>
<td>Major malposition</td>
<td>1 (1.0)</td>
<td>2 (1.6)</td>
<td></td>
</tr>
<tr>
<td>Minor malposition</td>
<td>3 (3.1)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Multiple puncture rate in successful cases</td>
<td>4 (4.1)</td>
<td>0 (0)</td>
<td>0.035</td>
</tr>
<tr>
<td>Insertion-associated complications</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bleeding</td>
<td>5 (5.1)</td>
<td>8 (6.3)</td>
<td>0.779</td>
</tr>
<tr>
<td>Thrombosis</td>
<td>1 (1.0)</td>
<td>2 (1.6)</td>
<td>0.714</td>
</tr>
<tr>
<td>Arrhythmia</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Exit site cellulitis</td>
<td>2 (2.0)</td>
<td>1 (0.8)</td>
<td>0.582</td>
</tr>
<tr>
<td>Systemic infection</td>
<td>2 (2.0)</td>
<td>4 (3.2)</td>
<td>0.698</td>
</tr>
</tbody>
</table>

Data are presented as median (interquartile range) or number (%).

PICC, peripherally inserted central catheter.

*Good catheter function with the catheter tip located between the superior vena cava and mid-portion of the right atrium.*

*Substandard inflow/outflow or catheter tip malposition.*

*Location of the catheter tip in the internal jugular or subclavian vein.*

*Placement of the catheter tip 1 to 2 cm above the superior vena cava or deep portion of the right atrium.*
incidence of complications such as venous thrombosis and infection. PICC use is acceptable only when the duration of use is scheduled to be longer than 6 days or non-peripherally compatible infusions are needed (e.g., sclerosing antibiotics or chemotherapy) [15]. Among patients with CKD stage 3b or higher (eGFR of <45 mL/min/1.73 m²), PICC use is generally considered unacceptable, largely due to the high likelihood of peripheral and central venous complications (including thrombosis) interrupting future hemodialysis access [16]. These types of cases require nephrology consultation prior to PICC placement for assessment of risk vs. benefit; PICCs are only strongly argued for in cases of clinical necessity. When venous access is necessary for 5 or fewer days, experts recommend placement of peripheral intravenous catheters in the dorsum of the hand (avoiding the forearm veins) for infusion of peripherally compatible infusates. If venous access is needed for longer durations or for infusion of a non-peripherally compatible drug, the use of tunneled small-bore central catheters (for example, 4-Fr single-lumen or 5-Fr double-lumen catheters inserted in the jugular vein and tunneled toward the chest) is considered appropriate [17]. This study excluded patients with CKD (stage 3b and above) who did not undergo dialysis and patients receiving maintenance dialysis.

A PICC is commonly inserted in the angiography room, but insertion can be conducted at the patient’s bedside when risks associated with moving the patient are considered too high [18,19]. Nephrologists have accumulated considerable experience in the use of ultrasound for insertion of tunneled catheters; therefore, they can perform ultrasound-guided procedures without problems. In the current study, it was difficult to insert the guidewire or catheter in some cases. In these cases, the cause was stenosis or excessive curvature of the vein. In cases of passage disturbance of the guidewire, a fluoroscopic venogram can be performed for guidewire rerouting or an alternate puncture site can be used. In ultrasound-guided bedside procedures, this can be conducted by selecting a different puncture site or using a more proximal vein.

In particular, depending on the angle at which the cephalic arch meets the subclavian vein, guidewire passage is sometimes difficult. The basilic vein is preferred as it is the largest diameter upper extremity vessel and affords a non-tortuous entry route into the subclavian vein. The cephalic vein is smaller than the basilic vein and makes a 90° angle at its entry to the terminal portion of the axillary vein, making catheter advancement somewhat difficult. Brachial veins lie deep in the center of the mid to upper arm and cannot be outwardly visualized or palpated; ultrasound guidance is required for access. In this study, malposition-prone access veins were not definite. First, malposition events were rare. Second, a minor malposition depends on length rather than type of access vein. Of the 11 patients with a dialysis catheter in group 1, six patients had a PICC implanted on the ipsilateral side and five patients had a PICC implanted on the other side. No entry barrier to the guidewire was found during insertion in either group (data not shown).

Selecting the exact location of the PICC at the bedside is difficult without fluoroscopic images. This can lead to possible position abnormalities. In existing studies, the probability of location abnormality was variously reported to be 3% to 37% [20–23], 8.5% [4], and 7.9% [5]. However, there is no widespread agreement between experts regarding the correct position for the tip of a PICC [24–26]. Most American recommendations (Association for Vascular Access, Food and Drug Administration) [27,28] suggest that the tip be in the inferior third of the SVC, while European guidelines [11,29] recommend positioning of the tip in the RA (specifically, in the upper area) appropriate. A widely accepted opinion is that the optimal site is proximal to the area between the SVC and RA [30]. If the catheter tip is in a higher position (i.e., in the brachiocephalic, internal jugular, or subclavian vein), there is an increased risk of malfunction [31] and an increased risk of venous thrombosis compared to a position lower in the SVC or close to the cavoatrial junction [32]. If the tip is positioned “too low” (RA, right ventricle, or inferior vena cava), there is a risk of arrhythmia, tricuspid valve dysfunction or lesions, and thrombosis [33,34].

In addition, PICC removal and reinsertion due to abnormal location may be difficult, particularly if blood vessel condition is poor. In this study, catheters malpositioned near the SVC or RA had good function and long-term patency. Position abnormality corrections can be accomplished by assessing the internal jugular veins with ultrasound during insertion. The absence (Supplementary Fig. 2) or presence (Supplementary Fig. 3) of the guidewire can be easily checked with ultrasound, and, if visible, the guidewire can be moved back to the heart through shaping of the catheter tip. This can reduce the incidence of positional abnormality on chest radiograph after the procedure from 7.4% to 0.7% [35].
Infection (cellulitis, abscesses, or bacteremia and systemic infections), phlebitis/infiltration, mechanical malfunction, air embolism, cardiac arrhythmias, and catheter occlusions are the main complications associated with PICC insertion [7]. In this study, the most common complications were exit site bleeding that was controlled by compression dressing. One patient (Supplementary Fig. 5, available online) went into cardiogenic shock because of acute massive myocardial infarction. Low blood pressure may lead to the need to apply ECMO, and subsequent AKI can lead to CRRT using the ECMO line. These scenarios are common in modern ICU AKI patients. These patient require a PICC line for long-term hospitalization. In the current study, two patients had successful PICC insertion without bleeding complications despite persistent heparin anticoagulation. Furthermore, thrombosis and infection were rare, neither group had serious complications, and no mortalities occurred in either group.

This study has some limitations that should be considered. First, because insertions were performed by one practitioner at a single center, the results cannot be generalized to other nephrologists. Second, only short-term in-hospital clinical outcomes during admission were analyzed. Long-term outcomes and patient survival taking into account recovery from AKI and central venous stenosis should be assessed in future research.

In conclusion, PICC insertion by a nephrologist was highly successful and safe when performed in critically ill patients with comorbidities. Furthermore, the success rate of bedside PICC insertion was comparable to that of PICC insertion under fluoroscopic guidance. Adequate placement of the appropriate catheter is important in the management of critically ill patients to improve their prognosis and reduce avoidable complications. PICC insertion is generally contraindicated in CKD patients for arm-save, but in a life-threatening situation in the ICU, PICC insertion may be considered even in CKD patients, and under these circumstances, PICCs can be safely placed by nephrologists. It is expected that the role of interventional nephrologists in the insertion and management of central catheters will only increase over time.

**Conflicts of interest**

The author has no conflicts of interest to declare.

**ORCID**

Seong Cho, https://orcid.org/0000-0002-6183-1647

**References**

13. Gallieni M, Pittiruti M, Biffi R. Vascular access in oncology


Impact of acute kidney injury in deceased donors with high Kidney Donor Profile Index on posttransplant clinical outcomes: a multicenter cohort study

Woo Yeong Park\textsuperscript{1}, Yoon Kyung Chang\textsuperscript{2}, Young Soo Kim\textsuperscript{3}, Kyubok Jin\textsuperscript{1}, Chul Woo Yang\textsuperscript{4}, Seungyeup Han\textsuperscript{1}, Byung Ha Chung\textsuperscript{4}

\textsuperscript{1}Division of Nephrology, Department of Internal Medicine, Keimyung University Dongsan Hospital, Keimyung University School of Medicine, Daegeu, Republic of Korea
\textsuperscript{2}Division of Nephrology, Department of Internal Medicine, Daejeon St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Daejeon, Republic of Korea
\textsuperscript{3}Division of Nephrology, Department of Internal Medicine, Uijeongbu St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Uijeongbu, Republic of Korea
\textsuperscript{4}Transplant Research Center, Division of Nephrology, Department of Internal Medicine, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea

\textbf{Background:} This study evaluated the impact of acute kidney injury (AKI) on posttransplant clinical outcomes for deceased donor (DD) kidney transplantation (KT) using the Kidney Donor Profile Index (KDPI) system.

\textbf{Methods:} Overall, 657 kidney transplant recipients (KTRs) receiving kidneys from 526 DDs from four transplant centers were included. We divided them into the high and low KDPI donor groups by 65%, the KDPI score, and both groups were subdivided into the AKI-DDKT and non-AKI-DDKT subgroups according to AKI in DDs.

\textbf{Results:} There was no significant difference in the incidence of delayed graft function (DGF) between the high and low KDPI-KTR groups; however, the AKI-DDKT subgroup showed significantly higher incidence of DGF than the non-AKI-DDKT subgroup in both groups ($p = 0.001$, $p < 0.001$, respectively). The death-censored graft survival rate was significantly lower in the high KDPI-KTR group than in the low KDPI-KTR group ($p = 0.005$). Only in the high KDPI-KTR group, the death-censored graft survival rate was significantly lower in the KT from DDs with AKI stage 3 than KT from DDs with non-AKI or AKI stage 1 or 2 ($p = 0.040$). The interaction between AKI stage 3 in DDs and high KDPI on the allograft outcome was significant ($p = 0.002$).

\textbf{Conclusion:} KT from DDs with AKI stage 3 showed an adverse impact on the allograft outcome in the high KDPI-KTR group. Therefore, DDs with a high KDPI score should be managed carefully so that severe AKI does not occur prior to KT.

\textbf{Keywords:} Acute kidney injury, Brain death, Graft survival, Kidney transplantation, Mortality
Introduction

Although one of the biggest drawbacks of kidney transplantation (KT) is the problem of organ shortage, the number of discarded kidneys still increases worldwide [1–3]. In 2014, the Kidney Donor Profile Index (KDPI) system, a new allocation system in the United States (US), was introduced, but the number of discarded kidneys in the US is not decreasing, and there is still a disagreement about the utility of this system [1,4–6]. The major factor of this discard is reported as the donor kidney function at the time of KT [7–9]. Recently, the efficacy of conducting procurement biopsy before transplantation has been reported, but it is still not commercialized [10]. Thus, it is important to trust and actively apply the current allocation system [4]. In particular, a kidney injury during donor management affects the condition of the donor kidney, which is mainly affected by the hemodynamic condition [11].

Several researches have recently been published regarding the clinical impact of KT from deceased donors (DDs) with acute kidney injury (AKI) in deceased donor KT (DDKT) [12,13]. AKI is very commonly detected in individuals with brain death state for various causes [14,15]. The shortage of donor kidneys has also driven the use of the kidney from DDs with AKI. In addition, some research demonstrated that AKI does not affect the long-term allograft outcome although it results in lower allograft function in the early period after KT [16,17]. Our previous studies also showed that there was no significant difference in the long-term allograft outcome between the AKI-DDKT and non-AKI-DDKT groups or between the expanded criteria donor (ECD)-KT and standard criteria donor-KT groups, but AKI superimposed on ECDs or occurring in elderly DDs has a synergistically adverse impact on the long-term posttransplant allograft outcomes in the corresponding recipients [18]. Finally, the state of donor at the time of KT is important when AKI developed, but this issue is still controversial.

Recently, Koyawala and Parikh [12] have so far addressed this issue and insisted that there was no influence of DD with AKI on the long-term outcome. However, there are various limitations in this study, and it is still difficult to draw a clear conclusion on this issue as the new allocation system, KDPI score, has been published for approximately 4 years. In a previous study, the KDPI score was a useful tool to predict the allograft outcome in DDKT [19], but there was no significant difference in the long-term allograft outcome between the high and low KDPI-kidney transplant recipient (KTR) groups [20]. Based on these studies, we investigated the impact of AKI in DDs with a high or low KDPI score on posttransplant clinical outcomes. The short- and long-term clinical outcomes according to the presence of AKI on DDs in the low and high KDPI-KTR groups were analyzed. In addition, the association between AKI and high KDPI in DDs on posttransplant allograft survival was evaluated.

Methods

Study population

A total of 657 KTRs receiving kidneys from 526 DDs between October 1996 and December 2017 from four transplant centers (Seoul St. Mary’s Hospital, Uijeongbu St. Mary’s Hospital, Daeyejan St. Mary’s Hospital, and Keimyung University Dongsan Hospital) were included. We divided them into the high and low KDPI donor groups by 65%, which is the median value of the KDPI score, and both groups were subdivided into the AKI-DDKT and non-AKI-DDKT subgroups according to AKI in DDs. AKI in DDs was defined and staged according to the Kidney Disease: Improving Global Outcomes (KDIGO) criteria as described in previous reports [21]. The KTRs according to the KDPI score or presence of AKI in DDs are shown in Fig. 1. Among all DDs, there were 257 high KDPI donors (48.9%) and 269 low KDPI donors (51.1%). Among all KTRs, there were 338 high KDPI-KTRs (51.4%) and 319 low KDPI-KTRs (48.6%). In the high KDPI-KTR group, there were 239 cases (36.4%) in the high KDPI-AKI-DDKT subgroup and 99 cases (15.1%) in the high KDPI-non-AKI-DDKT subgroup. In the low KDPI-KTR group, there were 148 cases (22.5%) in the low KDPI-AKI-DDKT subgroup and 171 cases (26.0%) in the low KDPI-non-AKI-DDKT subgroup.

Clinical and laboratory parameters and clinical outcomes

The medical records of the study population were retrospectively analyzed. We investigated the data of DDs: age, sex, height, weight, body mass index (BMI, kg/m²), ethnicity, history of diabetes mellitus (DM) and hypertension (HTN), causes of brain death, serum creatinine, estimated glomerular filtration rate (eGFR) by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI), and medical condition of DDs. The KTRs were subdivided into the AKI-DDKT and non-AKI-DDKT subgroups according to AKI in DDs.
Disease Epidemiology Collaboration (CKD-EPI) at baseline and the admission day and prior to KT, hepatitis C virus state, and donation after cardiac death. When serum creatinine was normal at the time of admission, the serum creatinine at admission was defined as baseline creatinine even if there was no previous baseline creatinine, and serum creatinine was measured at least 2 to 3 times until KT. AKI was defined by the KDIGO guideline based on the serum creatinine at the time of admission regardless of the presence or absence of a baseline creatinine. CKD was defined when estimated GFR less than 60 mL/min/1.73 m$^2$ continued for 3 months after measuring baseline creatinine. We used the ECD criteria according to the United Network for Organ Sharing for the definition of marginal donors [22]. We calculated the KDPI score with the terminal serum creatinine level through the KDPI calculator in the website of the Organ Procurement and Transplantation Network [23]. When the KDPI score is calculated, the factors are used as follows; age, height, weight, ethnicity, history of HTN or DM, cause of death, serum creatinine, hepatitis C virus serology, and donation after cardiac death in the DD [6]. The data of KTRs were also investigated; age, sex, height, weight, BMI, ethnicity, dialysis vintage prior to KT, frequency of KT, causes of end-stage renal disease, history of DM and HTN, cold ischemic time, number of human leukocyte antigen (HLA) mismatches, types of immunosuppressive agents for induction and maintenance, and rate of panel-reactive antibodies (PRAs).

Biopsy-proven acute rejection (BPAR) was diagnosed according to the Banff classification [24,25]. Delayed graft function (DGF) was defined as at least one dialysis requirement within the first week after KT [26]. Death-censored allograft survival rate was defined as the proportion considering the return to the dialysis or retransplantation during the study period, except for patient death with a functioning allograft. Patient survival rate was defined as the proportion considering the death from all causes during the study period.

The primary outcome of this study was to investigate the impact of AKI in DDs on the death-censored allograft survival between the high and low KDPI-KTR groups. Therefore, we compared the death-censored allograft survival between the AKI-DDKT and non-AKI-DDKT subgroups in both high and low KDPI-KTR groups and analyzed the interaction between AKI and high KDPI score. The secondary outcomes were to investigate the incidences of DGF and BPAR and changes in allograft function during the first year after KT (1 week, 2 weeks, 1 month, 3 months, 6 months, and 12 months after KT; assessed by eGFR, calculated using the CKD-EPI [27]) between the AKI-DDKT and non-AKI-DDKT subgroups in both high and low KDPI-KTR groups. Patient survival between AKI-DDKT and non-AKI-DDKT subgroups in the high or low KDPI-KTR group was compared.

This study was approved by the Institutional Review Boards (IRBs) of Seoul St. Mary’s Hospital (No. XC15RIMI0061K), Uijeongbu St. Mary’s Hospital (No. XC15RIMI0061U), Daejeon St. Mary’s Hospital (No. XC15RIMI0061K), and Dongsan Hospital, Keimyung University School of Medicine (No. 2020-05-047). The requirements for informed consent were waived by the IRBs of the aforementioned four centers because the use of the patient’s data for research was informed to all donors’ families and all recipients prior to KT to protect the personal information. Our study did not contain any distinguishable personal information, and all methods were performed according to the relevant guidelines and regulations.

**Statistical analysis**

Continuous variables are expressed as mean ± standard deviation.
deviation or median (interquartile range) and analyzed using the Student t test or the Mann-Whitney test. Categorical variables are expressed as count and percentage and analyzed using the chi-square test and Fisher exact test. The death-censored graft survival and patient survival rates were analyzed using the Kaplan-Meier curves and log-rank tests. All missing data were excluded. The Cox proportional hazards regression analysis was performed to investigate the relationship of the KDPI score and AKI for the clinical outcomes in DDKT, considering the confounding factors such as recipient age, transplant year (1996–2005 vs. 2006–2010 vs. 2011–2017), transplant center, recipient HTN, and acute rejection. Interaction effects between AKI and high KDPI score were explored by adding interaction terms to the Cox proportional hazards model with backward elimination of variables. In other words, AKI * high KDPI score as an interaction effect was included in the Cox proportional hazards model. The p-values less than 0.05 were considered statistically significant. All statistical analyses were performed using IBM SPSS version 21.0 (IBM Corp., Armonk, NY, USA).

Results

Comparison of baseline characteristics between the high and low KDPI donors and between the high and low KDPI-KTR groups

The median follow-up duration of the study population was 48.0 months (interquartile range, 22.3–68.0). The mean age of the high KDPI donor group was significantly higher than that of the low KDPI donor group (55.0 ± 8.9 years vs. 35.5 ± 12.2 years, p < 0.001). The proportions of donors with HTN, DM, and death due to cerebrovascular accident (CVA) were significantly higher in the high KDPI donor group than in the low KDPI donor group (37.4% vs. 4.1%, p < 0.001; 17.1% vs. 2.1%, p < 0.001; 76.3% vs. 62.1%, p < 0.001, respectively). The baseline and allocation CKD-EPI eGFRs in DDs were significantly lower in the high KDPI donor group than in the low KDPI donor group (79.7 ± 20.1 mL/min/1.73 m² vs. 87.8 ± 28.9 mL/min/1.73 m², p = 0.001; 51.6 ± 29.6 mL/min/1.73 m² vs. 94.9 ± 44.6 mL/min/1.73 m², p < 0.001). The proportion of DDs with CKD stage 3 or above at allocation was significantly higher in the high KDPI donor group than in the low KDPI donor group (67.7% vs. 30.9%, p < 0.001). The proportion of AKI was also significantly higher in the high KDPI donor group than in the low KDPI donor group (69.3% vs. 42.8%, p < 0.001). The proportion of ECD donors was significantly higher in the high KDPI donor group than in the low KDPI donor group (57.6% vs. 0.4%, p < 0.001). There were no significant differences in donor sex and BMI between the high and low KDPI donor groups (Table 1).

In corresponding recipients, the mean age was also higher in the high KDPI-KTR group than in the low KDPI-KTR group (51.3 ± 10.1 years vs. 47.6 ± 9.8 years, p < 0.001). The proportions of KTRs with DM and use of antithymocyte globulin for induction immunosuppressant were significantly higher in the high KDPI-KTR group than in the low KDPI-KTR group (24.3% vs. 17.2%, p = 0.028; 33.7% vs. 25.1%, p = 0.017), but the proportion of retransplantation was significantly higher in the low KDPI-KTR group than in the high KDPI-KTR group (14.1% vs. 7.4%, p = 0.008). The mean HLA mismatch number was significantly higher in the high KDPI-KTR group than in the low KDPI-KTR group (3.8 ± 1.5 vs. 3.5 ± 1.5, p = 0.014). There was no significant difference in the distribution of recipient sex, dialysis duration before KT, cold ischemic time, and proportion of PRA > 50% between the high and low KDPI-KTR groups (Table 1).

Comparison of baseline characteristics between the high and low KDPI-KTR groups and between the AKI-DDKT and non-AKI-DDKT subgroups

In the high KDPI donor group, the proportions of male sex and cause of donor death by CVA were significantly higher in the AKI donor subgroup compared with those in the non-AKI donor subgroup (71.3% vs. 55.6%, p = 0.016; 78.7% vs. 70.9%, p = 0.024). The proportions of HTN and eGFR at baseline and allocation were significantly lower in the AKI donor subgroup compared with those in the non-AKI donor subgroup (79.7 ± 20.1 mL/min/1.73 m² vs. 87.8 ± 28.9 mL/min/1.73 m², p = 0.001; 51.6 ± 29.6 mL/min/1.73 m² vs. 94.9 ± 44.6 mL/min/1.73 m², p < 0.001). On the contrary, in the low KDPI donor group, the BMI and proportion of CKD stage 3 or above were significantly higher in the AKI donor subgroup compared with those in the non-AKI donor subgroup (30.9% vs. 51.9%, p = 0.002; 45.4 ± 26.6 vs. 81.0 ± 27.0, p < 0.001; 34.0 ± 21.0 vs. 77.7 ± 24.7, p < 0.001). The proportion of AKI in the non-AKI donor subgroup (24.1 ± 4.0 vs. 22.2 ± 3.9, p < 0.001; 48.7% vs. 36.4%, p = 0.046), but eGFRs at baseline and allocation were significantly lower in the AKI donor subgroup compared with those in the non-AKI donor subgroup (59.0 ± 36.0 vs. 102.3 ± 34.5, p < 0.001; 50.5 ± 32.0 vs. 106.7 ± 31.4, p < 0.001).
The incidence of DGF was not significantly different between the high and low KDPI-KTR groups (12.7% vs. 12.5%, p > 0.999) (Fig. 2A). In the subgroup analysis, the incidence of DGF was significantly higher in the AKI-DDKT subgroup compared with that in the non-AKI-DDKT subgroup in both high and low KDPI-KTR groups (23.0% vs. 6.1%, p < 0.001; 25.7% vs. 11.7%, p = 0.001) (Fig. 2B).

The incidence of BPAR within the first year after KT did not differ significantly between the high and low KDPI-KTR groups (12.7% vs. 12.5%, p > 0.999) (Fig. 2C). Moreover, there was no significant difference in the incidence of BPAR between the AKI-DDKT and non-AKI-DDKT subgroups in both high and low KDPI-KTR groups (13.0% vs. 12.1%, p > 0.999; 16.2% vs. 9.4%, p = 0.089) (Fig. 2B).

Allograft function for 12 months (1 week, 2 weeks, 1 month, 3 months, 6 months, and 12 months) after KT was significantly lower in the high KDPI-KTR group compared with that in the low KDPI-KTR group (39.4 ± 28.3 vs. 56.2 ± 33.3, p < 0.001; 52.0 ± 24.4 vs. 68.1 ± 29.0, p < 0.001; 48.4 ± 20.8 vs. 63.5 ± 23.6, p < 0.001; 56.0 ± 18.8 vs. 72.5 ± 20.5, p < 0.001; 54.8 ± 18.4 vs. 71.5 ± 20.1, p < 0.001; 57.6 ± 19.7 vs. 75.0 ± 22.5, p < 0.001) (Fig. 2E).

In the high KDPI-KTR group, allograft function within 3 months (1 week, 2 weeks, 1 month) after KT was significantly lower in the AKI-DDKT subgroup compared with that in the non-AKI-DDKT subgroup (33.7 ± 27.0 vs. 53.3 ± 26.5, p < 0.001; 48.4 ± 24.7 vs. 60.9 ± 21.5, p < 0.001; 46.1 ± 20.9 vs. 54.2 ± 19.6, p = 0.001), but there was no significant difference between 3 and 12 months (3 months, 6 months, and 12 months) (55.3 ± 18.5 vs. 57.8 ± 19.5, p = 0.273; 54.3 ± 18.0 vs. 56.1 ± 19.4, p = 0.413; 57.6 ± 19.3 vs. 57.4 ± 20.9, p < 0.001).

### Table 1. Comparison of clinical and laboratory parameters between high KDPI donor (or recipient) and low KDPI donor (or recipient)

<table>
<thead>
<tr>
<th>Variable</th>
<th>High KDPI</th>
<th>Low KDPI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Donor</td>
<td>257</td>
<td>269</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age at KT (yr)</td>
<td>55.0 ± 8.9</td>
<td>35.5 ± 12.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sex, male/female</td>
<td>171:86</td>
<td>197:72</td>
<td>0.106</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>23.1 ± 3.2</td>
<td>22.6 ± 3.9</td>
<td>0.223</td>
</tr>
<tr>
<td>HTN</td>
<td>96 (37.4)</td>
<td>11 (4.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>DM</td>
<td>44 (17.1)</td>
<td>6 (2.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cause of donor death, CVA</td>
<td>196 (76.3)</td>
<td>167 (62.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>eGFR (mL/min/1.73 m²)</td>
<td>79.7 ± 20.1</td>
<td>87.8 ± 28.9</td>
<td>0.001</td>
</tr>
<tr>
<td>At allocation</td>
<td>51.6 ± 29.6</td>
<td>94.9 ± 44.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CKD stage 3 or above stage</td>
<td>174 (67.7)</td>
<td>83 (30.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>AKI</td>
<td>178 (69.3)</td>
<td>115 (42.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Stage 1</td>
<td>61 (23.7)</td>
<td>52 (19.3)</td>
<td>0.106</td>
</tr>
<tr>
<td>Stage 2</td>
<td>55 (21.4)</td>
<td>27 (10.0)</td>
<td>0.003</td>
</tr>
<tr>
<td>Stage 3</td>
<td>62 (24.1)</td>
<td>36 (13.4)</td>
<td>0.003</td>
</tr>
<tr>
<td>ECD</td>
<td>148 (57.6)</td>
<td>1 (0.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Recipient</td>
<td>338</td>
<td>319</td>
<td>0.004</td>
</tr>
<tr>
<td>Transplant year</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1996–2005</td>
<td>0 (0)</td>
<td>8 (2.5)</td>
<td></td>
</tr>
<tr>
<td>2006–2010</td>
<td>44 (13.0)</td>
<td>55 (17.2)</td>
<td></td>
</tr>
<tr>
<td>2011–2016</td>
<td>294 (87.0)</td>
<td>256 (80.3)</td>
<td></td>
</tr>
<tr>
<td>Age at KT (yr)</td>
<td>51.3 ± 10.1</td>
<td>47.6 ± 9.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sex, male/female</td>
<td>201:137</td>
<td>118:131</td>
<td>0.937</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>23.3 ± 3.5</td>
<td>23.0 ± 4.1</td>
<td>0.297</td>
</tr>
<tr>
<td>HTN</td>
<td>290 (85.8)</td>
<td>263 (82.4)</td>
<td>0.242</td>
</tr>
<tr>
<td>DM</td>
<td>82 (24.3)</td>
<td>55 (17.2)</td>
<td>0.028</td>
</tr>
<tr>
<td>Dialysis duration before KT (yr)</td>
<td>7.3 ± 11.7</td>
<td>8.8 ± 8.6</td>
<td>0.289</td>
</tr>
<tr>
<td>Previous KT</td>
<td>25 (74)</td>
<td>45 (14.1)</td>
<td>0.008</td>
</tr>
<tr>
<td>Cause of ESRD</td>
<td></td>
<td></td>
<td>0.003</td>
</tr>
<tr>
<td>Glomerulonephritis</td>
<td>142 (42.0)</td>
<td>156 (48.9)</td>
<td></td>
</tr>
<tr>
<td>DM</td>
<td>70 (20.7)</td>
<td>44 (13.8)</td>
<td></td>
</tr>
<tr>
<td>HTN</td>
<td>70 (20.7)</td>
<td>45 (14.1)</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>56 (16.6)</td>
<td>74 (23.2)</td>
<td></td>
</tr>
<tr>
<td>Cold ischemic time (min)</td>
<td>247.9 ± 118.7</td>
<td>254.2 ± 129.8</td>
<td>0.531</td>
</tr>
<tr>
<td>HLA mismatch number</td>
<td>3.8 ± 1.5</td>
<td>3.5 ± 1.5</td>
<td>0.014</td>
</tr>
<tr>
<td>Induction</td>
<td></td>
<td></td>
<td>0.017</td>
</tr>
<tr>
<td>Basiliximab</td>
<td>224 (66.3)</td>
<td>239 (74.9)</td>
<td></td>
</tr>
<tr>
<td>ATG</td>
<td>114 (33.7)</td>
<td>80 (25.1)</td>
<td></td>
</tr>
<tr>
<td>Major immunosuppressant, tacrolimus-cyclosporine</td>
<td>335:3</td>
<td>312:6</td>
<td>0.251</td>
</tr>
<tr>
<td>PRA &gt; 50 %</td>
<td>50 (14.8)</td>
<td>64 (20.1)</td>
<td>0.048</td>
</tr>
<tr>
<td>Follow-up duration (mo)</td>
<td>44.1 ± 28.7</td>
<td>52.2 ± 39.9</td>
<td>0.003</td>
</tr>
</tbody>
</table>

Data are expressed as number only, mean ± standard deviation, or number (%). eGFR is calculated using Chronic Kidney Disease Epidemiology Collaboration. AKI, acute kidney injury; ATG, antithymocyte globulin; BMI, body mass index; CKD, chronic kidney disease; CVA, cerebrovascular accident; DM, diabetes mellitus; ECD, expanded criteria donor; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; HLA, human leukocyte antigen; HTN, hypertension; KDPI, Kidney Donor Profile Index; KT, kidney transplantation; PRA, panel-reactive antibody.
Table 2. Comparison of clinical and laboratory parameters according to AKI in high or low KDPI donor KTR

<table>
<thead>
<tr>
<th>Variable</th>
<th>Non-AKI-DDKT</th>
<th>AKI-DDKT</th>
<th>p-value</th>
<th>Non-AKI-DDKT</th>
<th>AKI-DDKT</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Donor</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at KT (yr)</td>
<td>79</td>
<td>178</td>
<td>0.173</td>
<td>154</td>
<td>115</td>
<td>0.261</td>
</tr>
<tr>
<td>Sex, male:female</td>
<td>44:35</td>
<td>127:51</td>
<td>0.016</td>
<td>107:47</td>
<td>90:25</td>
<td>0.126</td>
</tr>
<tr>
<td>BMI (kg/m(^2))</td>
<td>23.3 ± 3.3</td>
<td>23.1 ± 3.1</td>
<td>0.653</td>
<td>22.2 ± 3.9</td>
<td>24.1 ± 4.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HTN</td>
<td>41 (51.9)</td>
<td>55 (30.9)</td>
<td>0.002</td>
<td>8 (5.2)</td>
<td>3 (2.6)</td>
<td>0.362</td>
</tr>
<tr>
<td>DM</td>
<td>14 (17.7)</td>
<td>30 (16.9)</td>
<td>0.859</td>
<td>4 (2.6)</td>
<td>2 (1.7)</td>
<td>&gt;0.999</td>
</tr>
<tr>
<td>Cause of donor death, CVA</td>
<td>56 (70.9)</td>
<td>140 (78.7)</td>
<td>0.024</td>
<td>92 (59.7)</td>
<td>75 (65.2)</td>
<td>0.377</td>
</tr>
<tr>
<td>eGFR (mL/min/1.73 m(^2))</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>81.0 ± 27.0</td>
<td>45.4 ± 26.6</td>
<td>&lt;0.001</td>
<td>102.3 ± 34.5</td>
<td>59.0 ± 36.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>At allocation</td>
<td>77.7 ± 24.7</td>
<td>34.0 ± 21.0</td>
<td>&lt;0.001</td>
<td>106.7 ± 31.4</td>
<td>50.5 ± 32.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CKD stage 3 or above stage</td>
<td>37 (46.8)</td>
<td>85 (47.8)</td>
<td>1</td>
<td>56 (36.4)</td>
<td>56 (48.7)</td>
<td>0.046</td>
</tr>
<tr>
<td>ECD</td>
<td>39 (49.4)</td>
<td>109 (61.2)</td>
<td>0.1</td>
<td>0 (0)</td>
<td>1 (0.9)</td>
<td>0.428</td>
</tr>
<tr>
<td><strong>Recipient</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at KT (yr)</td>
<td>51.4 ± 10.7</td>
<td>51.3 ± 9.9</td>
<td>0.878</td>
<td>47.0 ± 8.8</td>
<td>48.3 ± 10.7</td>
<td>0.261</td>
</tr>
<tr>
<td>Sex, male:female</td>
<td>60:39</td>
<td>141:98</td>
<td>0.809</td>
<td>103:68</td>
<td>85:63</td>
<td>0.649</td>
</tr>
<tr>
<td>BMI (kg/m(^2))</td>
<td>23.3 ± 3.4</td>
<td>23.3 ± 3.5</td>
<td>0.981</td>
<td>22.7 ± 3.2</td>
<td>23.4 ± 4.9</td>
<td>0.141</td>
</tr>
<tr>
<td>HTN</td>
<td>84 (84.8)</td>
<td>206 (86.2)</td>
<td>0.735</td>
<td>141 (82.5)</td>
<td>122 (82.4)</td>
<td>&gt;0.999</td>
</tr>
<tr>
<td>DM</td>
<td>18 (18.2)</td>
<td>64 (26.8)</td>
<td>0.097</td>
<td>29 (17.0)</td>
<td>26 (17.6)</td>
<td>0.883</td>
</tr>
<tr>
<td>Dialysis duration before KT (yr)</td>
<td>7.0 ± 4.5</td>
<td>8.3 ± 13.6</td>
<td>0.895</td>
<td>9.0 ± 9.8</td>
<td>8.6 ± 7.1</td>
<td>0.728</td>
</tr>
<tr>
<td>Previous KT</td>
<td>6 (6.1)</td>
<td>19 (7.9)</td>
<td>0.652</td>
<td>18 (10.5)</td>
<td>27 (18.2)</td>
<td>0.054</td>
</tr>
<tr>
<td>Cause of ESRD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glomerulonephritis</td>
<td>45 (45.5)</td>
<td>97 (40.6)</td>
<td>0.956</td>
<td>95 (55.6)</td>
<td>61 (41.2)</td>
<td></td>
</tr>
<tr>
<td>DM</td>
<td>15 (15.2)</td>
<td>55 (23.0)</td>
<td>0.244</td>
<td>24 (14.0)</td>
<td>20 (13.5)</td>
<td></td>
</tr>
<tr>
<td>HTN</td>
<td>19 (19.2)</td>
<td>51 (21.3)</td>
<td>0.736</td>
<td>23 (13.5)</td>
<td>22 (14.9)</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>20 (20.2)</td>
<td>36 (15.1)</td>
<td>0.513</td>
<td>29 (17.0)</td>
<td>45 (30.4)</td>
<td></td>
</tr>
<tr>
<td>Cold ischemic time (min)</td>
<td>250.2 ± 112.6</td>
<td>247.0 ± 121.4</td>
<td>0.828</td>
<td>262.3 ± 124.7</td>
<td>245.1 ± 135.2</td>
<td>0.257</td>
</tr>
<tr>
<td>HLA mismatch number</td>
<td>3.7 ± 1.6</td>
<td>3.8 ± 1.4</td>
<td>0.541</td>
<td>3.5 ± 1.5</td>
<td>3.5 ± 1.4</td>
<td>0.634</td>
</tr>
<tr>
<td>Induction</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
<td></td>
<td></td>
<td>0.001</td>
</tr>
<tr>
<td>Basiliximab</td>
<td>83 (83.8)</td>
<td>141 (59.0)</td>
<td>141 (82.5)</td>
<td>98 (66.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ATG</td>
<td>16 (16.2)</td>
<td>98 (41.0)</td>
<td>0.307</td>
<td>30 (17.5)</td>
<td>50 (33.8)</td>
<td></td>
</tr>
<tr>
<td>Main immunosuppressant,</td>
<td>97 (97.0)</td>
<td>238.1</td>
<td>0.206</td>
<td>165/6</td>
<td>147:1</td>
<td>0.222</td>
</tr>
<tr>
<td>tacrolimus:cyclosporine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PRA &gt; 50%</td>
<td>13 (13.1)</td>
<td>37 (15.5)</td>
<td>0.864</td>
<td>32 (18.7)</td>
<td>32 (21.6)</td>
<td>0.779</td>
</tr>
</tbody>
</table>

Data are expressed as number only, mean ± standard deviation, or number (%).

eGFR is calculated using Chronic Kidney Disease Epidemiology Collaboration.

AKI, acute kidney injury; ATG, antithymocyte globulin; BMI, body mass index; CKD, chronic kidney disease; CVA, cerebrovascular accident; DDKT, deceased donor kidney transplantation; DM, diabetes mellitus; ECD, expanded criteria donor; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease, HLA, human leukocyte antigen; HTN, hypertension; KDPI, Kidney Donor Profile Index; KT, kidney transplantation; KTR, kidney transplant recipient; PRA, panel-reactive antibody.
In the low KDPI-KTR group, allograft function for 12 months (1 week, 2 weeks, 1 month, 3 months, 6 months, and 12 months) after KT was significantly lower in the AKI-DDKT subgroup compared with that in the non-AKI-DDKT subgroup (p < 0.001) (45.2 ± 34.6 vs. 65.7 ± 29.1, p < 0.001; 58.5 ± 30.4 vs. 76.4 ± 24.9, p < 0.001; 58.1 ± 23.9 vs. 68.1 ± 22.4, p < 0.001; 68.2 ± 21.6 vs. 76.2 ± 18.7, p < 0.001; 67.5 ± 21.2 vs. 74.8 ± 18.6, p = 0.002; 70.4 ± 23.3 vs. 78.7 ± 21.1, p = 0.001) (Fig. 2G).

**Comparison of the impact of AKI in DDs on the death-censored allograft survival between the high and low KDPI-KTR groups**

A total of 49 cases (49 of 657, 7.5%) of graft failure developed, including 31 cases (4.7%) in the high KDPI-KTR group (20 and 11 patients in the AKI-DDKT and non-AKI-DDKT subgroups, respectively) and 18 cases (2.7%) in the low KDPI-KTR group (7 and 11 patients in the AKI-DDKT and non-AKI-DDKT subgroups, respectively). There were no significant differences in the distribution of the causes of allograft failure between the AKI-DDKT and non-AKI-DDKT subgroups in the high or low KDPI-KTR group (Table 3). The death-censored graft survival rate was significantly lower in the high KDPI-KTR group compared with that in the low KDPI-KTR group (p = 0.005) (Fig. 3A). However, there was no significant difference in the death-censored graft survival rates between the AKI-DDKT and non-AKI-DDKT subgroups in the high or low KDPI-KTR group (Fig. 3B, C). In the multivariate analysis, a high KDPI score was an
independent risk factor for allograft failure after adjustment for recipient age, transplant year, transplant center, recipient HTN, and acute rejection (hazard ratio [HR], 3.096; 95% confidence interval [CI], 1.642–5.838; p < 0.001), not donor AKI. There was not a significant interaction between AKI in DDs and high KDPI DDs for allograft failure (p for interaction = 0.088). There was no significant difference in the incidence of death-censored graft failure according to the AKI stage in the high and low KDPI-KTR groups (Supplementary Table 1, available online). However, in the high KDPI-KTR group, AKI stage 3 showed the lowest death-censored allograft survival rate in comparison with non-AKI and AKI stages 1 and 2 (P = 0.040) (Fig. 3D), but not in the low KDPI-KTR group (Fig. 3E). In the multivariate analysis, the combination of high KDPI score and AKI stage 3 was an independent risk factor for allograft failure after adjustment for recipient age, transplant year, transplant center, recipient HTN, acute rejection, PRA > 50%, HLA mismatch, and induction immunosuppressant (HR, 2.707; 95% CI, 1.324–5.536; p = 0.006). There was a significant interaction between AKI stage 3 in DDs and high KDPI DDs for allograft failure (p for interaction = 0.002) (Table 4).

**Comparison of the impact of AKI in DDs on the patient survival between the high and low KDPI-KTR groups**

A total of 33 patients (33 of 657, 5.0%) died, 18 cases (2.7%) of whom were in the high KDPI-KTR group (14 and 4 patients in the AKI-DDKT and non-AKI-DDKT subgroups, respectively) and 15 cases (2.3%) of whom were in the low KDPI-KTR group (3 and 12 patients in the AKI-DDKT and non-AKI-DDKT subgroups, respectively). There were no significant differences in the distribution of the cause of patient death between the AKI-DDKT and non-AKI-DDKT subgroups in the high or low KDPI-KTR group (Table 3). There was no significant difference in the patient survival rate between the high and low KDPI-KTR groups (Fig. 4A). In the high KDPI-KTR group, there was no significant difference in the patient survival rate between the AKI-DDKT and non-AKI-DDKT subgroups in the high or low KDPI-KTR group (Fig. 4B, C).

**Discussion**

For a long time, the ECD criteria have been used to determine to accept or discard DD kidneys. Our previous study reported that the allograft outcome was poor when ECD was accompanied by AKI [18]. Our other study also reported that the elderly donor had a poor allograft outcome when accompanied by AKI [28]. In other words, the poor kidney state of the DDs prior to KT can have a synergistic effect when this situation is accompanied by AKI. Therefore, it is very important to evaluate the kidney state of the DDs prior to KT.

**Table 3. Comparison of clinical outcomes according to AKI in high or low KDPI donor KTR**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Non-AKI-DDKT</th>
<th>AKI-DDKT</th>
<th>p-value</th>
<th>Non-AKI-DDKT</th>
<th>AKI-DDKT</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Causes of graft failure</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute rejection</td>
<td>4 (36.4)</td>
<td>8 (40.0)</td>
<td>0.170</td>
<td>6 (54.5)</td>
<td>3 (42.9)</td>
<td>0.952</td>
</tr>
<tr>
<td>Chronic rejection</td>
<td>1 (9.1)</td>
<td>8 (40.0)</td>
<td></td>
<td>1 (9.1)</td>
<td>1 (14.3)</td>
<td></td>
</tr>
<tr>
<td>Recurrent glomerulonephritis</td>
<td>2 (18.2)</td>
<td>2 (10.0)</td>
<td></td>
<td>1 (9.1)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Ischemia</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td></td>
<td>2 (18.2)</td>
<td>2 (28.6)</td>
<td></td>
</tr>
<tr>
<td>Infection</td>
<td>1 (9.1)</td>
<td>1 (5.0)</td>
<td></td>
<td>0 (0)</td>
<td>1 (14.3)</td>
<td></td>
</tr>
<tr>
<td>BK virus-associated nephropathy</td>
<td>3 (27.3)</td>
<td>1 (5.0)</td>
<td></td>
<td>1 (9.1)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td><strong>Causes of death</strong></td>
<td></td>
<td></td>
<td>0.530</td>
<td></td>
<td></td>
<td>&gt;0.999</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>2 (50.0)</td>
<td>4 (28.6)</td>
<td></td>
<td>2 (16.7)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Cerebrovascular accident</td>
<td>0 (0)</td>
<td>1 (7.1)</td>
<td></td>
<td>0 (0)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Infection</td>
<td>1 (25.0)</td>
<td>5 (35.7)</td>
<td></td>
<td>5 (41.7)</td>
<td>3 (100)</td>
<td></td>
</tr>
<tr>
<td>Malignancy</td>
<td>0 (0)</td>
<td>1 (7.1)</td>
<td></td>
<td>2 (16.7)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal bleeding</td>
<td>1 (25.0)</td>
<td>0 (0)</td>
<td></td>
<td>1 (8.3)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>0 (0)</td>
<td>3 (21.4)</td>
<td></td>
<td>2 (16.7)</td>
<td>0 (0)</td>
<td></td>
</tr>
</tbody>
</table>

Data are expressed as number (%).

KDPI, Kidney Donor Profile Index; KTR, kidney transplant recipient; AKI, acute kidney injury; DDKT, deceased donor kidney transplantation.
Figure 3. Comparison of the death-censored graft survival rates according to the KDPI group and AKI subgroup and the death-censored graft survival rates according to the AKI stage. (A–C) Comparison of the death-censored graft survival rate (A) between the high KDPI-KTR and low KDPI-KTR groups, (B) between AKI-DDKT and non-AKI-DDKT subgroups in the high KDPI-KTR group, and (C) between AKI-DDKT and non-AKI-DDKT subgroups in the low KDPI-KTR group. (D, E) Comparison of the death-censored graft survival rate according to the AKI stage (D) in the high KDPI-KTR group and (E) in the low KDPI-KTR group.

AKI, acute kidney injury; DDKT, deceased donor kidney transplantation; KDPI, Kidney Donor Profile Index; KTR, kidney transplant recipient.

Table 4. Odds ratios (OR) for allograft failure on the status of AKI or high KDPI donor in deceased donor

<table>
<thead>
<tr>
<th></th>
<th>Unadjusted OR (95% CI)</th>
<th>p-value</th>
<th>Adjusted OR (95% CI)</th>
<th>p-value</th>
<th>p-value for interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>AKI-KT</td>
<td>0.884 (0.422–1.849)</td>
<td>0.742</td>
<td>1.011 (0.484–2.114)</td>
<td>0.976</td>
<td>0.088*</td>
</tr>
<tr>
<td>AKI stage 3-KT</td>
<td>1.349 (0.701–2.596)</td>
<td>0.370</td>
<td>1.357 (0.583–3.155)</td>
<td>0.479</td>
<td>0.002*</td>
</tr>
<tr>
<td>High KDPI-KT</td>
<td>2.304 (1.262–4.205)</td>
<td>0.007</td>
<td>3.096 (1.642–5.838)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

AKI, acute kidney injury; CI, confidence interval; KDPI, Kidney Donor Profile Index; KT, kidney transplantation.
\*Adjusted by recipient age, transplant year, transplant center, recipient hypertension, acute rejection, panel-reactive antibody of >50%, human leukocyte antigen mismatch, and induction immunosuppressant. \^An interaction between AKI in deceased donors and high KDPI deceased donors for allograft failure. \&An interaction between AKI stage 3 in deceased donors and high KDPI deceased donors for allograft failure.

and predicting allograft outcome [19]. Furthermore, we performed this current study based on the previous one.

First, we compared the clinical characteristics of the high and low KDPI donors. The mean age of donor at KT and proportions of HTN, DM, CVA, AKI, and ECD were significantly higher, and the mean CKD-EPI eGFRs at baseline and allocation were significantly lower in the high KDPI donors than in the low KDPI donors perhaps because
the KDPI score contains donor age, creatinine, history of HTN and DM, and cause of death (CVA) [29]. The mean age of recipient at KT was significantly higher in the high KDPI-KTR group than in the low KDPI-KTR group. Most elderly candidates received KT from marginal donors because of the benefit of old for old KT and the prevention of death prior to KT during the waiting period for DDKT [30–33]. Since the presence of DM or HTN can suggest an underlying chronic tissue injury irrespective of allograft function, such donors could be diagnosed with CKD [34]. In addition, the allograft function at baseline and allocation, as calculated by the CKD-EPI equation, was significantly lower and proportion of donors with CKD stage 3 or above was higher in the high KDPI donor group than in the low KDPI donor group. These findings showed that a significantly higher proportion of DDs with a high KDPI score had underlying CKD compared with DDs with a low KDPI score.

In the short-term clinical outcomes between the high and low KDPI-KTR groups, the occurrence of AKI in DDs with a high KDPI score led to a higher incidence of DGF after KT. These findings suggested that AKI or high KDPI score on DDs was an independent risk factor for DGF; and this result is consistent with previous studies [26,35,36]. Recently, AKI on DDs and the recipients’ factors may have a more significant impact on the development of DGF compared with the baseline chronic damage of the allograft [37]. However, there was no difference in the development of BPAR according to the occurrence of AKI on DDs in the high or low KDPI-KTR groups. This finding suggests that the donor state prior to KT does not significantly affect the immunological response after KT.

A research reported that allograft function in the early period after KT was significantly lower in the KT from marginal DDs [35]. On the contrary, another research reported that the poor kidney state of the DDs prior to KT can cause persistent low graft function after KT [38]. In our previous study, there was no difference in the allograft function among KTs from DDs with a stable kidney state, but KT from DDs with a poor kidney state such as elderly DDs or high KDPI DDs showed persistent low allograft function after KT [19,28]. In our study, the high KDPI-KTR group showed significantly lower allograft function compared with the low KDPI-KTR group. However, the AKI-DDKT subgroup showed lower allograft function within 3 months after KT compared with the non-AKI-DDKT subgroup in the high KDPI-KTR group. On the contrary, the AKI-DDKT subgroup showed lower allograft function for 12 months after KT compared with the non-AKI-DDKT subgroup in the low KDPI-KTR group.

Our main hypothesis is that AKI in DDs has a different impact on the long-term allograft survival in the high and low KDPI-KTR groups. The death-censored graft survival rate was significantly lower in the high KDPI-KTR group than in the low KDPI-KTR group. However, in the subgroup

---

**Figure 4. Comparison of the patient survival rates.** Comparison of (A) between the high KDPI-KTR and low KDPI-KTR groups, (B) between AKI-DDKT and non-AKI-DDKT subgroups in the high KDPI-KTR group, and (C) between AKI-DDKT and non-AKI-DDKT subgroups in the low KDPI-KTR group.

AKI, acute kidney injury; DDKT, deceased donor kidney transplantation; KDPI, Kidney Donor Profile Index; KTR, kidney transplant recipient.
analysis, there was no significant difference in the death-censored graft survival rates between the AKI-DDKT and non-AKI-DDKT subgroups in the high or low KDPI-KTR group. Interestingly, in the high KDPI-KTR group, AKI stage 3 was the lowest in the death-censored graft survival rate in comparison with non-AKI and AKI stages 1 and 2 but not in the low KDPI-KTR group. In the multivariate analysis using the Cox proportional hazards regression model, the coexistence of high KDPI and AKI stage 3 in DDs was a significant contributor to allograft failure, and we found a significant interaction between high KDPI and AKI stage 3 in DDs on allograft failure as suggested in Table 4. The aforementioned findings suggest that AKI stage 3 in DDs has a significant impact on the allograft outcomes in the high KDPI-KTR group but not in the low KDPI-KTR group.

In contrast to the death-censored allograft survival rate, the patient survival rate was not significantly different between the high and low KDPI-KTR groups, and the distribution of the cause of death did not depend on the KDPI score. There was also no significant difference in the patient survival rate between the AKI-DDKT and non-AKI-DDKT subgroups in the high or low KDPI-KTR group. It may be because the number of patient death was too small to evaluate the impact of AKI in DDs for the patient survival in the high and low KDPI-KTR groups. Therefore, a large, well-designed prospective study is required to overcome the small sample size.

Both donor and recipient factors are important in the prognosis of DDKT, but donor factors are particularly important for short-term outcomes such as DGF or allograft function at the time of early stage after KT. Therefore, an allocation system for selecting an appropriate donor is currently needed above all. In 2014, the KDPI score was introduced as a new allocation system in the US and it is currently needed above all. In 2014, the KDPI score was introduced as a new allocation system in the US and it has been studied not only in the US but also in various countries around the world. We demonstrated that the presence of AKI in ECDs significantly impacted the long-term allograft outcomes of KTRs [18]. Furthermore, we also demonstrated that AKI in elderly DDs can significantly affect long-term allograft outcomes of KTRs [28]. In other words, when the underlying kidney status of the donor was bad, the prognosis was poor when AKI occurred. In evaluating these underlying kidney status, KDPI was more effective than the ECD criteria. Comparing ECD criteria with KDPI score, ECD criteria is a binary score that takes into account the factors of four donors, and on the other hand, the KDPI score is a continuous score that considers 10 donor factors. Therefore, the KDPI score can determine the donor status more diversely than the ECD criteria. Finally, among the variables of KDPI score, donor age and kidney function at allocation with chronic change were very important factors according to our studies. Furthermore, AKI in DDs was also an important factor. In addition, we reported that the KDPI score is effective in predicting the long-term prognosis as well as the short-term clinical course. In our previous research, we demonstrated that the KDPI scoring system was useful in predicting allograft outcomes in a Korean DDKT cohort, in particular, KT from DDs with a marginal kidney [19].

Although the KDPI score is helpful to evaluate the effect of the DD factors and predict the prognosis of posttransplant clinical outcomes, there were some limitations in our studies. First, these were retrospective studies, so the KDPI score was calculated retrograde after KT. Therefore, well-designed large-scale prospective study is needed because the KDPI score is a prospective predictor. Second, it is known that the predictive power of the KDPI is only moderate (c-statistic = 0.60). Third, all donor factors associated with graft outcomes are not included with pathologic findings. Fourth, there is a selection bias for the prognosis of KT since clinicians want to selectively perform DDKT with good quality of kidney although they consider the KDPI score.

Our study has some limitations like our previous reports using this cohort. First, because this was a retrospective cohort study, this could have selection bias. However, we analyzed the medical records of four centers considering the characteristics such as multiple transplant centers and transplant year without the loss of KTRs during the study period in the multivariate analysis. Second, because KT from both kidneys in the same transplant center was not performed, the clinical outcome of the contralateral kidney transplanted in the other transplant center could not be known. The tracking system for all transplanted or discarded kidneys is needed to overcome this problem. Lastly, the Korean allocation rule has been applied for the allocation when the brain death donor occurred. Because the KDPI system has not been validated in Korea, it has not been used in the real world. We only used the KDPI score for the research retrospectively. In spite of these limitations, this study is valuable because it is a very useful research as basic
data for improving the allocation system, given the reality that the allocation criteria are not clear although DDKT with donor AKI is expanding year by year in Korea.

In conclusion, KTs from DDs with AKI stage 3 showed an adverse impact on the allograft outcome in the high KDPI-KTR group. Therefore, although AKI occurs in DDs with a high KDPI score, it is recommended to perform KT from donor kidney with AKI stages 1 and 2, and it would be better to judge more carefully for donor kidney with AKI stage 3 using additional tools such as procurement biopsy. In addition, donor management should be performed more carefully not to proceed to AKI stage 3 during donor management before allocation.

Conflicts of interest

All authors have no conflicts of interest to declare.

Funding

This study was supported by a grant from the Korean Health Technology R&D Project, Ministry of Health & Welfare, Republic of Korea (HI20C0317) and also was supported by the First Research Support Project of the National Research Foundation of Korea (NRF) funded by the Ministry of Science and ICT in 2018 (NRF-2017R1C1B5076739).

Authors’ contributions

Conceptualization: All authors
Data curation: WYP, YKC, YSK, KJ, CWY
Funding acquisition: WYP, BHC
Investigation: YKC, YSK, KJ
Writing–original draft: WYP, SH, BHC
Writing–review & editing: WYP, CWY, SH, BHC
All authors read and approved the final manuscript.

ORCID

Woo Yeong Park, https://orcid.org/0000-0003-2662-2898
Yoon Kyung Chang, https://orcid.org/0000-0003-4193-2034
Young Soo Kim, https://orcid.org/0000-0001-8478-0566
Kyubok Jin, https://orcid.org/0000-0002-7836-8863
Chul Woo Yang, https://orcid.org/0000-0001-9796-636X
Seungyeup Han, https://orcid.org/0000-0002-7561-6534

Byung Ha Chung, https://orcid.org/0000-0003-0048-5717

References

Telemedicine is a broad term that encompasses the use of electronic information and communication technologies to provide healthcare remotely [1]. It involves the use of messages, telephone calls, video calls, and e-mail. Utilization of telemedicine began in the 1960s, but its use has not gained much ground in India. However, with the onset of the coronavirus disease 2019 (COVID-19) pandemic along with its restrictions on movement and financial constraints, it became imperative to start offering consults electronically.

Telemedicine offers remote consults, thereby saving time and travel cost and the associated inconvenience and pollution. It aids in timely referrals and prevents direct social interaction in cramped outpatient departments (OPDs). With most nephrologists located in urban areas, it provides important healthcare opportunities for the rural population.

Telemedicine, through video conferencing, was started in the month of May 2020 at our tertiary care hospital. It is handled by a trained clinic manager. Time and again relevant telephone numbers are advertised in national newspapers. The patients are required to call on these numbers to obtain an appointment for the respective department. They are given a fixed date and time at which they are expected to be near a video call enabled phone number provided by them. At the time of the slated appointment, a video call is made to the patient. If there is no response, an audio call is subsequently made. After a live two-way conversation, a prescription is forwarded to the patient in a portable document format (pdf). At the time of discussion with the patient, one consultant and one resident are present. Nephrology consultation is currently being offered once a week with the potential to further increase in frequency depending on the response to telemedicine services. In total, 15 to 25 consultations are completed in a single sitting. If needed, appointments for further follow-up are scheduled. Full responsibility for ethical considerations including privacy, informed consent, and confidentiality of the consults is undertaken by the hospital administration. Apart from this, digital consults are also being provided on WhatsApp (WhatsApp LLC) or via e-mail/message directly by the respective consultants.

Although good internet speed is maintained by the hospital (20–30 Mbps), disruptions due to poor signal/technical issues on the patient’s side are occasionally seen. As this is altogether new to the patients, sometimes they have difficulty communicating about accessibility problems along with minor camera focus issues. Also, the
emotional connection, which is crucial in explaining the severity of the disease or offering a new therapy like dialysis initiation, is often missing. This arrangement is not meant for sicker patients for whom an in-person visit to the hospital emergency department is the only option. Interdepartmental referrals are not possible in the same sitting and a new appointment for a later date is given. The number of patients seen is limited and dramatically decreased compared to regular OPDs, which leaves a wide gap in unmet need.

Compilation of the data (April to June 2020) revealed that 86% of patients seen through this setup were regular follow-ups (Table 1). Of these 69% of patients were chronic kidney disease patients. Most of these were either advised to continue the same treatment or were offered minor changes. The second most frequent were consults offered to patients with primary/secondary glomerulonephritis on active immunosuppression who were not able to visit OPDs because of travel constraints. The age of the patients ranged from 18 to 60 years.

Despite these limitations, telemedicine remains a viable option for patients in remote or rural areas or otherwise not able to attend in-person appointments who may continue to benefit from virtual consultation even in a post-COVID era. Because nephrological evaluation relies primarily on history and lab workup, an electronic setup might be sufficient, though it does not completely replace a thorough examination. Telemedicine is better suited to patients who have already been evaluated locally or are in a regular follow-up in the hospital OPD. It should aim to provide effective services ensuring safe and timely solutions to patients’ problems. There should also be a feedback system in place to verify the patient satisfaction [2]. The current scenario demands integration of this relatively new communication system into the existing doctor-patient interactive relationship. Other than being a tool for effective patient management, its utility can be extended to impart knowledge via educational and awareness interventions, which may benefit the community as a whole.

**Conflicts of interest**

All authors have no conflicts of interest to declare.

**Authors’ contributions**

Conceptualization: AC, NR
Data curation: All authors
Investigation: AC, NR
Project administration: All authors
Writing–original draft: All authors
Writing–review & editing: All authors
All authors read and approved the final manuscript.

**ORCID**

Abhilash Chandra, https://orcid.org/0000-0002-9055-4351
Namrata Rao, https://orcid.org/0000-0002-5733-4218
Divya Srivastava, https://orcid.org/0000-0003-1050-8521

**References**


---

**Table 1. Nephrology telemedicine consultations**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Data (n = 225)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follow-up</td>
<td>193 (85.8)</td>
</tr>
<tr>
<td>New patients</td>
<td>32 (14.2)</td>
</tr>
<tr>
<td>Sex, male:female</td>
<td>162 (72.0):63 (28.0)</td>
</tr>
<tr>
<td><strong>Distribution by diagnosis</strong></td>
<td></td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>133 (59.1)</td>
</tr>
<tr>
<td>eGFR (mL/min/1.73 m²)</td>
<td></td>
</tr>
<tr>
<td>&gt;60</td>
<td>18</td>
</tr>
<tr>
<td>45–60</td>
<td>23</td>
</tr>
<tr>
<td>30–44</td>
<td>33</td>
</tr>
<tr>
<td>15–29</td>
<td>36</td>
</tr>
<tr>
<td>&lt;15</td>
<td>23</td>
</tr>
<tr>
<td>Acute kidney injury</td>
<td>12 (5.3)</td>
</tr>
<tr>
<td>Nephrotic syndrome</td>
<td>30 (13.3)</td>
</tr>
<tr>
<td>Glomerulonephritis</td>
<td>32 (14.2)</td>
</tr>
<tr>
<td>Postrenal transplant</td>
<td>18 (8.0)</td>
</tr>
</tbody>
</table>

Data are presented as number (%) or number only.

eGFR, estimated glomerular filtration rate by Chronic Kidney Disease-Epidemiology Collaboration.
1. Manuscript Submission

Manuscripts for *Kidney Research and Clinical Practice* (KRCP) should be submitted online at https://www.editorialmanager.com/krcp. All submissions to KRCP must conform to the International Committee of Medical Journal Editors (ICMJE) uniform requirements for manuscripts submitted to biomedical journals. Our requirements reflect those of the ICMJE, although we also have specific requirements for different types of article. For editorial questions, please contact us via e-mail (registry@ksn.or.kr), telephone (+82-2-3486-8736), or fax (+82-2-3486-8737).

**Important information**

Articles should be prepared in the simplest form and submitted in the format of Microsoft Word (*.doc or *.docx). Manuscripts must be typed in English and double-spaced. All pages must be numbered consecutively starting from the title page. You may use automatic page numbering, but do NOT use other kinds of automatic formatting such as footnotes. Place text, references, tables and legends in one file with each table on a new page.

Please ensure that the following submission documents are also included, where applicable:

1. A cover letter. It must include your name, address, telephone and fax numbers, e-mail address, and state that all authors have contributed to the paper and have never submitted the manuscript, in whole or in part, to other journals.
2. A conflict of interest disclosure statement (see relevant section 4.2 below).
3. All studies involving human subjects, human data or any material derived from human must be approved by the relevant review or ethics committee. Articles must include a statement on ethics approval, the name of the relevant committee that approved the study and the committee’s approval number. Manuscripts may be rejected at any time if the authors of the research fail to provide the approval number validated by the relevant committee (see relevant section 4.1 below).
4. Articles covering the use of animals in experiments must be approved by the relevant authorities.
5. Articles where human subjects can be identified in descriptions, photographs or pedigrees must be accompanied by a signed statement of informed consent to publish (in print and online) the descriptions, photographs and pedigrees from each subject who can be identified.
6. The terms sex (when reporting biological factors) and gender (identity, psychosocial or cultural factors) should be correctly used. The sex and/or gender of study participants, the sex of animals or cells should be reported, and the methods used to determine sex and gender should be described. If the study was done involving an exclusive population, for example in only one sex, authors should justify why, except in obvious cases (e.g., ovarian cancer).
7. Clinical trials should be registered at a primary national clinical trial registration site such as www.clinicaltrials.gov, https://cris.nih.go.kr/cris/index.jsp, or other sites accredited by the World Health Organization or the International Committee of Medical Journal Editors.
8. Where material has been reproduced from other copyrighted sources, letter(s) of permission from the copyright holder(s) to use the copyrighted sources must be supplied.
9. Articles should be written in English (using American English spelling) and meet the following basic criteria: the material is original; the information is important; the writing is clear, concise and grammatically correct; the study methods are appropriate; the data are valid; and the conclusions are reasonable and supported by the data. The articles should be readable to native English users, and we recommend using professional language editing service (e.g., American Journal Experts) prior to submission to avoid delays with the review processes.
10. All authors must register and update information about academic degree, affiliation, and position when they register or submit a journal online at https://www.editorialmanager.com/krcp.
11. The copyright transfer agreement has been incorporated into KRCP submission system to collect digital signatures from each author. Upon submission of a manuscript, an email will be sent to each author for electronic signature prior to starting review process. The manuscript will not be reviewed as planned until all signatures are received. The paper submitted without the signatures of all authors on all statements will be finally removed from the system without further notice.

2. Types of Articles

2.1. Original Articles

These are expected to present major advances and important
new research results. Section headings should include Abstract, Introduction, Methods, Results, Discussion, Conflicts of interest, Acknowledgments (if applicable), and References. The text should be limited to 4,000 words (excluding tables, figures and references) and 40 references.

2.2. Review Articles
These describe new developments of significance in the field of nephrology and highlight unresolved questions and future directions. Most reviews are solicited by the editors, but unsolicited submissions may also be considered for publication. Review articles should include Abstract, Introduction, brief main headings, and References. The text should be limited to 5,000 words (excluding tables, figures and references) and 100 references.

2.3. Special Articles
Articles in this section should provide insightful analysis and commentary about any important topic in medicine, research, ethics, or health policy. They may also address consensus statements, guidelines, statements from task forces, or recommendations. Most reviews are solicited by the editors, but unsolicited submissions may also be considered for publication. The text should be limited to 5,000 words (excluding tables, figures and references) and 50 references.

2.4. Correspondence
Correspondence generally takes one of the following forms: (1) Reader’s comment on an article previously published in KRCP and/or a reply from the authors; (2) An article that may not fit to the format of original or review article but suggest creative perspectives for medical issues; (3) A brief report of any kind that presents important research findings adequate for the journal’s scope and of particular interest to the readers. The submitted manuscript includes title page, main text, conflict of interest, acknowledgments (if applicable) and references. No abstract is included, and the text should be limited to 800 words (excluding tables, figures and references) and 8 references. A maximum of 2 figures or tables may be included.

2.5. Editorials
These are manuscripts that are related to materials within the current issue; they raise challenging questions or explore controversies. The editor solicits such opinion pieces. The order of the submitted manuscript includes title page, integrated discussion, conflict of interest, acknowledgments (if applicable) and references. The text should be limited to 1,500 words and 10 references. A maximum of 2 figures or tables may be included.

2.6. Images in Practice
These present classic or unique images of common medical conditions in clinical nephrology. Images are an important part of much of what we do and learn in clinical practice. The text should be limited to 400 words. There should be no more than two figures. No tables or references are included.

3. Manuscript Preparation

3.1. Title Page
The title page should include article title, each author’s first and last names, positions (associate professor, fellow, student, etc.), and ORCID identifiers, and the institutions with which they are affiliated, short running title not exceeding 50 characters, separate word count for abstract and text, and details of the corresponding author (name, address, phone, and e-mail information). Funding sources should be included, and the individual contribution of each co-author must also be detailed (see relevant section 4.3 below).

3.2. Abstract and Keywords
Abstract should not exceed 250 words in original, review or special articles. It must be written for easy reading with no abbreviations. The abstract of the original article should be divided into four subsections: Background, Methods, Results, and Conclusion. Four to six keywords should be listed alphabetically below the abstract. For selecting keywords, refer to the Index Medicus Medical Subject Headings (available from: http://www.ncbi.nlm.nih.gov/mesh).

3.3. Main Text
The text for original articles, for example, should include the following sections: Introduction, Methods, Results, and Discussion. The Introduction should be as concise as possible, without subheadings. The Methods section should be sufficiently detailed. Subheadings may be used to organize the Results and Discussion. Each section should begin on a new page.

3.4. Acknowledgments
General acknowledgments for consultations, statistical analysis and so on should be listed after main body of text, before the References section, including the names of the individuals involved. All financial and material support for the research
and the work should be stated here clearly and explicitly.

3.5. References
References should be cited with Arabic numerals in square brackets. References are numbered consecutively in order of appearance in text. References are limited to those cited in text and listed in numerical order. List all authors if there are less than or equal to six authors. List the first three authors followed by “et al” if there are more than six authors. If an article has been published online but has not yet been given an issue or pages, the digital object identifier (DOI) should be supplied. Journal titles should be abbreviated in the style used in Index Medicus. Other types of references not described below should follow The NLM Style Guide for Authors, Editors, and Publishers (https://locatorplus.gov/cgi-bin/Pwebrecon.cgi?DB=local&v1=1&ti=1,1&Search_Arg=101318441&-Search_Code=0359&CNT=1&SID=1). The authors may format the citations and references using the KRCP EndNote style file, but we generally recommend the authors to type the citation numbers and references manually.

Journal articles:

Online publication but not yet in print:

Entire Book:

Book chapter:

Website:

3.6. Tables
Tables are numbered consecutively using Arabic numerals in the order of their citation in text. Table titles should be short and descriptive (e.g. Table 1. Demographic characteristics of patients). If numerical measurements are given, the unit of measurement should be included in the column heading. The statistical significance of observed differences in the data should be indicated by the appropriate statistical analysis. All nonstandard abbreviations should be defined in footnotes. Lower case letters in superscripts (\(^{a},^{b},^{c}\)) should be used for special remarks.

3.7. Figures
Figure legends should be submitted for all figures. They should be brief and specific, and placed on a separate sheet after the References section. Figures are numbered consecutively using Arabic numerals in the order of their citation in the text. Figures should be uploaded as separate files, not embedded in the manuscript file. Figures that are line drawing or photographs must be submitted separately in high-resolution EPS or TIF format (or alternatively in high-resolution JPEG format). Only high-resolution figure files (preferably 300 dpi for color figures and 1,200 dpi for line art and graphs) should be submitted. The files are to be named according to the figure number and format (e.g., Fig1.tif). Figures that are reproduced from other published sources require written permission from the authors and copyright holders.

3.8. Supplementary Digital Contents
Authors can submit supplementary digital contents to supplement the information provided in the print version of the manuscript. Supplementary materials will be published online-only. When uploading supplementary files through the online system, please use the “supplemental” file designation. Supplementary materials must be cited consecutively in the main body of the submitted manuscript and include the type of material submitted (e.g., “Supplementary Table 1”; “Supplementary Fig. 1”).
4. Ethical Considerations

4.1. Ethical Approval of Studies
For human or animal experimental investigations, appropriate institutional review board or ethics committee approval is required. Such approval and the approval number should be stated in the Methods section of the manuscript. For those investigators who do not have formal ethics review committees, the principles outlined in the Declaration of Helsinki as revised in 2013 should be followed (World Medical Association. Declaration of Helsinki: Ethical principles for medical research involving human subjects. Available at: https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/). For all relevant clinical transplant articles, KRCP requires authors state in the Methods section their adherence to the Declaration of Istanbul (Available at: http://www.declarationofistanbul.org/). Copies of written informed consent and Institutional Review Board (IRB) approval for clinical research should be kept. If necessary, the editor or reviewers may request copies of these documents to resolve questions about IRB approval and study conduct.

4.2. Conflicts of Interest
The corresponding author must inform the editor of any potential conflicts of interest that could influence the authors’ interpretation of the data. Examples of potential conflicts of interest include financial support from or connections to pharmaceutical companies, political pressure from interest groups, and academically related issues. Conflict of interest statements will be published at the end of the text of the article, before the References section. Please consult the Committee on Publishing Ethics guidelines (http://www.publicationethics.org/) on conflict of interest. All sources of financial support for the study should be stated in Acknowledgments (see relevant section 3.4 above).

4.3. Authorship
Authorship credit should be based on 1) conception or design, or analysis and interpretation of data; 2) drafting the article or revising it; 3) providing intellectual content of critical importance to the work described; and 4) final approval of the version to be published. Authors should meet above four conditions. The title page should include a list of each author’s role for the submitted paper.

4.4. Redundant Publication or Duplicate Submission
Submitted manuscripts are considered with the understanding that they have not been published previously in print or electronic format (except in abstract or poster form) and are not under consideration in totality or in part by another publication or electronic medium. Authors must state that neither the manuscript nor any significant part of it is under consideration for publication elsewhere or has appeared elsewhere in a manner that could be construed as a prior or duplicate publication of the same, or very similar, work. When malpractices are found in an article submitted to KRCP, we will follow the flowchart by the Committee on Publication Ethics (COPE, https://publicationethics.org/resources/flowcharts) for settlement of any misconduct. Although the editors and referees make every effort to ensure the validity of published manuscripts, the final responsibility rests with the authors, not with KRCP, its editors, or the Korean Society of Nephrology.

5. Review Process
All submissions are sent to peer reviewers. Authors will usually be notified within 4 weeks by e-mail of whether the submitted article is accepted for publication, rejected, or subject to revision before publication. Revised manuscripts must be submitted online by the corresponding author. Failure to re-submit the revised manuscript within 3 months of the editorial decision is regarded as a withdrawal.

6. Visual Abstract Guidelines
Visual Abstracts are brief graphical summaries of Original Articles published online. They serve to summarize the work for readers and may be used in social media postings. Authors do not need to include a Visual Abstract with their initial submission but will be required to submit one at the revision stage for all original research articles. The submitted visual abstract will be reviewed along with the revised manuscript.

6.1. Creating Your Visual Abstract
Select one of the visual abstract templates provided (https://www.krcp-ksn.org/file/KRCP_Visual_Abstracts_v1.0.pptx). There are multiple layouts to accommodate author preferences as well as graphical constraints. The visual abstract should
include a title, methods, outcome and a concluding sentence. Please fill in the template as it’s laid out and do not alter the basic components of the template.

Keep in mind the following:
• Avoid excessive detail and clutter and keep text to a minimum.
• Any descriptive text should be at least 12 pt font size.
• The visual abstract should be saved as an editable Power Point file as staff will add the article DOI and may edit the text for clarity.

6.2. Adding Visual Details
It is critical that you only use images for which you have permissions or rights. To avoid any potential problems, either use the copyright filter during an image search online or subscribe to an icon image bank. There are many image banks on the internet, which are free to use. The images used for visual abstract is recommended only open source, and the author is responsible for copyright issues of visual abstract. Researchers who frequently prepare visual abstracts may benefit from purchasing a subscription to access higher quality icons (e.g. Shutterstock, Getty Images, iStock, etc.).

Guiding principles:
• Select bold, solid color icons
• Avoid highly detailed icons as the intricacy may be lost in the small format
• Exclude trade names, logos, or images of trademarked items.
• Graphics should be 440 pixels wide by 350-365 pixels tall.

7. Peer Review
This journal operates blind review processes. All contributions will be initially assessed by the editor for suitability for the journal. Papers deemed suitable are then sent to a minimum of two independent expert reviewers to assess the scientific quality of the paper. The Editor is responsible for the final decision regarding acceptance or rejection of articles. The Editor’s decision is final. For more information, please refer to Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals (Available at: http://www.icmje.org/icmje-recommendations.pdf).

8. Copyright
KRCP is the official peer-reviewed publication of the Korean Society of Nephrology. Manuscripts published in the Journal become the permanent property the Korean Society of Nephrology. All articles published in the Journal are protected by copyright, which covers the exclusive rights to reproduce and distribute the article, as well as translation rights. No KRCP article, in part or whole, cannot be reproduced, stored, or transmitted for commercial purposes, without prior written permission from the Korean Society of Nephrology.

9. Similarity Check
Similarity Check is a multi-publisher initiative to screen published and submitted content for originality. To find out more about Similarity Check, visit http://www.crossref.org/crosscheck/index.html. All manuscripts submitted to KRCP may be screened, using the iThenticate tool, for textual similarity to other previously published works.

10. Open Access Policy
Every peer-reviewed research article in this journal is freely available via our website (https://www.krcp-ksn.org). Articles published in KRCP are distributed under the terms of the Creative Commons Attribution Non-Commercial and No Derivatives License (https://creativecommons.org/licenses/by-nc-nd/4.0/), which permits unrestricted non-commercial use, distribution of the material without any modifications, and reproduction in any medium, provided the original works properly cited. ANY USE of the open access version of this Journal in whole or in part must include the customary bibliographic citation, including author and publisher attribution, date, article title, Kidney Research and Clinical Practice (Kidney Res Clin Pract), and the URL https://www.krcp-ksn.org and MUST include a copy of the copyright notice. If an original work is subsequently reproduced or disseminated not in its entirety but only in part or as a derivative work this must be clearly indicated. For any commercial use of material from the open access version of the journal, permission MUST be obtained from KRCP. If necessary, please contact the Editorial Board through our editorial office (registry@ksn.or.kr); Proprietary rights notice for KRCP online were available at: https://www.krcp-ksn.org/authors/permission.php
11. Data Sharing Policy

For clarification on data accuracy and reproducibility of the results, raw data or analysis data will be deposited to a public repository, for example, Harvard Dataverse (https://dataverse.harvard.edu/) after acceptance of the manuscript. Therefore, submission of the raw data or analysis data is mandatory when requested by reviewers. If the data is already a public one, its URL site or sources should be disclosed. If data cannot be publicized, it can be negotiated with the editor. If there are any inquiries on depositing data, authors should contact the editorial office.

12. After acceptance

12.1. Article-in-press publication

After the manuscript is finally accepted, it will be published online in PDF format through the English editing, author proofing and final editorial correction process. The corresponding author should promptly and appropriately respond to this editing process. Online publication will take place within several weeks depending on the proof process. A Digital Object Identifier (DOI) is allocated, making it fully citable and searchable by title, author name(s), and the full text. Since our journal is officially published every 3 months interval, the volume, issue, and page will be finally allocated sequentially according to the order of accepted articles.

12.2. Publication charges

In order to cover the costs of reviewing, copy editing, layout, and online hosting and archiving, KRCP charges an article processing fee upon acceptance of submitted original, review or special articles as follows:

KRW 500,000 (Korea)
USD 500 (rest of world)

There are no additional charges based on color, length, figures or other elements. No fee applies to correspondences and images in practice. The publication costs for invited papers are covered by the Korean Society of Nephrology. Payments are processed by a department unconnected to KRCP’s editorial board.

• Publication charge waiver policy

Our mission is to share the achievements in the nephrology field with researchers worldwide including the scientists in the low-income countries. We continue to apply the publication charge waiver policy to encourage the academic activity and support the limited funding for their research. To request a publication charge waiver, please send an application to registry@ksn.or.kr. Corresponding author from low-income countries could be waived. Waiver application must contain the manuscript number and country of corresponding author.
INDICATIONS
1. Renal anemia
2. Chemotherapy-induced anemia in solid cancer patients

DOSEAGE AND ADMINISTRATION
- Intravenous administration

Initial dose
- The usual dose of NESP in adult patients is 20 μg, to be administered as a single intravenous injection once weekly.
- Initial dose at the switching from erythropoietin preparations: See Precautions related to Dosage and Administration.

Maintenance dose
- When correction of anemia is achieved, the usual dose of NESP in adult patients is 30-120 μg as darbepoetin alfa (parenteral reconstitution), to be administered as a single injection once every two weeks subcutaneously or intravenously. If a deviation of anemia is maintained by once every two weeks injection, the frequency of administration can be changed to once every four weeks with a initial dose set to be two-thirds of the dose in the once every two weeks injection. In this case, the usual dose in adult patients is 60-180 μg administered as a single injection once every four weeks subcutaneously or intravenously. In all cases, the dose should be adjusted in one of the degree of anemia symptoms and the patients' age, and should not exceed 180 μg as a single injection. The target of anemia correction is around 11 g/dL of hemoglobin level.

Precautions related to Dosage and Administration
1. Initial dose at the switching from an erythropoietin preparation.
- When NESP is started in substitution for an erythropoietin preparation, the dose and the frequency of administration should be determined on the basis of the dose of the erythropoietin preparation that has been used. See the table (package insert).
- Patients who have been treated with an erythropoietin preparation take weekly or three times weekly, calculate the total dose of the erythropoietin preparation administered during the week before the switching, and then determine the initial dose of NESP according to the table below. The treatment should be started once weekly basis.
- Patients who have been treated with an erythropoietin preparation once weekly or once every two weeks, calculate the total dose of the erythropoietin preparation administered during the two weeks before the switching, and then determine the initial dose of NESP according to the table below. The treatment should be started once every two weeks basis.

2. Dose adjustment
- Dose adjustment is required, for example, when the increase in the hemoglobin concentration of the hemodialysis patients cannot be achieved in correction phase, or when the hemoglobin concentration of the hemodialysis patients deviates from the target range for successive two weeks in maintenance phase, the dose should be increased or decreased according to the table below. Any dose increase should be performed stage by stage in principle.

PRESENTATION
- NESP 20 μg, 30 μg, 40 μg, 60 μg, 120 μg, respectively

STORAGE
- Store in a lightproof container at 2-8 °C and avoid freezing.

PACKAGING
- 1 vial, 10 vials, for NESP 20 μg, 30 μg, 40 μg, 60 μg, 120 μg, respectively.

MANUFACTURED BY:
- Taiho Pharmaceutical Co., Ltd. 1040-22 Matsumoto Takamatsu-shi Gifu, Japan
- Kyowa Hakko Kirin Co., Ltd. 100-1 Hagiyama-machi, Tatsukokuchi, Gunma, Japan

IMPORTED BY:
- Tel: 02-3471-6823 Fax: 02-3471-6822
- http://www.kyowakirin-korea.com
요독소를 흡착하여
투석 시작을 지연시키는
"만성신부전 진행억제제"

spherical adsorptive
carbon 2g

크레메진 세림

MIRCERA exists because life is long

It exists because CKD in a long life requires a long treatment

It exists because We want to provide a prolonged stability of Hemoglobin levels along the long treatment

It exists because we believe that a prolonged stability will overcome the long treatment and give longer hope to your longer life

MIRCERA exists because we believe in the power of longer stability

A long-lasting changes caused by long-acting effects including Non-dialysis CKD, PD, and HD

Purple Effect MIRCERA


MIRCERA
methoxy polyethylene glycol-calcipotriol beta

MIRCERA pre-filled syringe
Presentation vehicle, identifier code C49

MIRCERAERT pre-filled syringe

Purple Effect MIRCERA

hyperkalaemia, hyponatraemia, mood disturbances, sleep disorder, somnolence, syncope, palpitations, tachycardia, allergic reactions, pemphigoid, hyperhydrosis, eczema, arthralgia, myalgia, renal insufficiency, erectile dysfunction, chest volume expansion. (3)

be closely monitored. Similar considerations apply to patients with ischemic heart or cerebrovascular disease in whom an increased blood pressure is unmasked or exacerbated by antihypertensive treatment. In patients at high risk of symptomatic hypotension, initiation of therapy and dose adjustment should

Symptomatic hypotension is seen rarely in uncomplicated hypertensive patients and is more likely to occur in patients who have received large dose reductions or discontinuation of antihypertensive treatment. (2) In patients at high risk of symptomatic hypotension, initiation of therapy and dose adjustment should

haemolytic anaemia in patients with a congenital deficiency of G-6PDH, confusion, angina pectoris, arrhythmia, myocardial ischemia, myocardial infarction, fever, chills, neck stiffness, pneumonia, rhinitis, pancreatitis, hepatitis either cytolitic or cholestatic, erythema multiform, acute renal failure. (1)

(1) Stable Coronary Artery Disease

ACEI and ARB should not be used concomitantly in patients with diabetic nephropathy. (17) Patients who administer Neprilysin(NEP) inhibitor or within 36 hours after discontinuation.

Pregnancy or potential pregnancy, lactation. (7) The drug is usually not administered in case of combinations with ACE-inhibitors, ARBs, beta blockers or thiazide-type diuretics. (4) In patients with unstable angina or coronary syncope, treatment with an ACE inhibitor should be initiated with caution and with frequent monitoring of serum potassium. (6)

Anaphylactoid reactions during desensitization: Patients receiving ACE inhibitors during dialysis with high flux membranes may be at risk of severe anaphylactic reactions. So, ACE inhibitor should not be administered to these patients. However, if the patient needs rapid control of ACE inhibitors during dialysis in US, adequate, these reactions were avoided by temporarily withdrawing ACE inhibitor therapy at 4 hours prior to dialysis. (9) Pregnancy When pregnant is diagnosed a treatment with ACE inhibitors is stopped immediately. (10) Combination therapy involving the active substance in any of the combinations with an ACE inhibitor. (10) History of angioedema associated with previous ACE inhibitors. (11) Worsening or discontinue angioedema. (12) Patients receiving treatment with ACE inhibitors, ARBs, beta blockers or thiazide-type diuretics may also be at risk of severe anaphylactic reactions. (4)

Clinical studies of ACE inhibitors in patients with a history of myocardial infarction have shown a reduction of the risk of cardiovascular mortality or non-fatal myocardial infarction in patients with a history of myocardial infarction and/or revascularization. - Adults: 5 mg once daily for two weeks, then increased to 10 mg on day 2, then 20 mg on day 4, then 40 mg on day 7, then 80 mg once daily. The dose may be increased to 160 mg once daily after one month of treatment. Patients with a history of angioedema associated with previous ACE inhibitors. (10) Antihypertensive therapy is started with a lower than usual initial dose and titrated upwards with a careful monitoring of e.g. serum potassium and plasma renin activity. (8) Antihypertensive therapy is started with a lower than usual initial dose and titrated upwards with a careful monitoring of e.g. serum potassium and plasma renin activity. (8)

Children and adolescents (< 18 years). (12) Kidney transplant patients. (13) Patients with rare hereditary problems of G-6PDH: Agranulocytosis or pancytopenia, haemoglobin decreased and haematocrit decreased, leucopenia/neutropenia, thrombocytopenia, anuria, acute renal failure, Steven-Johnson syndrome. (2)

Common(≥1/10, <1/10): Headache, dizziness, vertigo, paraesthesia, visual disturbances, tinnitus, hypotension and effects on blood pressure, angioedema. (3) Uncommon(≥1/1,000, <1/100): Cough, dyspepsia, diarrhoea, constipation, rash, prurit, muscle cramps, asthenia. (2) Rare(<1/1,000): Anaphylactoid reactions during desensitization. (4) Very rare(<10,000): Anaphylactoid reactions during desensitization. (4)

Special care: Antidiabetic agents (insulins, oral hypoglycaemic agents), Baclofen, Non-potassium sparing diuretics, NSAIDs. (3) Other precautions: Diuretics, Antihypertensive agents, Propranolol, Clonidine, Nifedipine. (2)

ACE-AAD-20202-K-1.0

Primary aldosteronism: use not recommended in patients with primary hyperaldosteronism (not responding to drugs acting through inhibition of the renin-angiotensin system).

Primary aldosteronism: use not recommended in patients with primary hyperaldosteronism (not responding to drugs acting through inhibition of the renin-angiotensin system).
is an anticoagulant during extracorporeal blood circulation in patients with bleeding complications or bleeding tendency.1

- Due to its short half life (5–8 min), its anticoagulant activity is almost limited to extracorporeal circuit.2,3,4
- Increase of bleeding risk was not noted in HD patients with bleeding risk.5,6,7
- The filter-life is significantly prolonged during CRRT.8,9,10

Summary of Prescribing Information1

PRODUCT NAME IN KOREA - Futhan for Inj. (nafamostat mesilate) - Futhan50 for Inj. (nafamostat mesilate) INGREDIENT - Futhan for Inj.: 1 vial contains 10mg of nafamostat mesilate - Futhan50 for Inj.: 1 vial contains 50mg of nafamostat mesilate INDICATION AND USAGE 1. For improvement of acute symptoms of pancreatitis (acute pancreatitis, acute exacerbation of chronic pancreatitis, acute postoperative pancreatitis, ERCP–induced acute pancreatitis, traumatic pancreatitis) – Futhan for Inj. only 2. Disseminated intravascular coagulation (DIC) 3. To prevent coagulation of blood during extracorporeal blood circulation (ex. hemodialysis, plasmapheresis) in patients with bleeding complications or bleeding tendency. DOSAGE AND ADMINISTRATION 3. To prevent coagulation of blood during extracorporeal blood circulation (ex. hemodialysis, plasmapheresis) in patients with bleeding complications or bleeding tendency. For priming, wash and fill the blood route with 20mg of nafamostat mesilate dissolved in 500mL of saline after dissolving in the small amount of 5% glucose solution or water for injection. After beginning of extracorporeal circulation, inject continuously at a rate of 20–50mg/hr as nafamostat mesilate dissolved in 5% glucose solution into anticoagulant injection line. The dosage should be appropriately adjusted according to the patient’s symptoms. The average dosage from clinical study is 35mg/hr as nafamostat mesilate. Manufactured by Yuhan corporation, Distributed by SK chemicals Revised: May 28, 2018.

References
We provide one-stop service by building an integrated pipeline.

We always put the patient's health first and care for the whole life.

We devote for continuous product development and service improvement.

We work with therapists to find the optimal solution.

Boryung Renal Business Unit provides **TOTAL RENAL CARE**

Boryung Renal Business Unit
Boryeong Building, 136 Changgyeonggung-ro, Jongno-gu, Seoul
Customer Service Center Tel 080.708.8088 Fax 02.741.5291 www.boryung.co.kr
Patients with aHUS can be at continuous risk of the life-threatening consequences of unpredictable complement-mediated TMA1,2

Chronic, uncontrolled complement activity in aHUS leads to ongoing endothelial injury, organ damage, and sudden death.3

---

References:
Improving lives together

Fresenius Medical Care is the world’s leading provider of dialysis products and services, offering life-sustaining care for people living with chronic kidney failure.

In Asia Pacific, we draw on our decades of experience and expertise to deliver our vision – **Creating a future worth living. For patients. Worldwide. Every day.**

Get in touch

Fresenius Medical Care Korea
(14/F, FKI Tower) 24 Yeouí-daero,
Yeongdeungpo-gu, Seoul, 07320, Rep. of Korea
Telephone: +822 2146 8800
Fax: +822 3453 9213
www.freseniusmedicalcare.asia
The 1st launched medicine of Calcium polystyrene sulfonate in Korea

Various formulations for medication convenience (Powder/Granule/Suspension)

Treatment agent of Hyperkalemia

KALIMATE
Powder / Granule / Suspension

The most prescribed treatment agent of Hyperkalemia in Korea

REFERENCES
1. 식품의약품안전처. 루리알약물사전: 약리동정백. 카바메트.
2. 2019 3Q MAT, IQVIA DATA 기준( 국내 고혈압증 치료제 판매량 )

KabaMete sands

KabaMete sands is made from high-purity, high-purity calcium polystyrene sulfonate, which is 100% biocompatible and biodegradable. It is obtained by a unique process of extraction and purification that ensures its purity and purity. The product is free from contaminants and impurities, ensuring its safety and effectiveness. It is used as an active ingredient in various formulations for medication convenience, including powder, granules, and suspensions. KabaMete sands is widely prescribed as a treatment agent for hyperkalemia in Korea.

A new formulation of KabaMete sands has been launched in Korea, making it the 1st launched medicine of Calcium polystyrene sulfonate. It is available in various formulations, including powder, granules, and suspensions, providing convenient medication options for patients. KabaMete sands is highly prescribed for the treatment of hyperkalemia in Korea, with a high prescription rate among healthcare providers.

KabaMete white

KabaMete white is a well-known and trusted pharmaceutical company, with a long history of producing high-quality products. The company is committed to delivering safe and effective medications to patients. KabaMete white is dedicated to innovation and research, continuously improving its products and formulations to meet the evolving needs of patients.

KabaMete blue

KabaMete blue is a pharmaceutical company that focuses on the development and production of high-quality pharmaceutical products. The company is headquartered in Korea and has a strong presence in the local market. KabaMete blue is committed to delivering safe and effective medications to patients, and it continuously invests in research and development to improve its products and formulations.

KabaMete green

KabaMete green is a pharmaceutical company that specializes in the development and production of high-quality medications. The company is committed to delivering safe and effective medications to patients, and it continuously invests in research and development to improve its products and formulations. KabaMete green has a strong presence in the local market and is a trusted supplier for healthcare providers.

KabaMete red

KabaMete red is a well-known and trusted pharmaceutical company, with a long history of producing high-quality products. The company is committed to delivering safe and effective medications to patients. KabaMete red is dedicated to innovation and research, continuously improving its products and formulations to meet the evolving needs of patients.

KabaMete yellow

KabaMete yellow is a pharmaceutical company that focuses on the development and production of high-quality pharmaceutical products. The company is headquartered in Korea and has a strong presence in the local market. KabaMete yellow is committed to delivering safe and effective medications to patients, and it continuously invests in research and development to improve its products and formulations.
Dialog+ and Adimea®
Monitoring the dialysis dose continuously and in real-time

Only those who are aware of the nature of the path are able to reach their destination safely and quickly.

Adimea® stands for Accurate Dialysis Measurement (precise measurement of the dialysis conditions). This real-time measurement system is able to determine the Kt/V precisely in any given dialysis treatment scenario.

The measuring principle of this innovative system from B. Braun is simple: a UV light sensor installed in the dialysate drain of the Dialog+ machine measures the absorption of light and thus changes in the concentration of uremic substances as they drain off. This means that insufficient dosages are identified immediately.

The advantages are obvious: the user is able to adjust relevant parameters during treatment so as to model the Kt/V, meaning efficient and optimized dialysis treatment is guaranteed for the patient at all times and without any detours. That’s for sure.
Monitoring the dialysis dose continuously and in real-time

Only those who are aware of the nature of the path are able to reach their destination safely and quickly.

Adimea® stands for Accurate Dialysis Measurement (precise measurement of the dialysis conditions). This real-time measurement system is able to determine the Kt/V precisely in any given dialysis treatment scenario. The measuring principle of this innovative system from B. Braun is simple: a UV light sensor installed in the dialysate drain of the Dialog® machine measures the absorption of light and thus changes in the concentration of uremic substances as they drain off. This means that insufficient dosages are identified immediately.

The advantages are obvious: the user is able to adjust relevant parameters during treatment so as to model the Kt/V, meaning efficient and optimized dialysis treatment is guaranteed for the patient at all times and without any detours. That's for sure.
OPTIMIZE TROUGH LEVEL
START LIFE-LONG JOURNEY\textsuperscript{1,2}

\textsuperscript{1} Prograf* 제품설명서(제출일 2020.05.14).
REXCEED™ Series
Hemodialyzer / REXCEED™
Our Perfect Solution for HD
Combining the Best with a Large Line-UP
WET TYPE Polysulfone

REXCEED-A
The high flux dialyzer with best removal performance among our wet-type product range for all patient groups.

REXCEED-M
Dialyzer with best removal performance among our wet-type high flux product range.

REXCEED-L
Dialyzer with best removal performance among our wet-type low flux product range.

Improved design for ideal dialysate flow
Effective removal of small toxins and low molecule weight proteins
Superior biocompatibility

AY Trading Co., Ltd.
TEL: 02-585-7661 / FAX: 02-585-7664
Slow ADPKD. Preserve Hope.
Introducing Samsca — The first and only treatment proven to slow cyst progression

Samsca® Tablet ADPKD product information summary [INDICATION] To slow the progression of cyst development and renal insufficiency of autosomal dominant polycystic kidney disease (ADPKD) in adults with CKD stage 1 – 4 at initiation of treatment with evidence of rapidly progressing disease. [DOSAGE & ADMINISTRATION] Tolvaptan must only be prescribed by physicians who got registered in Risk Management Program to the patients who have agreed and signed on conditions specified in Risk Management Program. Patient should follow this program. And, to mitigate the risk of significant and/or irreversible liver injury, blood testing for hepatic transaminases and bilirubin is required prior to initiation of SAMSCA, continuing monthly for 18 months and at regular 3 monthly intervals thereafter. The initial dose is 60 mg tolvaptan per day as a split-dose regimen of 45 mg + 15 mg (45 mg taken upon waking and prior the morning meal and 15 mg taken 8 hours later). The initial dose is to be titrated upward to a split-dose regimen of 90 mg tolvaptan (60 mg + 30 mg) per day and then to a target split-dose regimen of 120 mg tolvaptan (90 mg + 30 mg) per day, if tolerated, with at least weekly intervals between titrations. Dose titration has to be performed cautiously to ensure that high doses are not poorly tolerated through overly rapid up-titration. Patients may down-titrate to lower doses based on tolerability. Patients have to be maintained on the highest tolerable tolvaptan dose. x Samsca® Tablet has an indication for hyponatremia as well. For further information, please refer to the latest prescribing information at www.otsuka.co.kr.
COUNT ON FABRAZYME

Treat your Fabry disease patients with Fabrazyme

1 mg/kg
once every 2 weeks

Fabrazyme®
agalsidase beta
1 mg/kg once every 2 weeks

SANOFI GENZYME

MAT-PR-200436-10-1020