GLP-1 receptor agonists in diabetic kidney disease: current evidence and future directions

Korean Society of Nephrology hemodialysis unit accreditation report (2016–2020) and future directions

Evaluating a shared decision-making intervention regarding dialysis modality: development and validation of self-assessment items for patients with chronic kidney disease

Mental illness in patients with end-stage kidney disease in South Korea: a nationwide cohort study

Effect of shared decision-making education on physicians’ perceptions and practices of end-of-life care in Korea
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), DOI/Crossref, Google Scholar, KoMCI, KoreaMed, ScienceCentral, CAS, Current Content Clinical Medicine and Essential Science Indicators.

This journal was supported by the Korean Federation of Science and Technology Societies Grant funded by the Korean Government (Ministry of Education).

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
#301, (Miseung Bldg.) 23, Apgujenog-ro 30-gil, Gangnam-gu, Seoul 06022, Korea
Tel: +82-2-3486-8736 Fax: +82-2-3486-8737 E-mail: registry@ksn.or.kr

Publishing office
M2PI
8th FL, DreamTower, 66 Seongsu-aro, 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, 2022

KIDNEY RESEARCH AND CLINICAL PRACTICE

plISSN 2211-9132  elISSN 2211-9140  www.krcp-ksn.org

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
Heeyeon Cho
Seoul, Korea
Bum Soon Choi
Seoul, Korea
Mary E. Choi
New York, USA
Byung Ha Chung
Seoul, Korea
Jørgen Frøkiær
Aarhus, Denmark
Hyo Wook Gil
Cheonan, Korea
Reiko Inagi
Tokyo, Japan
Faïcal Jarraaya
Sfax, Tunisia
Jong Hyun Jhee
Seoul, Korea
Kamyar Kalantar-Zadeh
Torrance, USA
Seok Hui Kang
Daegu, Korea
Jwa-Kyung Kim
Hallym University, Anyang, Korea
Sejoong Kim
Seongnam, Korea
Yang Gun Kim
Seoul, Korea
Mori Kiyoshi
Kyoto, Japan
Ho Seok Koo
Seoul, Korea

Soon Hyo Kwon
Seoul, Korea
So-Young Lee
Seongnam, Korea
Dusit Lumlertgul
Chiang Mai, Thailand
Kyung Chul Moon
Seoul, Korea
Søren Nielsen
Aalborg, Denmark
Babu Padanilam
Omaha, USA
Hyeong Cheon Park
Seoul, Korea
Woo Yeong Park
Daeju, Korea
Philip Poronnik
Darlington, Australia
Thyago Proença de Moraes
Curitiba, Brazil
JungHwa Ryu
Seoul, Korea
Jae Il Shin
Seoul, Korea
Sung Joon Shin
Gyeonggi, Korea
Sang Heon Song
Busan, Korea
Cheuk Chun Szeto
Hong Kong, China
Yasuhiko Tomino
Tokyo, Japan
Min-Hwa Tseng
Taoyuan, Taiwan
Weidong Wang
Guangzhou, China
Kyung Don Yoo
Ulsan, Korea

Manuscript Editor
Yun Joo Seo
InfoLumi, Korea

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

133  The importance of psychiatric disorders in end-stage kidney disease patients 

*Eun Lee*

# Review Articles

136  GLP-1 receptor agonists in diabetic kidney disease: current evidence and future directions 

*Ji Hee Yu, So Young Park, Do Young Lee, Nan Hee Kim, Ji A Seo*

150  Peritoneal dialysis adequacy: a paradigm shift 

*Chang Huei Chen, Isaac Teitelbaum*

156  Recent advances in novel diagnostic testing for peritoneal dialysis–related peritonitis 

*Winston Wing-Shing Fung, Philip Kam-Tao Li*

# Special Article

165  Korean Society of Nephrology hemodialysis unit accreditation report (2016–2020) and future directions 

*Ji Hyeon Park, Young-Ki Lee, Kiwon Kim, Dae Joong Kim*

# Original Articles

175  Evaluating a shared decision-making intervention regarding dialysis modality: development and validation of self-assessment items for patients with chronic kidney disease 

*Soojin Kim, Jung Tak Park, Sung Joon Shin, Jae Hyun Chang, Kyung Don Yoo, Jung Pyo Lee, Dong-Ryeol Ryu, Soontae An, Sejoong Kim*

188  Additive harmful effects of acute kidney injury and acute heart failure on mortality in hospitalized patients 

*Hyung Eun Son, Jong Joo Moon, Jeong-min Park, Ji Young Ryu, Eunjil Baek, Jong Cheol Jeong, Ho Jun Chin, Ki Young Na, Dong-wan Chae, Seung Seok Han, Sejoong Kim*

200  Association between serum osteoprotegerin level and renal prognosis in nondialysis patients with chronic kidney disease in the Korean Cohort Study for Outcomes in Patients with Chronic Kidney Disease (the KNOW–CKD Study) 

*Tae Ryom Oh, Chana Myeong, Su Hyun Song, Hong Sang Choi, Sang Heon Suh, Chang Seong Kim, Eun Hui Bae, Wookyung Chung, Kyu Hun Choi, Kook Hwan Oh, Seong Kwon Ma, Soo Wan Kim*

209  Clinical features and outcomes of elderly patients with antineutrophil cytoplasmic antibody–positive vasculitis: a single-center retrospective study 

*Hyo Jin Kim, Miyeun Han, Sang Heon Song, Eun Young Seong*
First snapshot on behavioral characteristics and related factors of patients with chronic kidney disease in South Korea during the COVID-19 pandemic (June to October 2020)
Yaerim Kim, Inae Lee, Jeonghwan Lee, Jae Yoon Park, Jung Nam An, Kyung Don Yoo, Yong Chul Kim, Woo Yeong Park, Kyubok Jin, Younglim Kho, Myoungsoon You, Dong Ki Kim, Kyungho Choi, Jung Pyo Lee

Mental illness in patients with end-stage kidney disease in South Korea: a nationwide cohort study
Min-Jeong Lee, Eunyoung Lee, Bumhee Park, Inwhee Park

Effect of shared decision-making education on physicians’ perceptions and practices of end-of-life care in Korea
Byung Chul Yu, Miyeun Han, Gang-Jee Ko, Jae Won Yang, Soon Hyo Kwon, Sungjin Chung, Yu Ah Hong, Young Youl Hyun, Jang-Hee Cho, Kyung Don Yoo, Eunjin Bae, Woo Yeong Park, In O Sun, Dongryul Kim, Hyunsuk Kim, Won Min Hwang, Sang Heon Song, Sung Joon Shin

Incidence of acute cholecystitis underwent cholecystectomy in incidence dialysis patients: a nationwide population-based cohort study in Korea
Hanlim Choi, Soon Kil Kwon, Joung-Ho Han, Jun Su Lee, Gilwon Kang, Minseok Kang

Correspondence
Focal segmental glomerulosclerosis following the Pfizer-BioNTech COVID-19 vaccine
Cho A Lim, Hyun Soon Lee, Songuk Yoon, Eun Jung Kim, Jang Won Seo, Ja-Ryong Koo, Seon Ha Baek

The image on the front cover: Hemodialysis accreditation rate in Korea. The accreditation rate is the highest in Jeju (100%) and is 87.7% in Seoul.
It is uncertain why psychiatric comorbidities are important for end-stage kidney disease (ESKD) patients. Epidemiological studies have demonstrated that physical health is associated with mental health, and psychiatric problems can adversely affect health by exacerbating the onset, course, complications, and mortality of physical diseases. Research into these relationships has focused on psychiatric conditions that have a relatively high prevalence (such as depression, anxiety, and sleep disturbances) in conjunction with physical diseases that are relevant to public health due to high prevalence or high mortality, such as cardiovascular disease, cancer, organ transplantation, and diabetes [1]. The incidence, severity, and mortality rates of ESKD are also affected by psychiatric problems, such as depression [2]. In this context, studies such as that of Lee et al. [3], who conducted large-scale investigations of the prevalence of psychiatric diseases in ESKD patient populations, are rare. Studies that have examined the prevalence of comorbidities among patients with both psychiatric problems and physical diseases exhibit wide differences in results due to the varying measurement methods used. Diagnoses of psychiatric disorders are typically concluded by a psychiatrist who determines whether diagnostic criteria have been met through a structured interview [4]. Self-report questionnaires filled out by patients have the potential risk of overestimating the prevalence of psychiatric disorders. For example, a meta-analysis of studies that examined depression among dialysis patients with ESKD as measured through psychiatric interviews reported a prevalence of 23%, whereas the incidence rate of depression as assessed via a questionnaire completed by the patient or the patient’s physician was 39% [5]. Both of these values are much higher than the prevalence in the general population without any physical disease.

Questionnaire-based assessments completed by physicians or patients can evaluate specific symptom domains, such as depression and anxiety, but cannot be considered psychiatric diagnostic tools due to their low specificity. Ideally, the comorbidity rates of psychiatric diseases should be assessed with precise diagnostic interviews conducted by psychiatrists, but few such studies have been published. Thus, well-designed studies that can accurately assess the comorbidity of psychiatric disorders are urgently needed. In a 4-year observational study in which psychiatrists made diagnoses based on criteria after interviewing 508 hemodi-
alysis patients, the one-year incidence of psychiatric disorders such as dementia, major depression, and delirium was 10.6% [6]. As it is challenging to diagnose psychiatric diseases, researchers often use questionnaires tailored for several specific psychiatric problems, such as depression and sleep disturbances. Studies that have examined insurance claim codes for psychiatric disorders have similar limitations as those of studies that use questionnaires. Nevertheless, a study by Lee et al. [3] has academic significance in several respects. First, their study was representative of ESKD patients in Korea because the data of more than 100,000 patients were investigated using claims information from a health insurance review and assessment service. Second, although not all psychiatric disorder codes were investigated, a wide range of psychiatric diagnostic codes was examined to study as many comorbidities as possible. Finally, their study was reflective of the psychiatric problems of ESKD patients observed in daily nephrology practice.

Understanding the mechanisms behind the interaction between psychiatric problems and physical diseases is another issue that requires further research. Many retrospective studies have evaluated psychiatric problems in dialysis patients [5]. However, these studies did not identify the direction or mechanisms of interactions and only speculated on the details of possible interactions between psychiatric problems and ESKD. Retrospective studies cannot conclusively determine whether a patient’s psychiatric problems affected the onset of ESKD, if their psychiatric problems occurred during the course of ESKD, or whether preexisting psychiatric problems were treated after the onset of ESKD. In addition, the results of a study that examined the progenitor symptoms commonly reported by ESKD patients demonstrated that it can be difficult to identify any such relationships [7]. For example, one study reported that 71% of ESKD patients experience fatigue, 49% have anorexia, 47% complain of pain, 44% have sleep disturbances, 38% experience anxiety, and 27% suffer from depression. Fatigue, loss of appetite, pain, and sleep disturbances also are diagnostic criteria for depression, suggesting that depression might be overestimated in this population.

Studies that have examined the mechanisms by which psychiatric problems affect the course of ESKD are urgently needed. Although most research that has been aimed at determining the mechanisms of psychiatric diseases has occurred over the last 30 years, a number of influences has long been assumed to indirectly affect the course of physical diseases by inducing changes in behavior. For example, depression can indirectly affect the course of ESKD by reducing patient adherence to treatment, dietary management, and exercise regimens, but it also can impact ESKD through direct effects, such as changes in the immune system and alterations in neurotransmitter production. Bautovich et al. [8] proposed a number of reasons for the high prevalence of depression among ESKD patients: 1) lifestyle and socioeconomic factors, such as a sedentary lifestyle or poor diet, which affect both depression and ESKD; 2) inflammatory reactions that impact both diseases or changes that take place in the immune system after the onset of kidney disease; 3) depression caused by changes in the immune system due to underlying kidney pathology; 4) worsening of kidney disease due to depression-associated poor adherence to renal disease management regimens; 5) depression caused by fatigue, sleep disturbances, or kidney disease-related pain; and 6) financial difficulties secondary to the costs of kidney disease management and depression caused by loss of job opportunities.

Interactions between depression and physical diseases are believed to be mediated by the immune system, which regulates central nervous system functions via cytokine production and so also affects behavior [9]. Cytokine signals interact with physiological, social, and external environmental conditions through the central nervous system. In addition, cytokines affect the immune system via pathways such as the hypothalamic-pituitary axis or sympathetic nervous system, thereby affecting the course of physical diseases.

It is unknown to what extent comorbid psychiatric problems affect the outcome of ESKD. Few long-term observational studies examining this question have been conducted to date. A 2-year study of 917 incident dialysis patients found strong associations between depressive symptoms and all-cause deaths, cardiovascular disease deaths, and cardiovascular events (adjusted relative hazard: 2.22, 3.27, and 1.68, respectively) [10]. Unfortunately, the results on the effect of psychiatric treatment on ESKD have been unclear. The reality that many physical conditions interfere with active psychiatric treatment and that it remains difficult to follow the course of ESKD over a long period of time has led to skepticism concerning the benefits of active treatment of psychiatric problems in such patients.
In summary, although ESKD is clinically significant due to its high prevalence and mortality rates, few studies have examined the course of the disease in patients with psychiatric diseases [10]. Additional standardized and systematic studies of a diverse array of psychiatric problems are needed, as are evaluations of the effects of therapeutic interventions on the course of ESKD that examine indicators in the brain, immune system, and kidneys.

**Conflicts of interest**

The author has no conflicts of interest to declare.

**Funding**

This work was supported by the National Research Foundation of Korea, which is funded by the Ministry of Science, ICT, and Future Planning, Republic of Korea (grant number, 2017R1A2B3008214 to Eun Lee).

**ORCID**

Eun Lee, https://orcid.org/0000-0002-7462-0144

**References**

GLP-1 receptor agonists in diabetic kidney disease: current evidence and future directions

Ji Hee Yu, So Young Park, Da Young Lee, Nan Hee Kim, Ji A Seo

Division of Endocrinology and Metabolism, Department of Internal Medicine, Korea University Ansan Hospital, Korea University College of Medicine, Ansan, Republic of Korea

With the emergence of various classes of blood glucose-lowering agents, choosing the appropriate drug for each patient is emphasized in diabetes management. Among incretin-based drugs, glucagon-like peptide 1 (GLP-1) receptor agonists are a promising therapeutic option for patients with diabetic kidney disease (DKD). Several cardiovascular outcome trials have demonstrated that GLP-1 receptor agonists have beneficial effects on cardiorespiratory outcomes beyond their blood glucose-lowering effects in patients with type 2 diabetes mellitus (T2DM). The renal protective effects of GLP-1 receptor agonists likely result from their direct actions on the kidney, in addition to their indirect actions that improve conventional risk factors for DKD, such as reducing blood glucose levels, blood pressure, and body weight. Inhibition of oxidative stress and inflammation and induction of natriuresis are major renoprotective mechanisms of GLP-1 analogues. Early evidence from the development of dual and triple combination agents suggests that GLP-1 receptor agonists will probably become popular treatment options for patients with T2DM.

Keywords: Diabetic nephropathies, Glucagon-like peptide 1, Type 2 diabetes mellitus

Introduction

The number of patients with diabetes mellitus (DM) continues to increase worldwide, and DM is the main cause of chronic kidney disease (CKD) and end-stage renal disease (ESRD) [1]. In Korea, the prevalence of diabetes was 13.8% in adults older than 30 years in 2018 [2], and it was predicted to be 29.2% in men and 19.7% in women by 2030 [3]. The total number of new patients who started renal replacement therapy (RRT) for ESRD increased from 10,000 in 2011 to 18,642 in 2019 [4], and the proportion of patients with DM as the underlying cause of ESRD increased from 19.5% in 1992 to 50.6% in 2012 [5], making DM the most common cause of ESRD in Korea [4]. Despite advances in medical technology and treatments, the need for RRT is increasing worldwide and is expected to more than double by 2030 compared with 2010 [6].

Diabetic kidney disease (DKD) is the main cause of morbidity and mortality in diabetes [7,8]. Therefore, inhibiting the onset and progression of DKD, in part by developing therapeutic approaches to prevent or delay it, is critical. Controlling blood sugar and blood pressure using...
angiotensin-converting enzyme inhibitors or angiotensin receptor blockers is the current goal in DKD management [9], and no special drugs or other therapeutic options are widely used to delay DKD progression. However, several cardiovascular outcome trials (CVOTs) have demonstrated that sodium-glucose cotransporter 2 (SGLT2) inhibitors and glucagon-like peptide 1 (GLP-1) receptor agonists have beneficial effects on cardiorenal outcomes, especially in patients with type 2 DM (T2DM) who are at high risk for cardiovascular disease (CVD) [10–12]. Based on the results of clinical trials, the current guidelines of the American Diabetes Association and Korean Diabetes Association recommend that clinicians consider prescribing SGLT2 inhibitors or GLP-1 receptor agonists after metformin as part of the glucose-lowering regimen for patients with T2DM and CKD [13,14]. In this review article, we focus on GLP-1 agonists and discuss the clinical and preclinical evidence for their nephroprotective effects and the potential mechanisms underlying those effects.

**Physiology and metabolic effects of glucagon-like peptide 1**

Oral intake of glucose causes the secretion of more insulin than does an injection of glucose due to the presence of gut hormones called **incretins** [15]. Gastrointestinal peptide (GIP) and the GLPs (GLP-1, GLP-2) are incretin hormones produced by enteroendocrine L-cells of the distal small bowel and colon [16]. In humans, fasting concentration of total GLP-1 ranges from 5 to 10 pmol/L and can increase to 40–50 pmol/L in response to meals [17]. Plasma concentration of biologically active, intact GLP-1 is much lower than that (fasting, <2 pmol/L; peak postprandial concentrations, 5–10 pmol/L) [18].

GLP-1 release after a meal occurs in a biphasic manner. An initial rapid rise in circulating GLP-1 level occurs 15 to 30 minutes after a meal, followed by a second minor peak at 90 to 120 minutes [19,20]. The rapid increase in GLP-1 secretion after meals is related to the proximal-distal loop regulated by neurotransmitters such as acetylcholine and gastrin-releasing peptide [21]. The second later peak of GLP-1 is believed to occur as ingested nutrients travel down the lumen and interact directly with distal L-cells [22,23].

Native GLP-1 has an extremely short half-life, less than 2 minutes, due to cleavage by dipeptidyl-peptidase IV (DPP IV) enzymes and renal elimination [24]. DPP IV enzymes cleave the active forms of GLP-1 [9–36] and GLP-1 [7–37] to produce inactive GLP-1 [9–36] or GLP-1 [9–37], respectively, which have low affinity for the GLP-1 receptor [25,26]. Only 10% to 15% of secreted GLP-1 reaches the pancreas via systemic circulation [25], and both the active and inactive forms of GLP-1 are rapidly cleared from the circulation via the kidneys. Although the initial DPP IV-mediated degradation of GLP-1 is unaffected by impairments in renal function, GLP-1 clearance is delayed in patients with renal insufficiency [24].

In humans, the GLP-1 receptor is expressed in the pancreas, lungs, brain, kidneys, stomach, and heart but not in the liver, skeletal muscle, or adipose tissue [27]. Binding between GLP-1 and its receptor activates adenylylate cyclase, which is followed by increase in cyclic AMP level and cytoplasmic Ca²⁺ that induces insulin secretion [28]. In addition to GLP-1’s short-term effect of enhancing the glucose-dependent stimulation of insulin secretion, continuous GLP-1 activation also increases insulin synthesis [29], modulates β-cell proliferation [30], and inhibits β-cell apoptosis [31] and glucagon release [32]. Incretin hormones also decrease gastric emptying [33], inhibit food intake [34], and increase natriuresis and diuresis [35,36].

**Classification of glucagon-like peptide 1 receptor agonists**

GLP-1 receptor agonists have two main backbone structures and are classified as exendin-4- or human GLP-1-based compounds [37]. They are divided into short- and long-acting agents, and some formulations are mixed with insulin (Table 1). Exendin-4 is a protein isolated in 1992 from the saliva of the Gila monster lizard (*Heloderma suspectum*) [38]. This protein is composed of 39 amino acids and has 53% similarity in base sequence to native human GLP-1. Exenatide and lixisenatide are based on the structure of exendin-4. Exenatide is a recombinant form of the peptide exendin-4 and was the first GLP-1 receptor agonist to be developed for T2DM treatment. Lixisenatide is an exendin-4 analog with an additional six lysines attached to the C-terminus, which gives it a longer half-life than exenatide. These exendin-4-based agents have relatively short half-lives (~3 hours) and strongly inhibit gastric emptying [39], which can cause gastrointestinal side-effects such as...
### Table 1. Characteristics of GLP-1 receptor agonists

<table>
<thead>
<tr>
<th>Generic</th>
<th>Commercial</th>
<th>Backbone</th>
<th>Dosage</th>
<th>Administration</th>
<th>Half-life</th>
<th>Renal dose adjustment</th>
<th>Route of elimination</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Short-acting compound</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exenatide</td>
<td>Byetta</td>
<td>Exendin-4</td>
<td>5 μg, 10 μg</td>
<td>Twice daily, SC</td>
<td>~2.4 hr</td>
<td>Not recommended for patients with CrCl &lt; 30 mL/min; caution needed for patients with CrCl 30–50 mL/min</td>
<td>Glomerular filtration followed by proteolysis; eliminated in the urine</td>
</tr>
<tr>
<td>Lixisenatide</td>
<td>Lyxumia</td>
<td>Exendin-4</td>
<td>10 μg, 20 μg</td>
<td>Once daily, SC</td>
<td>~3 hr</td>
<td>Not recommended for patients with CrCl &lt; 30 mL/min</td>
<td>Glomerular filtration and proteolysis; excreted in the urine</td>
</tr>
<tr>
<td><strong>Long-acting compound</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liraglutide</td>
<td>Victoza</td>
<td>Human GLP-1</td>
<td>0.6–1.8 mg</td>
<td>Once daily, SC</td>
<td>~13 hr</td>
<td>No dosage adjustment required; not recommended for patients with CrCl &lt; 15 mL/min</td>
<td>Proteolysis; excreted via urine and feces</td>
</tr>
<tr>
<td>Liraglutide</td>
<td>Saxenda</td>
<td>Human GLP-1</td>
<td>0.6–3 mg</td>
<td>Once daily, SC</td>
<td>~13 hr</td>
<td>No dosage adjustment required; not recommended for patients with CrCl &lt; 15 mL/min</td>
<td>Proteolysis; excreted via urine and feces</td>
</tr>
<tr>
<td>Exenatide ER</td>
<td>Bydureon</td>
<td>Exendin-4</td>
<td>2 mg</td>
<td>Once weekly, SC</td>
<td>~1 wk</td>
<td>Not recommended for patients with an eGFR &lt; 45 mL/min/1.73 m² or ESRD</td>
<td>Glomerular filtration followed by proteolysis; eliminated in the urine</td>
</tr>
<tr>
<td>Dulaglutide</td>
<td>Trulicity</td>
<td>Human GLP-1</td>
<td>0.75 mg, 1.5 mg</td>
<td>Once weekly, SC</td>
<td>~5 day</td>
<td>No dosage adjustment required; not recommended for patients with CrCl &lt; 15 mL/min</td>
<td>Proteolytic degradation</td>
</tr>
<tr>
<td>Semaglutide</td>
<td>Ozempic</td>
<td>Human GLP-1</td>
<td>0.5 mg, 1.0 mg</td>
<td>Once weekly, SC</td>
<td>~1 wk</td>
<td>No dosage adjustment required; not recommended for patients with CrCl &lt; 15 mL/min</td>
<td>Proteolysis; excreted via urine and feces</td>
</tr>
<tr>
<td>Albiglutide</td>
<td>Tanzeum</td>
<td>Human GLP-1</td>
<td>30 mg, 50 mg</td>
<td>Once weekly, SC</td>
<td>~5 day</td>
<td>No dosage adjustment required; not recommended for patients with CrCl &lt; 15 mL/min</td>
<td>Not available</td>
</tr>
<tr>
<td><strong>Oral agent</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Semaglutide</td>
<td>Rybelsus</td>
<td>Human GLP-1</td>
<td>3 mg, 7 mg, 14 mg</td>
<td>Once daily, oral</td>
<td>~1 wk</td>
<td>No dosage adjustment required</td>
<td>Proteolysis; excreted via urine and feces</td>
</tr>
<tr>
<td><strong>Fixed-dose combination</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lixisenatide + glargine</td>
<td>Soliqua</td>
<td>Exendin-4</td>
<td>20 μg/iGlar 40 IU, 20 μg/iGlar 60 IU</td>
<td>Once daily, SC</td>
<td>~3 hr</td>
<td>Closely monitor patients with CrCl 15–30 mL/min; not recommended for patients with CrCl &lt; 15 mL/min</td>
<td>Glomerular filtration and proteolysis; excreted in the urine</td>
</tr>
<tr>
<td>Liraglutide + degludec</td>
<td>Xultophy</td>
<td>Human GLP-1</td>
<td>1.8 mg/iDeg 50 IU</td>
<td>Once daily, SC</td>
<td>~13 hr</td>
<td>Not studied in severe renal impairment; liraglutide is not recommended for patients with CrCl &lt; 15 mL/min</td>
<td>Proteolysis; excreted via urine and feces</td>
</tr>
</tbody>
</table>

CrCl, creatinine clearance; eGFR, estimated glomerular filtration rate; ER, extended-release; ESRD, end-stage renal disease; GLP-1, glucagon-like peptide-1; iDeg, insulin degludec; iGlar, insulin glargine; SC, subcutaneous.

*Marketing was discontinued in 2018.
nausea. But they also have robust postprandial antihyperglycemic effects and could potentially replace rapid-acting mealtime insulin [39]. These shorter-acting agents are less effective at decreasing fasting glucose levels because of their short half-lives.

Human GLP-1–based agents are more structurally similar to native GLP-1 than to those based on exendin-4. They have 90% to 97% amino-acid homology to endogenous human GLP-1 and an extended half-life conferred by DPP IV resistance and noncovalent binding to serum albumin. These longer-acting agents lead to a greater reduction of fasting plasma glucose and hemoglobin A1c (HbA1c) levels than the shorter-acting agents [39,40]. The human GLP-1 compounds are liraglutide, albiglutide, dulaglutide, and semaglutide, all of which are injectable agents. Albiglutide and dulaglutide are large molecules conjugated to large proteins, which extends their half-life and enables once-weekly administration. Semaglutide is available in both injectable and oral forms. With withdrawal of albiglutide from the market for commercial reasons, liraglutide, dulaglutide, and semaglutide (oral and subcutaneous) are the currently available, approved human GLP-1 receptor agonists.

Table 1 shows the recommended uses of GLP-1 receptor agonists according to estimated glomerular filtration rate (eGFR). Human GLP-1–derived dulaglutide, liraglutide, and semaglutide are not excreted via the kidneys and can be used down to an eGFR of 15 mL/min/1.73 m²; there is insufficient experience to recommend using those agents for eGFR values lower than that [41]. Conversely, exenatide and lixisenatide, which are eliminated by the kidneys, are contraindicated below an eGFR of 30 mL/min/1.73 m² due to the risk of accumulation and toxicity [24]. Exenatide should be used with caution in patients with an eGFR of 30–50 mL/min/1.73 m² (Table 1).

Renal effects of glucagon-like peptide 1 receptor agonists in patients with type 2 diabetes mellitus

Several CVOTs have examined GLP-1 receptor agonists; however, none have focused on the primary endpoint of renal events; renal outcomes have been reported as secondary outcomes after primary cardiovascular outcomes. This section focuses on the renal outcomes of GLP-1 receptor agonist treatment reported by randomized controlled trials (Table 2).

The first CVOT for a GLP-1 receptor agonist was the ELIXA (Evaluation of Lixisenatide in Acute Coronary Syndrome) trial, the results of which were published in 2015 [42]. A total of 6,068 participants with T2DM, history of myocardial infarction or unstable angina, average baseline HbA1c of 7.7%, and a median follow-up of 25 months was enrolled. Although renal events were not investigated in the primary ELIXA trial, an exploratory analysis of renal outcomes was performed [43]. After a median follow-up of 108 weeks, lixisenatide reduced progression of the urinary albumin-to-creatinine ratio (UACR) in macroalbuminuric patients and was associated with a lower risk of new-onset macroalbuminuria after adjustment for baseline and on-trial HbA1c and other traditional renal risk factors. No significant differences in eGFR decline were identified between treatment groups. This study had a short follow-up period of 2 years, a high percentage of participants on statin therapy, and low compliance with the medication compared with the other trials in Table 2.

In the LEADER (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results) trial published in 2016 [44], participants with T2DM were either 50 years of age or older with at least one cardiovascular condition or 60 years or older with at least one cardiovascular risk factor. A total of 9,340 participants with a median follow-up of 3.8 years was enrolled, and the average baseline HbA1c was 8.7%. Approximately 23% of participants had moderate-to-severe CKD, suggesting a very high-risk population. Of note, this trial included 220 individuals with an eGFR of 15–30 mL/min/1.73 m². Liraglutide decreased the risk of the secondary composite renal endpoint (new-onset macroalbuminuria, sustained serum creatinine duplication, initiation of RRT, or renal death) by 22% (hazard ratio, 0.78; 95% confidence interval [CI], 0.67–0.92; p = 0.003) [45]. This finding was driven primarily by a reduction in new-onset persistent macroalbuminuria. That study was the first to show that a GLP-1 agonist had cardiovascular benefit, although it might not apply in patients with low cardiovascular risk.

The SUSTAIN-6 (Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes) was the next CVOT, also published in 2016 [46]. A total of 3,297 patients was randomly assigned, and 3,232 patients completed the trial over a median fol-
### Table 2. Renal endpoints in cardiovascular outcome trials of GLP-1 receptor agonists

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Participants (n)</strong></td>
<td>Lixisenatide</td>
<td>Liraglutide</td>
<td>Semaglutide</td>
<td>Exenatide ER</td>
<td>Albilutide&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Dulaglutide</td>
<td>Semaglutide (oral)</td>
<td>Efglenatide</td>
</tr>
<tr>
<td>6,068</td>
<td>9,340</td>
<td>3,297</td>
<td>14,752</td>
<td>9,463</td>
<td>9,901</td>
<td>3,183</td>
<td>4,076</td>
<td></td>
</tr>
<tr>
<td><strong>Baseline HbA1c (%)</strong></td>
<td>7.7</td>
<td>8.7</td>
<td>8.7</td>
<td>8</td>
<td>8.7</td>
<td>7.2</td>
<td>8.2</td>
<td>8.9</td>
</tr>
<tr>
<td><strong>Baseline BP (mmHg)</strong></td>
<td>130</td>
<td>136/77</td>
<td>136/77</td>
<td>135/78</td>
<td>135/77</td>
<td>137/78</td>
<td>136/76</td>
<td>135/77</td>
</tr>
<tr>
<td><strong>Established CVD (%)</strong></td>
<td>100</td>
<td>81</td>
<td>83.0</td>
<td>73.1</td>
<td>100</td>
<td>31</td>
<td>84.7</td>
<td>89.6</td>
</tr>
<tr>
<td><strong>Baseline eGFR &lt; 60 mL/min/1.73 m² (%)</strong></td>
<td>23.2</td>
<td>23.1</td>
<td>24.1</td>
<td>21.6</td>
<td>23.5</td>
<td>22.2</td>
<td>26.9</td>
<td>31.6</td>
</tr>
<tr>
<td><strong>Baseline eGFR, mL/min/1.73 m²</strong></td>
<td>78</td>
<td>80</td>
<td>80</td>
<td>77</td>
<td>79</td>
<td>75</td>
<td>74</td>
<td>72</td>
</tr>
<tr>
<td><strong>Albuminuria (%)</strong></td>
<td>25.3</td>
<td>11.0</td>
<td>NA</td>
<td>22.0</td>
<td>NA</td>
<td>34.5</td>
<td>33</td>
<td>48.5</td>
</tr>
<tr>
<td><strong>ACEI or ARB (%)</strong></td>
<td>85.0</td>
<td>82.8</td>
<td>83.5</td>
<td>79.9</td>
<td>81.6</td>
<td>81.5</td>
<td>NA</td>
<td>80.0</td>
</tr>
<tr>
<td><strong>Renal composite outcomes&lt;sup&gt;b&lt;/sup&gt;</strong></td>
<td>0.84 (0.68–1.02)</td>
<td>0.78 (0.67–0.92)</td>
<td>0.64 (0.46–0.88)</td>
<td>0.88 (0.76–1.01)</td>
<td>NA</td>
<td>0.85 (0.77–0.93)</td>
<td>NA</td>
<td>0.68 (0.57–0.79)</td>
</tr>
<tr>
<td><strong>New-onset persistent macroalbuminuria</strong></td>
<td>0.81 (0.66–0.99)</td>
<td>0.74 (0.60–0.91)</td>
<td>0.54 (0.37–0.77)</td>
<td>0.87 (0.70–1.07)</td>
<td>NA</td>
<td>0.77 (0.68–0.87)</td>
<td>NA</td>
<td>0.68 (0.58–0.80)</td>
</tr>
<tr>
<td><strong>Persistent doubling of serum creatinine</strong></td>
<td>1.16 (0.74–1.83)</td>
<td>0.89 (0.67–1.19)</td>
<td>1.28 (0.64–2.58)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td><strong>End-stage renal disease&lt;sup&gt;b&lt;/sup&gt;</strong></td>
<td>NA</td>
<td>0.87 (0.61–1.24)</td>
<td>0.91 (0.40–2.07)</td>
<td>NA</td>
<td>0.75 (0.39–1.44)</td>
<td>NA</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td><strong>Death due to renal disease&lt;sup&gt;b&lt;/sup&gt;</strong></td>
<td>NA</td>
<td>1.59 (0.52–4.87)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td></td>
</tr>
</tbody>
</table>

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BP, blood pressure; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; ER, extended-release; GLP-1, glucagon-like peptide-1; HbA1c, hemoglobin A1c; NA, not assessed.

<sup>a</sup>Marketing was discontinued in 2018. <sup>b</sup>Hazard ratio (95% confidence interval).
The effects of injectable dulaglutide on cardiovascular outcomes in T2DM was the REWIND (Researching Cardiovascular Events with a Weekly Incretin in Diabetes) trial [53,54], published in 2019. This study was designed to demonstrate superiority, unlike the previous trials. A total of 9,901 participants with T2DM was followed up for a median of 5.4 years, a longer period than in the previous trials. This trial was unique in that the participants were low risk, with an average baseline HbA1c of 7.2%, median eGFR of 74.9 mL/min/1.73 m², baseline prevalence of CVD of 31.5%, and baseline prevalence of albuminuria of 35.0%. The composite renal outcome occurred significantly less frequently in the dulaglutide group than in the placebo group (HR, 0.85; 95% CI, 0.77–0.93; p = 0.0004), and the largest effect was a reduction in the development of macroalbuminuria in the dulaglutide group (HR, 0.77; 95% CI, 0.68–0.87; p < 0.0001).

The PIONEER 6 (Peptide Innovation for Early Diabetes Treatment) trial was designed to evaluate the cardiovascular outcomes from once-daily oral semaglutide in T2DM patients at high cardiovascular risk [55], and its results were published in 2019. This study recruited 3,183 participants who were followed up for a median of 15.9 months, which is the shortest duration of the trials listed in Table 2. However, no renal endpoint was predefined for assessment in this trial.

The most recent CVOT for GLP-1 agonists was the AMPLITUDE-O (Effect of Efpeglenatide on Cardiovascular Outcomes) trial in patients with T2DM and a history of either CVD or CKD [56]; the results were published in 2021. Once-weekly injectable efpeglenatide is a new exendin-4-based GLP-1 receptor agonist. A total of 4,076 participants was enrolled and followed up for a median of 1.81 years. Compared with placebo, efpeglenatide led to a 32% lower risk of a composite renal outcome event (incident macroalbuminuria, increase in UACR of ≥30% from baseline, sustained decrease in eGFR of ≥40%, initiation of RRT, or sustained eGFR of <75 mL/min/1.73 m²), independently of baseline use of SGLT2 inhibitors or metformin and baseline eGFR (HR, 0.68; 95% CI, 0.57–0.79; p < 0.001). However, a kidney function outcome event, defined as a composite of a decrease in eGFR of at least 40% for ≥30 days, ESRD, or death from any cause, did not differ between the efpeglenatide group and the placebo group (HR, 0.77; 95% CI, 0.57–1.02; p = 0.07).
Suggested nephroprotective mechanisms of glucagon-like peptide 1 receptor agonists

Indirect effects by improving conventional risk factors for diabetic kidney disease

Hyperglycemia plays a critical role in the pathogenesis of DKD [57,58], and GLP-1 receptor agonists have potent glucose-lowering effects [59–62]. The Kidney Disease: Improving Global Outcomes (KDIGO) 2020 clinical practice guidelines recommend GLP-1 receptor agonists as an excellent option for patients with DKD who have not achieved their glycemic target or as an alternative for patients unable to tolerate metformin or an SGLT2 inhibitor [63]. Although glucose-independent mechanisms are also emphasized, the antihyperglycemic effects of GLP-1 receptor agonists are thought to contribute to their nephroprotective effects in patients with DKD. Furthermore, GLP-1 receptor agonists induce reduction in body weight, blood pressure, and dyslipidemia, which could also contribute to their antialbuminuric effects [64,65].

In the LEADER trial [44], the liraglutide group showed a 0.4% reduction in HbA1c compared with the placebo group. Weight loss was 2.3 kg higher and systolic blood pressure was 1.2 mmHg lower in the liraglutide group than in the placebo group. In the REWIND trial [54], participants in the once-weekly 1.5-mg dulaglutide group had a 0.61% lower HbA1c, 1.46 kg lower body weight, and 1.7 mmHg lower systolic blood pressure than participants in the placebo group. In the SUSTAIN-6 trial [46], the mean HbA1c level was 1.0 percentage point lower, mean body weight was decreased by 4.3 kg more, and mean systolic blood pressure was 2.6 mmHg lower in the group receiving 1.0 mg of semaglutide once weekly than in the placebo group. In the PIONEER 5 trial [55], once-daily oral semaglutide (14 mg) was superior to placebo at reducing HbA1c and body weight in patients with T2DM. However, statistical correction for on-trial HbA1c level, blood pressure change, and bodyweight decrease did not significantly alter the observed decreases in albuminuria induced by GLP-1 receptor agonists in several CVOTs [66], suggesting that the renal protective effects of GLP-1 receptor agonists are not entirely due to improvements in risk factors.

In addition to its actions on body weight, blood pressure, and glucose, GLP-1 also regulates lipid metabolism. Dyslipidemia is a strong risk factor for both CKD and DKD. Experimental studies have provided data to support the notion that lipid abnormalities contribute to initiation and progression of glomerular disease [67]. A systematic review and meta-analysis of 35 trials showed that GLP-1 receptor agonists are associated with reductions in total and low-density lipoprotein cholesterol and triglyceride levels [68]. GLP-1 inhibits gastric lipase secretion [69] and intestinal lipoprotein and chylomicron production in humans [70]. GLP-1 receptor signaling reduces hepatic triglyceride content and impairs lipogenesis in the liver by stimulating the AMP-activated protein kinase pathway [71,72]. It also increases peripheral use of triglyceride-rich lipoproteins through increased burning of fat and activation of brown adipose tissue function [73,74]. However, it is uncertain whether those actions directly contribute to the nephroprotective effects of GLP-1 receptor agonists.

Potential direct mechanisms accounting for the renal protective effects of glucagon-like peptide 1 receptor agonists

The GLP-1 receptor is expressed in the renal cortex and vasculature, as well as proximal tubular cells [75,76], although uncertainties remain regarding receptor localization in the kidney due to lack of antibodies with high sensitivity and specificity. Inhibition of oxidative stress and inflammation, induction of natriuresis, and reduction of intraglomerular pressure are potential direct mechanisms underlying the renal protective effects of GLP-1 analogues (Fig. 1). Systemic oxidative stress increases the stage of incipient DKD [77]. A study in diabetic rats revealed that recombinant human GLP-1 attenuated oxidative stress in the glomeruli and in glomerular microvascular endothelial cells by inhibiting protein kinase C and activating protein kinase A (PKA) [78]. Liraglutide also reduced oxidative stress and albuminuria in streptozotocin-induced type 1 DM rats via PKA-mediated inhibition of renal nicotinamide adenine dinucleotide phosphate oxidases [79]. Exendin-4 was shown to activate the Nrf2 signaling pathway, which plays a key role in preventing oxidative stress and maintaining redox homeostasis, in vascular smooth muscle cells [80,81].

Inflammation plays a central role in the development of DKD. Accumulating experimental data suggest that anti-inflammatory activity underlies the nephroprotective effects of GLP-1 receptor agonists.
The natriuretic effect of GLP-1 receptor agonists has been proposed to underly the GLP-1–induced reduction in blood pressure reported in large CVOTs. GLP-1–mediated natriuresis and diuresis appear to involve redistribution and reduction of Na⁺/H⁺ exchanger 3 (NHE3) activity, which is located at the brush border of renal proximal tubules [89]. GLP-1 receptor agonists phosphorylated NHE3 at the PKA consensus sites Ser552 and Ser605, reducing its activity [36]. GLP-1 receptor agonists also increased natriuresis and diuresis by increasing renal blood flow in rats [90]. Human studies have shown that GLP-1 infusion reduces proximal tubular sodium reabsorption and decreases plasma angiotensin II concentration [91]. In addition, a single subcutaneous injection of liraglutide increased sodium excretion in people with T2DM [92]. Inhibition of NHE3 by GLP-1 could also affect glomerular hemodynamics by activating tubuloglomerular feedback. The increase in sodium delivery to the macula densa due to low NHE3 activity results in afferent arteriolar vasoconstriction and lower glomerular hyperfiltration and pressure. Liraglutide is associated with an acute reduction in eGFR and subsequent stabilization over time, suggesting that GLP-1 has renal hemodynamic effects [93].

Ongoing studies and candidate drugs under development

The FLOW trial (NCT03819153) to evaluate the effect of once-weekly semaglutide on progression of renal impairment is currently in progress. The primary renal outcome comprises a persistent ≥50% reduction in eGFR or a persistent eGFR of <15 mL/min/1.73 m², initiation of RRT, or death from kidney disease or CVD. This study recently began recruiting more than 3,000 T2DM patients with moderate/advanced CKD and albuminuria, and its estimated completion date is 2024. This trial will be the first to investigate the effects of a GLP-1 receptor agonist on primary kidney outcomes.

In addition, the SOUL trial (NCT03914326) is a currently ongoing CVOT to evaluate the hypothesis that oral semaglutide lowers the risk of cardiovascular events in T2DM patients at high risk for CVD. This study recently began recruiting more than 3,000 T2DM patients with moderate/advanced CKD and albuminuria, and its estimated completion date is 2024. This trial will be the first to investigate the effects of a GLP-1 receptor agonist on primary kidney outcomes.
semaglutide received the approval of the U.S. Food and Drug Administration in September 2019. 

Polypharmacology refers to the combination of several structurally related hormones into a single entity. Treatment with GLP-1/glucagon dual agonists produced weight loss and antihyperglycemic efficacy superior to that of GLP-1 selective agonists alone in mice with diet-induced obesity [94]. GLP-1 and glucagon are structurally similar, and glucagon also acts on the GLP-1 receptor [95], raising expectations that a combination of the two drugs could be more efficacious than the use of either drug on its own. Several phase 2 clinical trials of GLP-1/glucagon dual agonists are currently in progress. In addition, dual GLP-1/GIP agonists have prolonged half-lives due to fatty acylation or PEGylation. A once-weekly GLP-1/GIP co-agonist, named tirzepatide (LY3298176), was superior to dulaglutide in terms of weight loss and improved HbA1c level in a phase 2 study of patients with T2DM [96]. Phase 1 clinical trials for GLP-1/glucagon/GIP triple combination agents have been performed by Hannmi Pharmaceuticals (HM15211) and Novo Nordisk (NNC9204-1706).

GLP-1-based combination therapies have been found to offer metabolic benefits greater than those achieved by treatment with either compound alone. Based on the improved efficacy of GLP-1/glucagon and GLP-1/GIP co-agonists, it is reasonable to determine whether dual or triple agonists might provide greater efficacy than the respective mono-agonists. Various possible combinations are GLP-1 with GLP-2 [97], leptin [98], gastrin [99], amylin [100], peptide YY [101], cholecystokinin [102], insulin [103], adiponectin [104], fibroblast growth factor 21 [105], estrogen [106], dexamethasone [107], a proprotein convertase subtilisin/kexin type 9 antibody [108], melanocortin-4 agonist [109], farnesoid-x [110], or an SGLT2 inhibitor [111]. Future studies are required to evaluate whether any of these combinations of agents have nephroprotective effects superior to those of GLP-1 mono-agonists in DKD patients.

Conclusions and future perspectives

GLP-1 receptor agonists are promising therapeutic options for patients with DKD, with benefits beyond their blood glucose-lowering activity. These agents seem to predominantly affect macroalbuminuria, whereas their effects on hard renal endpoints are less clear. Although these agents can be used in CKD patients with an eGFR down to 15 mL/min/1.73 m$^2$, the safety of GLP-1 receptor agonists in DKD patients with stage 5 CKD needs to be investigated. In terms of future research direction, more studies similar to the ongoing FLOW trial should be conducted to evaluate the primary kidney outcomes of GLP-1 receptor agonist treatment. In addition, it is necessary to explore whether combination treatment with GLP-1 receptor agonists and other classes of agents with beneficial effects on the kidney will have synergistic renoprotective effects in patients with DKD.

Conflicts of interest

All authors have no conflicts of interest to declare.

Funding

This research was supported by the Bio & Medical Technology Development Program of the National Research Foundation (NRF) funded by the Korean government (MSIT) (2018R1D1A1B07049123, 2020R1F1A1074265) and by a Korea University grant (K1824431).

Authors’ contributions

Conceptualization, Funding acquisition: JHY, JAS
Investigation: SYP, DYL, NHK
Project administration: JAS
Writing—original draft: JHY
Writing—review & editing: SYP, DYL, NHK, JAS
All authors read and approved the final manuscript.

ORCID

Ji Hee Yu, https://orcid.org/0000-0003-1907-2859
So Young Park, https://orcid.org/0000-0002-7973-5944
Da Young Lee, https://orcid.org/0000-0002-8211-2393
Nan Hee Kim, https://orcid.org/0000-0003-4378-520X
Ji A Seo, https://orcid.org/0000-0002-1927-2618

References


76. Schlatter P, Beglinger C, Drew J, Gutmann H. Glucagon-like
peptide 1 receptor expression in primary porcine proximal tu-
77. Fujita H, Sakamoto T, Komatsu K, et al. Reduction of circulating
superoxide dismutase activity in type 2 diabetic patients with
microalbuminuria and its modulation by telmisartan therapy.
Hypertens Res 2011;34:1302–1308.
78. Yin W, Jiang Y, Xu S, et al. Protein kinase C and protein kinase
A are involved in the protection of recombinant human gluca-
gon-like peptide-1 on glomeruli and tubules in diabetic rats. J
79. Hendarto H, Inoguchi T, Maeda Y, et al. GLP-1 analog liraglutide
protects against oxidative stress and albuminuria in streptozoto-
cin-induced diabetic rats via protein kinase A-mediated inhibi-
80. Wang C, Li C, Peng H, et al. Activation of the Nrf2-ARE pathway
attenuates hyperglycemia-mediated injuries in mouse podo-
81. Zhou T, Zhang M, Zhao L, Li A, Qin X. Activation of Nrf2 con-
tributes to the protective effect of Exendin-4 against angiotensin
II-induced vascular smooth muscle cell senescence. Am J Phys-
iol Cell Physiol 2016;311:C572–C582.
82. Ye Y, Zhong X, Li N, Pan T. Protective effects of liraglutide on glo-
merular podocytes in obese mice by inhibiting the inflammato-
ry factor TNF-a-mediated NF-xB and MAPK pathway. Obes Res
receptor agonist ameliorates renal injury through its anti-in-
flammatory action without lowering blood glucose level in a rat
antiinflammatory effect. J Clin Endocrinol Metab 2012;97:198–
207.
lating cardiovascular risk biomarkers independently of changes
86. Zhang H, Zhang X, Hu C, Lu W. Exenatide reduces urinary trans-
forming growth factor-β1 and type IV collagen excretion in pa-
ients with type 2 diabetes and microalbuminuria. Kidney Blood
analogue therapy directly modulates innate immune-mediated
inflammation in individuals with type 2 diabetes mellitus. Dia-
betologia 2014;57:781–784.
88. Rizzo M, Abate N, Chandalia M, et al. Liraglutide reduces oxida-
tive stress and restores heme oxygenase-1 and ghrelin levels
Endocrinol Metab 2015;100:603–606.
89. Yip KP, Tse CM, McDonough AA, Marsh DJ. Redistribution of
Na+/H+ exchanger isoform NHE3 in proximal tubules induced
F575.
90. Ronn J, Jensen EP, Wever Albrechtsen NJ, Holst JI, Sorensen CM.
Glucagon-like peptide-1 acutely affects renal blood flow and
urinary flow rate in spontaneously hypertensive rats despite sig-
nificantly reduced renal expression of GLP-1 receptors. Physiol
Rep 2017;5:e13503.
(GLP-1): effect on kidney hemodynamics and renin-angiotensin-
aldosterone system in healthy men. J Clin Endocrinol Metab
on kidney function and vasoactive hormones in type 2 diabetes:
a randomized clinical trial. Diabetes Obes Metab 2016;18:581–
589.
Glucagon-like peptide 1 receptor agonist (GLP-1 RA): long-term
effect on kidney function in patients with type 2 diabetes. J Dia-
1/glucagon receptor dual agonism reverses obesity in mice. Di-
95. Capozzi ME, Svendsen B, Encisco SE, et al. § Cell tone is defined
by proglucagon peptides through cAMP signaling. JCI Insight
2019;4:e126742.
96. Frias JP, Nauck MA, Van J, et al. Efficacy and safety of LY3298176,
a novel dual GIP and GLP-1 receptor agonist, in patients with
type 2 diabetes: a randomised, placebo-controlled and active
97. Madsen KB, Askov-Hansen C, Naimi RM, et al. Acute effects of
continuous infusions of glucagon-like peptide (GLP)-1, GLP-2
and the combination (GLP-1+GLP-2) on intestinal absorption
in short bowel syndrome (SBS) patients: a placebo-controlled
responsiveness in diet-induced obese mice using an optimized
leptin analog in combination with exendin-4 or FGF21. J Pept
99. Suarez-Pinzon WL, Power RF, Yan Y, Wasserfall C, Atkinson M,
Rabinovitch A. Combination therapy with glucagon-like pep-
tide-1 and gastrin restores normoglycemia in diabetic NOD


Peritoneal dialysis adequacy: a paradigm shift

Chang Huei Chen, Isaac Teitelbaum

Department of Medicine, University of Colorado Anschutz Medical Campus, Aurora, CO, USA

For the past 30 years, nephrologists have focused on a single minimal threshold of Kt/V\text{urea} to determine the adequacy of peritoneal dialysis (PD). To date, there is no evidence that shows Kt/V\text{urea} to be a good surrogate measure of uremic symptom control or nutritional state in patients on PD. Volume of distribution (V\text{urea}) generally is considered equivalent to total body water (TBW). Yet, accurate determination of TBW is difficult. The most recent International Society for Peritoneal Dialysis practice recommendations on prescribing high-quality PD emphasized incorporation of multiple measures rather than the single value of Kt/V\text{urea}. These measures include shared decision-making between the patient and the care team and assessment of health-related quality of life, burden of uremic symptoms, presence of residual kidney function, volume status, and biochemical measures including serum potassium and bicarbonate levels. In some cases, PD prescriptions can be tailored to the patient priorities and goals of care, such as in frail and pediatric patients. Overall, there has been a paradigm shift in providing high-quality care to PD patients. Instead of focusing on small solute clearance in the form of Kt/V\text{urea}, nephrologists are encouraged to use a more comprehensive assessment of the patient as a whole.

Keywords: Adequacy, Metabolic acidosis, Peritoneal dialysis, Residual kidney function, Volume overload

Introduction

For the past three decades, assessment of peritoneal dialysis (PD) adequacy has focused on a single minimal threshold of Kt/V\text{urea}. The 1997 National Kidney Foundation-Dialysis Outcomes Quality Initiative clinical practice guidelines for PD adequacy recommended that weekly Kt/V\text{urea} be at least 2.0 \cite{1}. This recommendation was based predominantly on two observational studies. The CANUSA study included 680 incident patients on continuous ambulatory PD (CAPD) in Canada and the United States. The study demonstrated an inverse relationship between weekly Kt/V\text{urea} and relative risk (RR) of death, with weekly Kt/V\text{urea} of 2.1 associated with 78% expected 2-year survival \cite{2}. Similarly, in an Italian study that evaluated prevalent CAPD patients, improved survival was observed in patients with weekly Kt/V\text{urea} of ≥1.96 \cite{3}. However, these findings were not supported by subsequent prospective randomized controlled trials.

Main texts

The ADEMEX study included 965 patients on CAPD who were randomized either into a control group undergoing four exchanges with 2-L fill volume or an intervention group in which the prescription was modified to achieve a
peritoneal creatinine clearance of 60 L/week/1.73 m² [4]. The average total \( Kt/V_{\text{urea}} \) was 1.80 in the control group vs. 2.27 in the intervention group. After 2 years of follow-up, patient survival was equivalent between the two groups, with a RR of 1.0. Thus, increasing \( Kt/V_{\text{urea}} \) to ≥2.0 was not associated with survival benefit. Another clinical trial performed in Hong Kong evaluated 320 CAPD patients who were randomized into one of three groups targeting \( Kt/V_{\text{urea}} \) of 1.5 to 1.7, 1.7 to 2.0, and >2.0 [5]. There were no significant differences in patient survival, hospitalization rate, or serum albumin among the three groups after 2 years. However, more patients in the lowest \( Kt/V_{\text{urea}} \) target group (i.e., 1.5–1.7) required erythropoietin treatment. Based on these studies, the 2006 International Society for Peritoneal Dialysis (ISPD) guidelines on PD recommended that the total \((\text{renal} + \text{peritoneal})\) \( Kt/V_{\text{urea}} \) not be less than 1.7 at any time [6].

Using \( Kt/V_{\text{urea}} \) to determine adequacy of PD poses several problems. To date, there is no evidence that prescribed peritoneal \( Kt/V_{\text{urea}} \) is a good surrogate measure of uremic symptom control or nutritional state in PD patients. There also are problems intrinsic to the measure itself. Volume of distribution of urea \( (V_{\text{urea}}) \) generally is considered equivalent to total body water \( (\text{TBW}) \), given that urea is highly soluble in both water and cell membranes but not adipose tissue. This assumption implies that \( V \) should be determined using ideal body weight rather than actual body weight to avoid overdialysis in obese patients and underdialysis in underweight patients. Unfortunately, determination of TBW is difficult. In a recent review article, Davies and Finkelstein [7] compared the three main methods used to estimate TBW: the gold-standard isotope dilution, bioimpedance, and anthropometric equations. They found wide limits of agreement among the methods. When comparing the commonly used anthropometric equations to isotope dilution, the 95% confidence interval was ±18% of the TBW [7]. This translates into a \( Kt/V_{\text{urea}} \) range of 1.44 to 2.06 in an individual with a measured \( Kt/V_{\text{urea}} \) of 1.7 whose TBW is 35 L. Based on this finding, the authors suggest that a \( Kt/V_{\text{urea}} \) target for an individual patient should be defined as an acceptable range that considers the uncertainty of the measurement rather than applying a single cutoff value. Furthermore, a recent report from the SONG-PD study group described the 10 most important outcomes for patients on PD and their caregivers: infection, mortality, fatigue, flexibility with time, blood pressure, PD failure, ability to travel, sleep, ability to work, and effect on family [8]. In contrast, dialysis solute clearance was ranked the 52nd of 56 outcomes.

In 2020, the ISPD published updated practice recommendations for high-quality PD, which emphasized incorporation of multiple measures to assess the quality of dialysis rather than focusing on the single value of \( Kt/V_{\text{urea}} \) [9]. These measures include shared decision-making between the patient and care team and assessment of health-related quality of life (HRQOL), uremic symptoms, residual kidney function (RKF), volume status, biochemical measures, nutritional status, and small solute clearance. Highlights of these practice recommendations are outlined in Fig. 1.

An integral part of providing high-quality dialysis therapy is to understand the patient’s priorities and goals of care and to utilize shared decision-making between patients and the care team [10]. This approach enables establishment of realistic care goals and expectations and allows clinicians to individualize care plans to maximize patient HRQOL. The relationship between amount of dialysis delivered and its impact on HRQOL is unclear. It is clear, however, that increasing the dose of dialysis did not correlate with improved clinical outcomes of PD patients in the Hong Kong study or the ADEMEX trial [4,5]. There is no evidence showing that increased dialysis delivery corresponds to improved HRQOL in PD patients. Furthermore, intensifying PD prescriptions by increasing the number of exchanges or duration of treatment can impact negatively on patient HRQOL. Thus, the most recent recommendation is that, in the absence of clinical symptoms and when volume and electrolytes are controlled, no PD prescription adjustment is needed for the sole purpose of reaching an arbitrary clearance target [9].

In contrast to \( Kt/V_{\text{urea}} \), there are several clinical and biochemical parameters for which achieving certain levels do appear to be associated with superior outcomes. A recent review article by Teitelbaum proposed the following clinical parameters and biochemical levels to target: systolic blood pressure, 111 to 159 mmHg; absence of rales and lower extremity edema on exam; serum albumin, ≥3.8 g/dL; serum potassium, 4.0 to 5.4 mEq/L; serum sodium, ≥135 mEq/L; serum bicarbonate, ≥24 mEq/L; hemoglobin, ≥11 g/dL; corrected serum calcium, 8.5 to 10.1 mg/dL; and serum phosphorus, ≤6.3 mg/dL [11].

www.krcp-ksn.org
Volume overload is a frequent complication in PD patients and is associated with adverse clinical outcomes. In a large European PD cohort study that included 639 patients from six countries, severe fluid overload was found in 25% of the patients [12]. Similarly, observational studies from Korea and China found the prevalence of volume overload in their PD patients to range from 27% to 67% [13,14]. In the Chinese study, the rate of cardiac events was significantly higher in patients with volume overload [14]. In the Korean study, chronic volume overload was associated with increased mortality [13]. A more recent systematic review including 42 cohorts of 60,790 patients with end-stage kidney disease (ESKD), of which 5% were on PD, showed that an overhydration index of >15% is an independent predictor of mortality (hazard ratio, 2.28) [15]. On the other hand, overly aggressive volume removal in PD patients can cause accelerated loss of RKF. The NECOSAD study in the Netherlands showed that dehydration was associated with more rapid decline in RKF in PD patients [16]. Incident PD patients who experienced hypotensive episodes, most commonly caused by excessive ultrafiltration, were found to lose RKF more rapidly [17]. Nevertheless, volume expansion did not lead to preservation of RKF and was found to negatively impact RKF in some studies [18–20]. Prescriptions of PD should aim to achieve and maintain clinical euvolemia while considering RKF and its preservation [21].

Maintaining electrolyte homeostasis and acid-base balance should be an important focus in the management of ESKD patients. Hypokalemia is common in PD patients because most PD dialysates do not contain potassium. The prevalence of hypokalemia (defined by serum potassium of <3.5 mEq/L) among PD patients ranges from 20% to 34% [22–24]. Hypokalemia has been associated with poor nutritional status and higher comorbidity score [22]. It is also an independent predictor of all-cause and cardiovascular mortality [22,23]. Moreover, in a retrospective Taiwanese cohort study, the prevalence of peritonitis was significantly higher in patients with hypokalemia compared to those without hypokalemia [25]. Management of hypokalemia in PD patients includes increased dietary potassium intake, use of oral potassium supplements, and use of potassium-sparing diuretics [26]. As discussed above, a serum potassium target in the range of 4.0 to 5.4 mEq/L is desired.

Persistent metabolic acidosis promotes protein catabolism, leading to selective breakdown of skeletal muscle protein, depression of myocardial contractility, and bone resorption [27–29]. In a large cohort study that included 121,351 prevalent ESKD patients undergoing dialysis at Da-Vita facilities, prevalence of metabolic acidosis (defined as serum bicarbonate of <22 mEq/L) was 25% in PD patients [30]. The adjusted risk for all-cause mortality was higher in patients with serum bicarbonate of <22 mEq/L, irrespective of dialysis modality [30]. Two clinical trials examined the clinical benefits of correction of acidosis in PD patients. A group from the United Kingdom randomized patients into two groups; high alkali dialysate (lactate of 40 mmol/
L) with oral bicarbonate supplement or low alkali dialysate (lactate of 35 mmol/L [31]). At 1-year follow-up, patients in the high alkali dialysate group had greater increase in mid-arm circumference, higher weight gain, and fewer hospital admissions than the low alkali dialysate group. Another study from Hong Kong randomized assigned patients to either an oral sodium bicarbonate group (900 mg, three times daily) or placebo group [32]. At 12-month follow-up, patients in the treatment group had better nutritional status, higher body muscle mass, and fewer hospital days compared to the placebo group [32]. Management of metabolic acidosis can include either oral sodium bicarbonate supplement or intensifying PD prescriptions.

As previously mentioned, efforts should be made to avoid compromising RKF, since several observational studies have demonstrated that maintenance of RKF is associated independently with increased survival in patients with ESKD. A 40% decrease in RR of death for each 10 L/week/1.73 m² increase in renal creatinine clearance was observed in patients on PD [33]. In a reanalysis of the CANUSA study, there was a 12% decrease in the RR of death with each 5 L/week/1.73 m² increment in glomerular filtration rate, while there was no association between higher peritoneal creatinine clearance and risk of death [34]. Declining RKF is one of the predictors of uncontrolled blood pressure in PD patients, suggesting that euvolemia is more difficult to achieve with loss of RKF [35]. Moreover, Wang et al. [36] found greater use of antihypertensive agents and higher left ventricular mass index in anuric PD patients. In the same study, the authors also found that anuric patients, compared to those with RKF, are more likely to have anemia, erythropoietin requirements, higher C-reactive protein level, hypoalbuminemia, and malnutrition. It is important to recognize that, while intensifying the PD prescription might compensate for the loss of urea clearance with declining RKF, it will not replace all functions of failing native kidneys. Therefore, preservation of RKF is an important therapeutic endpoint in management of PD patients and should be taken into consideration when evaluating the quality of a PD prescription.

As discussed earlier, provision of high-quality dialysis therapy requires an understanding of the patient’s priorities and goals of care. Two specific patient populations deserve special mention. Frailty presents as a composite of poor physical function, decreased physical activity, fatigue, and weight loss and is associated with increased risks of falls, cognitive impairment, hospitalization, and mortality [37]. Frailty is found more commonly in older patients with ESKD. The goal of providing PD to frail patients is to improve overall well-being while minimizing treatment burden. For example, PD prescription can be reduced by performing fewer exchanges or allowing days off to maximize quality of life, especially when RKF is present [38]. At the other end of the spectrum, in pediatric patients, selection of dialysis modality should be based on parent/caregiver choice, child age and size, availability of family support, and modality contraindications [39]. In general, the same principles used to assess the delivery of high-quality PD care in adult patients should be applied to pediatric patients [39].

Conclusion

Thus, the 2020 ISPD practice recommendations do indeed represent a paradigm shift. Rather than focusing on small solute clearance in the form of Kt/Vurea, these recommendations require a more comprehensive assessment of the patient as a whole. Clinicians are encouraged to embrace this change and provide patients with the highest possible quality of care.

Conflicts of interest

All authors have no conflicts of interest to declare.

Authors’ contributions

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

ORCID

Chang Huei Chen, https://orcid.org/0000-0003-4515-1964
Isaac Teitelbaum, https://orcid.org/0000-0002-7526-6837

References


Recent advances in novel diagnostic testing for peritoneal dialysis-related peritonitis

Winston Wing-Shing Fung, Philip Kam-Tao Li

Department of Medicine and Therapeutics, Carol and Richard Yu Peritoneal Dialysis Research Centre, Prince of Wales Hospital, The Chinese University of Hong Kong, Shatin, Hong Kong, SAR, China

Peritoneal dialysis-related peritonitis remains a significant complication and an important cause of technique failure. Based on current International Society for Peritoneal Dialysis guidelines, diagnosis of peritonitis is made when two of the three following criteria are met: 1) clinical features consistent with peritonitis; 2) dialysis effluent white blood cell count of >100 cells/μL; 3) positive effluent culture. However, early and accurate diagnosis can still be a challenge because symptoms can be vague and the investigation results may not be readily available (e.g., during out-of-hours). Furthermore, the PD effluent culture may not always identify the causative organisms and is “culture-negative,” ultimately affecting the guidance of choosing an effective antibiotic overall [8]. Because of the risk and the clinical impact of the delay in initiating antibiotics

Keywords: Diagnostic tests, Novel method, Peritoneal dialysis, Peritonitis
for peritonitis, the ISPD currently recommends that empirical treatment be started as soon as peritonitis is suspected [7].

There have been some improvements in the timeliness and accuracy of diagnosing peritonitis over the years. In this review, three aspects of these novel diagnostic tests will be reviewed: confirmation of the diagnosis, identification of the causative pathogens, and risk stratification of treatment response. Overall, this article will discuss the latest evidence and updates for these important unmet needs in the management of PD-related peritonitis.

**Advances in confirmatory test and the advent of point-of-care testing**

An ideal confirmatory test should have good diagnostic accuracy with high sensitivity, specificity, and predictive value. The test should be easy to perform, have a quick turnover time to minimize unnecessary delay, and be low cost and noninvasive. Thus, research has emphasized developing tests with improved accuracy and quick turnover time such as point-of-care testing. The PD effluent is traditionally sent for total cell counts with differentials after a minimum dwell time of 2 hours as the first investigation for suspected peritonitis. As mentioned, a WBC count of >100 cells/μL with >50% PMNs in the PD effluent is considered as a confirmation for peritonitis [7]. However, the total cell counts and differential counts in the PD effluent can vary greatly based on the dialysate fluid dwell time and the mode of dialysis [7,9]. Furthermore, the result may take some time to return and would cause a certain degree of delay. Thus, efforts have been made to investigate other means to detect signs of inflammation/infections other than the raised white cell counts in the peritoneal dialysate.

Leukocyte esterase reagents strips are a point-of-care test commonly used in urinalysis to detect the presence of leukocytes in urine, which may signify infection. These strips essentially detect the presence of esterase, which is an enzyme released by PMNs [10]. These strips have been reported to be useful in diagnosing spontaneous bacterial peritonitis, empyema, and meningitis [11-13]. Studies have also been done to assess whether these strips can be used to detect the presence of leukocytes in peritoneal dialysate [14-16]. Recently, Rathore et al. [17] assessed the efficacy of the strips to diagnose peritonitis in a prospective study in a single center. They followed a total of 166 patients, and 21 patients were diagnosed to have peritonitis during the study period. Among these 21 cases of peritonitis, 20 were reagent-strip positive. This was compared to the 145 cases without peritonitis, of which only seven cases tested positive. Overall, the authors reported that the strips have a sensitivity, specificity, positive predictive value, and negative predictive value of 95.2%, 95.2%, 74.1%, and 99.3%, respectively [17]. These values were comparable to the diagnostic performance for cases based on clinical signs or total cell count. The sensitivity, specificity, positive predictive value and negative predictive value for cases based on clinical signs were 76.2%, 97.2%, 80%, and 96.6%, respectively, and the values for the total cell counts were 90.5%, 98.6%, 95%, and 98.6%, respectively [17]. A positive predictive value of 74.1% of the test is noted, which is lower than the 95% using total cell counts. One should note that the sample sizes are small, and studies with better designs would be needed to further assess the suitability of these reagent strips.

Apart from leukocyte esterase, several proinflammatory cytokines are possible biomarkers for diagnosing peritonitis. In particular, several nuclear factor kappa B (NF-κB) downstream mediators, such as interleukin 6 (IL-6) and cyclooxygenase-2 (COX-2), have been examined [18]. IL-6 is present in the PD effluent and is a key regulator of acute peritoneal inflammation in response to infection [19]. Indeed, our group investigated the intraperitoneal level of IL-6 and COX-2 and found that patients with peritonitis had higher levels of COX-2 (4.97 ± 6.25 ng/mL vs. 1.60 ± 1.53 ng/mL, p = 0.007) and IL-6 (26.6 ± 17.4 pg/mL vs. 15.1 ± 12.3 pg/mL, p = 0.04) in the dialysate than those without peritonitis. There was also a significant correlation between number of episodes of peritonitis and IL-6 and COX-2 levels after 1 year [20]. Another cytokine implicated is the matrix metalloproteinase (MMP)-8, which is produced by activated neutrophils during acute inflammation and facilitates recruitment and trafficking of inflammatory cells [21]. MMP-8 has been detected in the PD effluent of polymicrobial peritonitis [22]. However, a cutoff value to increase their predictive efficacy is yet to be determined, which impairs these cytokines to be a useful biomarker. Therefore, it remains to have more large-scale clinical studies to determine a cutoff value and to assess the predictive efficacy of these proinflammatory cytokines as a diagnostic test in peritonitis.
Recently, a novel point-of-care device has been developed for rapid diagnosis of peritonitis. The test essentially detects the elevated presence of the two proinflammatory markers, IL-6 and MMP-8, in the peritoneal dialysate using a lateral flow assay. As the peritoneal fluid gets absorbed and has traveled through the nitrocellulose membrane in the device, the antibodies and the binding reagents situated at the detection line bind to the target markers, producing a visually interpretable result. The advantages of such a device are that it is easy to use and it only takes about 5 minutes to diagnose or exclude peritonitis [23]. Goodlad et al. [24] assessed the performance of this device in a real-world clinical environment, using a cohort of 107 PD effluent samples collected in their center. Among the 107 samples, 49 cases tested positive and 58 cases were negative using the device. Of the 49 device-positive cases, the device correctly identified 41 cases of peritonitis with the remaining eight cases being false positives. However, six of these cases had systemic sepsis with other causes of intraabdominal infection. Among the 58 device-negative cases, the device correctly identified 57 cases of peritonitis with the remaining one being a false-negative, which was likely a partially treated peritonitis. Overall, they reported that the device has a high negative predictive value of 98.3% (95% confidence interval [95% CI], 89.1–99.8) and positive predictive values of 83.7% (95% CI, 72.8–90.8); and high sensitivity and specificity of 97.6% (95% CI, 87.4–99.9) and 87.7% (95% CI, 77.2–94.5), respectively.

Given the high negative predictive value of 98.3%, the authors suggested that the test could offer a rapid exclusion of peritonitis for clinically healthy patients, minimizing waiting time and facilitating early discharge as well as sparing the use of unnecessary antibiotics. With symptomatic patients, a negative result may prompt investigation for an alternative diagnosis. However, follow-up studies are needed to further examine the utility of this device through day-to-day clinical practice and under various clinical situations (e.g., those with recurrent peritonitis, those with different dialysates like icodextrin, and those with chronic inflammatory disease).

Neutrophil gelatinase-associated lipocalin (NGAL), normally expressed by lymphocytes and renal tubular cells, is significantly increased in response to bacterial infection [25]. Studies also showed that severe acute peritonitis was associated with an increase of NGAL levels both in plasma and PD effluent [26–28]. Martino et al. [29] tried to validate the utility of using peritoneal NGAL levels for the diagnosis of peritonitis in their case-control study. They evaluated 182 patients during a study period of 19 months. Ninety-one patients had signs and symptoms of peritonitis and were allocated to the case group. The remaining 91 patients, who were scheduled for a routine visit, had no signs or symptoms of peritonitis and were designated as the control group. They then tested various biomarkers and compared them between the two groups. They found that the serum C-reactive protein (CRP) level, procalcitonin (PCT), peritoneal NGAL, and peritoneal WBC were all significantly different between the two groups, with the p-values of <0.001 for all markers. However, in the multivariate regression analysis model, only the WBC (odds ratio [OR], 24.84; p = 0.012) and peritoneal NGAL levels (OR, 136.6; p = 0.01) were independent predictors of peritonitis events [29].

The authors further tested the predictive efficacy of various biomarkers using the receiver operating characteristic (ROC) curve analysis. Both peritoneal WBC and the NGAL level have a very high area under the ROC curve (AUC) (0.973, p < 0.001 and 0.939, p < 0.001, respectively), suggesting a quite decent correlation for predicting peritonitis. Conversely, the AUCs of both CRP and PCT were only 0.719 (p = 0.048) and 0.754 (p = 0.042), respectively. To conclude, they suggested that the peritoneal NGAL may be a reliable diagnostic marker to predict peritonitis, especially when used as an adjunct to peritoneal white cell count. However, further study to test its utility in a real-life clinical setting would be needed. Furthermore, because peritoneal NGAL is influenced by local inflammation [30], studies to assess the relationship of peritoneal NGAL level in various inflammatory peritoneal states would be very helpful to distinguish local peritoneal inflammation during peritonitis from baseline local inflammation in the absence of acute peritonitis.

**Novel methods in pathogen identification**

Currently, the standard method to identify the causative pathogens remains the sending of PD effluent to the microbiology laboratories for routine culture. Different culture methods include concentration, WBC lysis, and the BacT/Alert system (BioMérieux, Durham, NC, USA) [7,31]. However, these methods may take a few days before the respon-
sible organism is grown and identified [32]. They may take even longer and be difficult to grow if the bacterial numbers are small, unculturable, or fastidious or from patients who have recently received antibiotic therapy [33,34]. Thus, emphasis has been on other methods to rapidly identify the pathogens.

A well-established tool for rapid identification of bacterial species is 16S ribosomal RNA (rRNA) gene sequencing [35]. The 16S rRNA gene is highly conserved between different species of bacteria, yet it has hypervariable regions that provide a species-specific sequence useful for identification. The gene is also not prone to mutation [36]. Furthermore, the 16S rRNA gene sequence of almost all common bacterial pathogens has been studied and is readily available in the gene bank [37,38]. Overall, these findings make 16S rRNA an ideal target for sequencing as a unique fingerprint for pathogen identification.

Ahmadi et al. [39] evaluated this technique in the PD population. They assessed 45 patients with confirmed peritonitis and compared the pathogens identified using the molecular method to the conventional culture method. Among the 45 cases, the culture method identified 35 bacterial pathogens and two fungal organisms. Comparatively, bacterial DNA was detected in 38 cases and fungal DNA in two cases using the 16S rRNA gene sequencing technique, which showed similar pathogens identifications as the 37 samples from the culture method. This study suggested that the molecular method may be a useful emerging technique in concordance with the traditional culture method.

Recently, another study was done to further assess 16S rRNA sequencing following advances in next-generation sequencing [40]. The authors assessed 25 PD samples with peritonitis and similarly compared the molecular technique with culture-based assays. They defined the concordance as the co-occurrence of the same taxa in both culture and 16S amplicon sequencing assays at a level of less than 10% of the total population operational taxonomic unit for each sample. They showed that the majority of the 16S sequencing results gave an accurate representation of the main pathogens (at the genus level), achieving 80% concordance with bacterial strains identified in the culture-based assays. This was increased to 100% when the test was blinded for fungal and unculturable bacteria. They also reported that the technique was highly sensitive and could identify 33 different bacteria, compared to 13 bacte-

rrial species using culture-based techniques. In fact, they speculated that peritonitis may often be a polymicrobial disease [40].

However, as both authors noted, this molecular technique mainly identifies the pathogens at the genus level and may not be able to distinguish pathogens with high genetic similarity [39,40]. While high sensitivity may be an advantage over the traditional culture method, the lack of specificity remains a limitation, making the test difficult when trying to distinguish nondominant fastidious contaminant species from the dominant bacterial species. Thus, further tests with larger sample size, more taxonomically informative bacterial sequences (more 16S rRNA regions and/or other genes), and the ability to accurately assess antibiotic sensitivity loci are needed to assess the suitability for this identification technique. Regardless, 16S rRNA gene sequencing is an emerging rapid and direct method to identify the pathogen and may be useful as an adjunct to the standard culture method, especially in those who have recently received antibiotics and in culture-negative cases.

Another similar method is the detection of bacterial DNA using quantitative polymerase chain reaction (PCR). Johnson et al. [41] previously compared this technique to conventional culture-based method in 14 cases of peritonitis and found a correlation with the conventional method with a reported sensitivity of 67% and specificity of 79%. Another group further assessed the suitability of this method coupled with the electrospray ionization mass spectrometry (PCR/ESI-MS) [42]. This assay essentially uses tailored PCR primers capable of generating amplicons from over 95% of the species associated with human infection, including samples with high concentrations of background human DNA [43-45]. At the same time, an automated desalting and DNA debulking platform and an ESI-MS platform are used to prepare amplicons for mass spectrometry [43,46] and to discriminate amplicon sequence variants from different species present in a single sample [47,48]. Similar to a previous study, Chang et al. [42] compared this novel technique with the conventional culture-based method. Of the 21 samples of PD effluent from patient with peritonitis, PCR/ESI-MS identified microorganisms in 18 samples. When comparing the samples that are positive for both PCR/ESI-MS and culture, there is 100% concordance between the two techniques at the genus levels and an 87.5%
concordance when compared at the species level. They suggested that PCR/ESI-MS is a potential tool [42].

We tried to validate the suitability of PCR/ESI-MS for rapid bacterial identification in our cohort with a much bigger sample size (73 cases). Compared to the bacterial culture, the assay only identified 34.3% of the causative organisms correctly and failed to identify any organism in 52.1% of cases [49]. The method also identified a different organism in 8.2% of cases [49]. The reason for the poor performance is not entirely clear and requires further study in another cohort. Given the conflicting results and unless this discrepancy is clarified, PCR/ESI-MS should not be used for identifying the causative organisms from PD effluent in peritonitis, and other diagnostic methods should be explored instead.

Matrix-assisted laser desorption/ionization mass spectrometry with time-of-flight detector (MALDI-TOF MS) is another novel method that may be used in the identification of pathogens in peritonitis. It involves the generation of mass spectra from the cellular samples, which are then matched to the known bacterial database for reference [50,51]. It has already been recognized as a fast and reliable method in pathogen identification [52,53]. It is also a cost- and time-effective alternative to the 16S rRNA gene sequencing [54].

Lin et al. [55] assessed the use of MALDI-TOF MS in the PD population as they compared this technique to the conventional culture-based method. They assessed whether there is any difference in the time taken to identify the pathogen and whether the difference can be translated into any meaningful clinical outcome. Among the 155 episodes of peritonitis, MALDI-TOF MS was able to identify the causative organism much earlier than the conventional culture-based method by a difference of 64 hours (mean ± standard deviation [SD], 71 ± 37 hours vs. 135 ± 55 hours; p < 0.001) [55]. Comparing the clinical outcome showed no difference in response of peritonitis between the two groups. However, the authors showed that there was a significantly shorter length of hospital stay in the MALDI-TOF MS group than the culture-based group (overall mean ± SD, 8.2 ± 4.5 days vs. 5.2 ± 4.8 days; p < 0.001) [55]. Their results suggested the usefulness of this novel technique in pathogen identification, allowing an earlier pathogen identification and timely pathogen-directed antibiotic therapy.

These emerging techniques offer an attractive alternative to the conventional methods, especially in terms of better sensitivity and quicker turnover time. However, some of the tests may be too sensitive and lack specificity at present. More studies with larger sample sizes are needed to assess their suitability. Thus, it is unlikely that these would replace the conventional culture method in the near future; these novel tests should be used as an adjunct, especially when the culture is repeatedly negative.

**Advances in predicting relapses/assess response**

Several advances have also been made in developing tests that can assess the response of peritonitis and predict the risk of relapse. Our group has assessed both bacterial-derived DNA fragments and bacterial endotoxin, which are implicated as possible predictors [56,57]. For the bacterial-derived DNA fragments, we assessed 104 patients with peritonitis, in which a serial level of bacterial-derived DNA fragments was taken every 5 days during the antibiotic treatment. We showed that patients with relapsing or recurrent peritonitis episodes had significantly higher levels of bacterial DNA fragment in PD effluent than those without relapsing or recurrence, both 5 days before (31.9 ± 3.4 cycles vs. 34.3 ± 3.0 cycles, p = 0.002) and on the day of the completion of antibiotics (32.3 ± 2.6 cycles vs. 34.1 ± 1.7 cycles, p < 0.001) [56]. Furthermore, when bacterial DNA fragments detectable by 34 PCR cycles 5 days before the completion of antibiotics are used as the cutoff, the test has a sensitivity of 88.9% and specificity of 60.5% for the prediction of relapsing or recurrent peritonitis [56]. However, the sample size of our study is small and done in a single PD center. Thus, external validity needs to be substantiated before the result can be extrapolated to other centers. Further studies are also needed for a more accurate quantification of bacterial DNA fragment level in PD effluent so that a reliable diagnostic cutoff can be identified before it can be validated for use in clinical setting.

We have also assessed the suitability of dialysate bacterial endotoxin as a prognostic indicator for treatment failure in peritonitis [57]. Similar to the previous design [56], we studied 325 episodes of peritonitis and collected the PD effluent every 5 days for endotoxin levels and WBC count. Endotoxin was detected in the PD effluent of 23 episodes only. Nineteen episodes were caused by gram-negative organisms, and four episodes were of mixed bacterial...
growth. For peritonitis caused by gram-negative bacteria, a detectable peritoneal endotoxin level on day 5 had a sensitivity of 66.7% and a specificity of 83.3% for predicting primary treatment failure [57]. In contrast, peritoneal leukocyte count of >1,000/mm$^3$ on day 5 had a highly superior sensitivity of 88.9% and a specificity of 89.1%. There was no significant difference in the endotoxin level between completed cured patients cure and those who relapsed ($p = 0.5$) [57]. Essentially, our study showed that a detectable peritoneal endotoxin 5 days after antibiotic therapy might predict primary treatment failure in peritonitis episodes caused by gram-negative organisms, although it was inferior to peritoneal WBC count. Again, it is likely that our sample size is too small, with few peritonitis episodes, before one could draw any meaningful analysis. Therefore, studies with a larger cohort and multicenter design would be needed before endotoxins can be validated as a prognostic indicator for clinical use.

Serial monitors of dialysate cell counts have also been suggested as a useful predictor of outcome. Our group previously showed that the dialysate WBC count taken on day 3 was an independent prognostic marker for treatment failure after adjusting for conventional risk factors (hazard ratio, 9.03; 95% CI, 4.40–18.6; $p < 0.0001$) [58]. Using WBC count of >1,090/mm$^3$ on day 3 as the cutoff, the sensitivity and specificity were 75% and 74%, respectively, for the prediction of treatment failure. At that time, external validation was needed to confirm these associations.

Recently, a group from Thailand developed a risk prediction tool for stratifying PD patients with peritonitis into different risks for treatment failure [59]. From their analysis, four predictors of treatment failure were identified that included diabetes, systolic blood pressure of <90 mmHg at presentation, a dialysate leukocyte count of >1,000/mm$^3$ on days 3 to 4, and a count of >100/mm$^3$ on day 5. The adjusted ORs for each predictor were 1.81 (95% CI, 1.09–3.01; $p = 0.022$), 4.36 (95% CI, 1.72–11.09; $p = 0.002$), 2.52 (95% CI, 1.50–4.23; $p < 0.001$); and 43.64 (95% CI, 25.69–74.16; $p < 0.001$), respectively [59].

The group went on to develop a risk-scoring system that ranged from 0 to 11.5 using these four predictors with a specific assigned risk score: diabetes (1 score), systolic blood pressure of <90 mmHg at presentation (2.5 score), a dialysate leukocyte count of >1,000/mm$^3$ on days 3 to 4 (1.5 score), and a count of >100/mm$^3$ on day 5 (6.5 score). The AUC for the prediction tools was 0.92 (95% CI, 0.89–0.94), and the $p$-value for the Hosmer-Lemeshow test was 0.93, indicating good agreement between observed outcome and predicted risk score [59]. For simplicity, the score was categorized into three risk group: low (<1.5), moderate (1.5–9), and high risk (>9) for treatment failure and the positive likelihood ratio for each risk group were 0.09 (95% CI, 0.05–0.15), 3.54 (95% CI, 3.03–4.12), and 25.16 (95% CI, 5.86–107.98), respectively. The observed treatment failure rate for each risk strata increased from 3.0% (95% CI, 1.6%–5.0%) in the low-risk group and 54.4% (95% CI, 48.8%–60.0%) in the moderate-risk group to 89.5% (95% CI, 66.9%–98.7%) in the high-risk group [59].

Overall, their risk-scoring system appears to accurately predict the risk of treatment failure and would be useful for risk stratification. Their result also validated our study and supported the use of serial dialysate cell count as a prognostic indicator of treatment failure. Large prospective external validation studies in different settings are needed to establish the transportability and generalizability of this prediction model.

**Future research and the emergence of artificial intelligence**

Given there are major advances in the development of big data analysis and artificial intelligence (AI), emphasis should be placed on utilizing these innovations to facilitate the development of autonomous diagnostic tests that are both effective and efficient. An example would be the emerging concept of “immune fingerprinting” and the development of AI-assisted pattern recognition of these fingerprints through a machine learning algorithm. It has been noted that each type of pathogen may have a distinctive physiological and immunological pattern, and one of the objectives is to exploit these features to develop a rapid and effective diagnostic tool [60–62].

Zhang et al. [63] recently carried out a detailed analysis of dialysate in 83 patients with peritonitis. They identified a panel of local immune cells, inflammatory and regulatory cytokines and chemokines, and tissue damage-related factors that would constitute specific immune fingerprints for various pathogens. Using machine learning algorithms, they were able to identify and describe distinct patterns of immunological and inflammatory markers associated
with gram-positive and gram-negative organisms and with culture-negative peritonitis. For instance, the combination of IL-15, IL-16, and soluble IL-6 receptor levels, total cell count, and MMP substrate turnover is associated with coagulase-negative staphylococcus infections, whereas a pattern of IL-1 beta, IL-15, MMP substrate, tumor necrosis factor-beta, and zymography is associated with enterococcal infection. They concluded that these patterns were sufficiently immunologically distinct to allow a pathogen-specific diagnosis in PD patients, and that efficiency is enhanced by the machine learning algorithm. The reported AUC based on the top five markers used specifically to distinguish each of the three pathogens of gram-negative, streptococcal, and coagulase-negative staphylococcal infections was all >0.9, suggesting these were highly predictive patterns. Furthermore, they suggested that there are prognostic implications for some of the immune patterns because several immune markers are associated with technique failure. This study demonstrated that immune fingerprinting is a viable and attractive adjunct in the diagnosis of peritonitis and might further promote the development of novel point-of-care diagnostic strategies in this field.

Taken together, the current ISPD diagnostic criteria for peritonitis remain reliable and indispensable. Nevertheless, these novel diagnostic and prognostic tests are promising and could certainly have impactful clinical applications in the future. Further studies are needed to assess the suitability of these emerging tests in real-world clinical settings.

Conflicts of interest

Philip Kam-Tao Li received speaker honorarium from FibroGen, AstraZeneca, and Baxter. Otherwise, there is no conflict of interest to declare.

Authors’ contributions

Conceptualization: WWSF, PKTL
Project administration: PKTL
Writing-original draft: WWSF
Writing-review & editing: WWSF, PKTL
All authors read and approved the final manuscript.

References

40. van Hougenhouck-Tulleken WG, Lebre PH, Said M, Cowan DA. Bacterial pathogens in peritoneal dialysis peritonitis: insights...
49. Szeto CC, Ng JK, Fung WW, et al. Polymerase chain reaction/electrospray ionization-mass spectrometry (PCR/ESI-MS) is not suitable for rapid bacterial identification in peritoneal dialysis effluent. Perit Dial Int 2021;41:96–100.
Background: Patients receiving hemodialysis have various complications with a high mortality rate and require specialized treatment at an institution equipped with an appropriate workforce, equipment, and facilities. The Korean Society of Nephrology (KSN) is conducting hemodialysis unit accreditation to manage the quality of hemodialysis institutions, present standard treatment guidelines, and establish a network between regional medical institutions for the safe treatment of hemodialysis patients. This study aimed to summarize the previous accreditation results and discuss future directions.

Methods: After the proposal of hemodialysis unit accreditation in 2009, pilot projects were undertaken for hemodialysis units and dialysis subspecialist training hospitals in the metropolitan area for 5 years. Since 2016, five hemodialysis unit accreditation projects have been conducted.

Results: The cumulative number of participating units was 599, and the number of accredited units was 473 (average accreditation rate, 79.0%). The participating units consisted of clinics (58.6%), non-university hospitals (28.2%), and university hospitals (13.2%). Overall, 92.4% of university hospitals, 81.2% of clinics, and 68.0% of non-university hospitals were accredited. Over 5 years, new units were added annually to apply for accreditation, and the rate of previous participants applying for reaccreditation was high (77.7%). However, considering that the total number of member institutions of the KSN is 637, the number of units with valid accreditation as of 2020 was low (267 [41.9%]).

Conclusion: The efforts of the KSN and its members, as well as institutional support from the government, are required for quality management of hemodialysis units through hemodialysis unit accreditation.

Keywords: Accreditation, Dialysis unit, Hemodialysis, Nephrology

Introduction
The prevalence and incidence rates of end-stage renal disease (ESRD) are increasing every year worldwide. The number of patients on hemodialysis in South Korea increased by 22.8%, from 74,013 in 2014 to 90,901 in 2018, and the total...
medical cost increased by 45.5%, from Korean won (KRW) 1.81 trillion in 2014 to KRW 2.63 trillion in 2018 [1]. In 2018, the average medical cost per patient was KRW 29 million, which is the highest medical cost for a single disease. In addition, the number of hemodialysis centers is also steadily increasing; the number increased by 18.0% to 1,042 in 2018 from 2014, and the number of hemodialysis machines increased by 28.7% to 26,837 machines in the same time period [1].

Most patients with ESRD already have various comorbidities, including heart disease, stroke, vascular disease, diabetes, high blood pressure, and infection, prior to starting dialysis. Since complications of almost all organs such as the heart, lungs, brain, blood vessels, and digestive organs can occur even after the start of dialysis, proper management of the facilities and equipment in the dialysis unit as well as the expertise of the healthcare workers in charge of these patients is essential [2].

Despite the rapid increase in the number of patients with ESRD, the expansion of the number of hemodialysis units, and the continuous increase in medical costs, some hemodialysis units still do not have adequate staff and facilities, thereby threatening patient access to healthcare [3,4]. According to the data of the sixth hemodialysis adequacy evaluation by the Health Insurance Review and Assessment (HIRA), dialysis specialists account for 75.0% of the total number of physicians working in hemodialysis units in South Korea, while in the hemodialysis units of nursing hospitals, only 39.7% were dialysis specialists [1]. As there is no regulation on the quality of hemodialysis units, each dialysis unit is dependent on its own management [5]. Therefore, it is necessary to continuously examine the status of hemodialysis centers, resolve problems, improve the quality of medical services, protect the right of patients to healthcare, and further establish medical orders. Hence, the Korean Society of Nephrology (KSN) is conducting hemodialysis unit accreditation to recommend and evaluate standard medical guidelines, to manage the quality of hemodialysis facilities for the safe treatment of patients on hemodialysis, and to establish a network of regional medical institutions. After the proposal for hemodialysis unit accreditation in 2009, pilot projects were undertaken for hemodialysis units and dialysis specialist training hospitals in the metropolitan areas over a period of 5 years [5]. Since 2016, five hemodialysis unit accreditation projects have been conducted [6–9].

This study aimed to summarize the previous accreditation results and discuss future directions.

**Methods**

**Process of accreditation**

Unlike other countries, South Korea currently does not have a hemodialysis center quality management system or a hemodialysis unit installation standard. Accordingly, in 2009, the KSN initiated a hemodialysis unit certification evaluation system. Prior to fanning out the accreditation project across the country, pilot projects were conducted. The first pilot project was conducted in the southwest region of Seoul and Gwangmyeong from 2009 to 2010; the second pilot project was undertaken in the southeast region of Seoul, Seongnam, and Icheon from 2010 to 2011; the third pilot project was carried out in the northeast region of Seoul, Ui-jeongbu, and Guri from 2011 to 2012; the fourth pilot project was conducted in the northwest region of Seoul, Ilsan, and Paju from 2012 to 2013; and the fifth pilot project was carried out for the dialysis specialist training hospitals from 2014 to 2015. In total, 183 units participated in the series of pilot projects, with a 70% participation rate and 73% accreditation rate.

After the pilot projects, nationwide hemodialysis unit accreditation was conducted from 2016. The medical institution eligible for the evaluation was a hemodialysis unit that had performed hemodialysis for a year or longer and where a KSN member worked. Patients who had been receiving hemodialysis for 3 months or longer were included in the evaluation. Each unit wishing to participate in the evaluation of accreditation entered data on the hemodialysis unit accreditation website (http://ksn.nephline.com). Once accreditation is approved, the accreditation is valid for 3 years.

The process of accreditation begins with the application for the accreditation project after the notice, and an online review is conducted based on the data entered online (Fig. 1). The online review was conducted by the dialysis committee of the KSN, and an ethics evaluation was conducted by the ethics committee. One or two members of the KSN committee then audited each unit through on-site assessment. The results of the online review and on-site assessment were combined, and if necessary, the participating units were requested to supplement the data. The final
The four evaluation items used for hemodialysis unit accreditation include structure, process, ethics, and medical records and reports. All four evaluation items must be satisfied for accreditation (Table 1).

The first evaluation item, structure, includes the staffing, facility and equipment, and water treatment system. The staffing requirements of the structure were evaluated based on the proportion of dialysis specialists, the average number of daily hemodialysis cases performed by a physician, the proportion of nurses with more than 2 years of experience in hemodialysis, and the average number of daily hemodialysis cases performed by a nurse. For the proportion of dialysis specialists, 3 points were given for 50% or more, 2 points for 30% to 49%, and 0 points for 30% or less. The average number of daily hemodialysis cases performed by a physician was evaluated according to the standard for the size of the unit. The standard was 24 cases a day for dialysis specialists in university hospitals, 26 cases for non-university hospitals, and 36 cases for clinics. Three points were allocated for the number of cases below the standard, 2 points for 101% to 120% of the standard, and 0 points for 120% or more of the standard. The scores for the proportion of dialysis specialists and the average number of daily hemodialysis cases performed by a physician were summed and a score of 4 points or higher was necessary to meet the requirements. Concerning the ratio of nurses with more than 2 years of experience, 3 points were given for 50% or more, 2 points for 40% to 49%, and 0 point for 40% or less. Regarding the average number of daily hemodialysis cases performed by a nurse, 3 points were given for ≤5 cases per day, 2 points for ≤6 cases per day, 1 point for ≤6.5 cases per day, and 0 points for more than 6.5 cases. Similar to the score for the physicians, the scores given for the proportion of nurses with more than 2 years of experience and the average number of daily hemodialysis cases performed by a nurse were summed and a total of 4 points or higher was necessary to meet the requirements. The facility and equipment requirements included compliance with firefighting...
Table 1. Evaluation standards for accreditation

1. Structure
   1) Staffing
      (1) Indicator: physician
         The sum of points ① and ② must be at least 4.
         ① Proportion of dialysis specialists among all regular working physicians in the hemodialysis unit
            - Over 50%: 3 points
            - 30%–49%: 2 points
            - Less than 30%: 0 points
         ② Average number of daily dialysis cases performed by a physician
            - Less than standard※: 3 points
            - 101%–120% of standard: 2 points
            - Over 120% of standard: 0 points
            ※ Standard according to the size the of institution:
               • University hospital: 24 cases a day
               • Non-university hospital: 26 cases a day
               • Clinic: 36 cases a day
      (2) Indicator: nurse
         The sum of points ① and ② must be at least 4.
         ① Proportion of nurses with more than 2 years of experience among total nurses working in the hemodialysis unit
            - Over 50%: 3 points
            - 40%–49%: 2 points
            - Less than 40%: 0 points
         ② Average daily dialysis cases performed by a nurse
            - ≤5 cases a day: 3 points
            - ≤6 cases a day: 2 points
            - ≤6.5 cases a day: 1 point
            - More than 6.5 cases a day: 0 points
   2) Facility and equipment
      (3) Indicator: safe and comfortable environment
         ① Air-conditioning and heating facilities
         ② Ventilation system
         ③ Separate disposal of infectious waste
      (4) Indicator: compliance of regulation on fire and firefighting in buildings
         ① Fire safety inspection
         ② Emergency exit open
         ③ Evacuation route signs
      (5) Indicator: quarantine of hepatitis B surface antigen-positive patients
      (6) Indicator: emergency equipment
         ① Oxygen and oxygen supply system
         ② Suction equipment
         ③ Airway
         ④ Electrocardiograph and monitor
         ⑤ Defibrillator
   3) Water treatment system
      (7) Indicator: regular water quality inspection for microorganisms, endotoxins, and contaminants
         ① Microorganism test: once a month
         ② Endotoxin test: once every 3 months
         ③ Contaminants: once a year

(Continued to the next page)
and fire regulations, emergency equipment, and quarantine of hepatitis B surface antigen-positive patients. The water treatment system requirements included regular inspection of microorganisms, endotoxins, and contaminants.

The second evaluation item, the process, included regular hemodialysis adequacy tests and regular laboratory testing of patients. The third evaluation item, ethics, prohibited any fee-for-service that did not meet the standard, unauthorized provision of transportation, patient solicitation, and exaggerated or false advertisement to prevent accreditation in units with unethical practices. Lastly, the fourth evaluation item, medical records and reports, included participation or enrollment in the ESRD registration program, keeping medical records, and documenting reports on deceased or transferred patients.

Investigation method

The results of the accreditation were analyzed based on the data collected by the KSN during the accreditation period from 2016 to 2020. After the application of each unit for accreditation was received, the units that passed all of the online reviews, the on-site assessment, comprehensive evaluation, and final evaluation were accredited; those who failed to pass the process were unaccredited. The units that withdrew their applications during the process were also unaccredited.

Results

Participation in accreditation and accreditation status

From 2016 to 2020, 599 units participated in accreditation over the five accreditation projects, and 473 of the units were accredited (79.0%). Table 2 shows the number of participating units and the number of accredited units per year. In 2016, the largest number of units participated in the first year of accreditation; 190 units applied for accreditation and 170 units obtained accreditation. In 2017 and 2018, there were continued new accreditation applications. In 2019, 163 units applied for accreditation and 133 units successfully obtained accreditation. Over the past 5 years, an average of 120 units participated in the accreditation per
In the first year of 2016, the accreditation rate was the highest at 89.5%, and the accreditation rate was the lowest in 2017 at 52.2%.

Over the 5-year accreditation period, there were 126 cumulative cases of failure to obtain accreditation. The most common cause of failure to obtain accreditation was staffing shortages of physicians, accounting for 31.0% (39 cases). Other causes of failure to obtain accreditation included staffing problems of nurses (29 cases), ethics problems (25 cases), inadequate facility and equipment (five cases), and nonparticipation in the ESRD registration program (three cases). Withdrawals for unknown reasons accounted for 23 cases and in two cases, the applicant was not a member of the KSN. Regarding the evaluation committee, the highest number of committee members participated in 2016 (133 members), and an average of 96 members participated in the on-site assessment.

As the accreditation is valid for 3 years, the enrolled institutions were duplicated because of reapplication after expiration of the validity period. Fig. 2 shows the number of units with valid accreditation by year. The number of units with valid accreditation by year has gradually increased since 2016; the total number of accredited units reached a maximum in 2018, with 282 units. As of March 2021, the total number of valid accredited units is 267. In each bar, the number of institutions according to the year of first accreditation is indicated.

<table>
<thead>
<tr>
<th>Variable</th>
<th>2016</th>
<th>2017</th>
<th>2018</th>
<th>2019</th>
<th>2020</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participating institution (n)</td>
<td>190</td>
<td>69</td>
<td>94</td>
<td>163</td>
<td>83</td>
</tr>
<tr>
<td>Accredited institution (n)</td>
<td>170</td>
<td>36</td>
<td>76</td>
<td>133</td>
<td>58</td>
</tr>
<tr>
<td>Accreditation rate (%)</td>
<td>89.5</td>
<td>52.2</td>
<td>80.9</td>
<td>81.6</td>
<td>69.9</td>
</tr>
<tr>
<td>Valid accredited institution (n)</td>
<td>170</td>
<td>206</td>
<td>282</td>
<td>245</td>
<td>267</td>
</tr>
</tbody>
</table>

**Table 2. Current status of participation in hemodialysis unit accreditation by year.**

![Figure 2. Number of units with valid accreditation by year.](attachment:image.png)
Evaluation results by region and size of the unit

The region with the highest number of participating and accredited units was Seoul, with 171 units accredited out of 195 units that participated, followed by Gyeonggi and Incheon, with 103 units accredited out of 139 units that participated. The least number of units (10 units) participated in Jeju, but all 10 of the participating units were accredited. Fig. 3A shows the accreditation rate by region. The accreditation rate was the highest in Jeju (100%), followed by Seoul and Jeollanam-do · Gwangju (87.5%). The accreditation rate in Chungcheongnam-do · Daejeon was the lowest at 59.6%.

Concerning the number of applications by unit size, clinics accounted for most of the applications (351 [58.6%]), followed by non-university hospitals (169 [28.2%]) and university hospitals (79 [13.2%]). The accreditation rate was the highest in university hospitals (92.4%), compared with 81.2% in clinics and 68.0% in non-university hospitals (Fig. 3B).

Discussion

The hemodialysis unit accreditation evaluates whether all basic requirements and minimum conditions for hemodialysis services are satisfied, rather than ranking by grade. This system aims to create a reliable medical environment for patients on hemodialysis and to establish a network and system among local medical institutions. It is based on the voluntary participation of KSN members, and online reviews and on-site assessments are conducted to ensure objective evaluation as much as possible. The KSN conducted five hemodialysis unit accreditation projects from 2016 to 2020. Since 2016, a total of 599 units have participated in accreditation, and 473 units have been accredited (79.0%). Among the 206 accredited units whose valid accreditation expired after 3 years, 132 units applied for reaccreditation, indicating a relatively high application rate for reaccreditation. In addition, new units apply for hemodialysis unit accreditation each year.

As of 2020, there were 267 valid accredited units, account-
ing for 41.9% of the 637 KSN member institutions; this proportion is rather low. The number of target institutions was not the same as that of the hemodialysis registry program because our accreditation project included only hemodialysis units of KSN members. The low participation rate may be because there is no clear economic compensation for accredited units and there is a lack of institutional regulation against unaccredited units. Furthermore, there are many hemodialysis units that do not meet the conditions of the KSN accreditation even among the KSN members’ institutions. We surmise that the hemodialysis units did not participate in the KSN accreditation projects and this also resulted in a low participation rate. In addition, since the HIRA hemodialysis adequacy evaluation is conducted every 1 to 2 years, the inconvenience of inputting data and the burden of work because of the overlapping evaluations may have contributed to the low participation rate. To resolve such limitations, the necessity of integrating the hemodialysis unit accreditation of the KSN and the hemodialysis adequacy evaluation of HIRA has been suggested. HIRA has been conducting hemodialysis adequacy evaluation for dialysis units since 2009 to improve the quality of nursing institutions and provide information to the public. With the hemodialysis adequacy evaluation of HIRA, the quality management of hemodialysis units has been improved in terms of the hemodialysis adequacy test. However, the available emergency equipment, water quality assessment, and the proportion of dialysis specialists and the proportion of nurses with more than 2 years of experience in hemodialysis have not improved. Moreover, the hemodialysis adequacy evaluation does not assess ethical issues. Since the hemodialysis adequacy evaluation in 2015, a pay-for-performance system has been introduced. However, this cannot be a fundamental countermeasure because it is applied only during the evaluation period. Integrating the hemodialysis unit accreditation of the KSN and the hemodialysis adequacy evaluation of HIRA will allow more efficient management of hemodialysis units in South Korea based on the experience of the experts in quality management and nationwide evaluation. The lack of ethics evaluation and on-site assessment in the hemodialysis adequacy evaluation by HIRA can be supplemented by the KSN’s accreditation project to ensure objectivity of the evaluation and additional reflection on quality management.

It is also necessary to make efforts to reward and promote accredited units. Considering that clinics account for 58.6% of all units participating in the accreditation, these clinics should be given priority for the referral of patients on hemodialysis from a higher level of medical institution to a clinic. It is also important to form networks within the community. Since the accredited units are posted on the KSN website, these materials should be more actively used. Currently, accredited units are given an accreditation mark, which may have an effect on public relations among patients and the community. In addition, the KSN should promote accredited hemodialysis units to patients and encourage patients to attend those institutions.

Finally, national support is urgently needed to create a safe medical treatment environment for patients on hemodialysis. Several countries worldwide implement quality management for hemodialysis units in the form of legal regulations or accreditation [10]. The United States operates both permit and accreditation systems [11]. In Germany and Singapore, the operation of hemodialysis units requires permission [12,13], whereas Hong Kong and Taiwan operate an accreditation system [14,15]. In Hong Kong, the Hong Kong College of Physicians and Central Renal Committee of Hospital Authority has issued guidelines for the accreditation of renal dialysis units. The guidelines state that only qualified nephrologists and renal nurses can provide hemodialysis services. The guidelines provide accreditation standards for equipment, water treatment systems, and hemodialysis machines. Similarly, in Taiwan, only nephrology specialists are allowed to operate hemodialysis units. The accreditation system in Taiwan provides management standards for hygiene and infection and dialysis units are inspected every 2 years by audit teams that consist of the Taiwan Society of Nephrology members and staff from insurance companies. The insurance coverage is affected by the results. In contrast, in South Korea, no permission is required to establish a hemodialysis unit and there are no laws and regulations related to facilities, staffing, quality management, and safety measures for patients on hemodialysis. Therefore, to ensure patients’ rights to an adequate hemodialysis service, improve the quality of medical services, and manage unethical hemodialysis units, it is necessary to introduce standards for the establishment of a hemodialysis unit. In 2011, the Ministry of Health & Welfare and the Korea Health Promotion Institute conducted a study on the establishment of standards for hemodialysis unit accreditation in South
Korea, but no subsequent actions have followed [10]. Additionally, it is necessary to introduce a registration system for patients with ESRD to understand the exact health and management status of patients with chronic kidney disease (CKD). The government has initiated many discussions on the systematic prevention and management of CKD. In November 2019, a CKD management bill was proposed, but it was automatically abolished after the end of the 20th National Assembly. If patient registration and hemodialysis unit accreditation are implemented with the approval of a CKD management bill, the start time of dialysis can be delayed by preventing deterioration of patients with CKD, and the survival rate of patients undergoing dialysis can be increased. This will allow the creation of a safe medical environment for patients with CKD and reduce unnecessary financial waste in healthcare through the quality management of hemodialysis units.

The KSN has been striving to improve the quality of hemodialysis units for a safe hemodialysis service through the five hemodialysis unit accreditation projects from 2016 to 2020. Although the number of accredited units is gradually increasing based on the voluntary participation of the expert group, the participation rate is not yet high compared with the total number of KSN members’ institutions. It is hoped that an environment in which hemodialysis patients are safely treated can be achieved based on the continuous efforts of the KSN, the active participation of experts, and national support.

**Conflicts of interest**

All authors have no conflicts of interest to declare.

**Acknowledgments**

The authors would like to thank the members of the Korean Society of Nephrology for supporting this article.

**Authors’ contributions**

Conceptualization: YKL, KK, DJK
Data curation: JHP, YKL, DJK
Formal analysis: JHP, YKL
Visualization: JHP
Writing–original draft: JHP, KK
Writing–review & editing: All authors
All authors read and approved the final manuscript.

**ORCID**

Ji Hyeon Park, https://orcid.org/0000-0002-7143-336X
Young-Ki Lee, https://orcid.org/0000-0003-3464-6144
Kiwon Kim, https://orcid.org/0000-0002-2885-0053
Dae Joong Kim, https://orcid.org/0000-0001-7526-1107

**References**

11. Centers for Medicare & Medicaid Services (CMS), HHS. Medicare and Medicaid programs; conditions for coverage for end-


Background: Shared decision-making is a two-way symmetrical communication process in which clinicians and patients work together to achieve the best outcome. This study aimed to develop self-assessment items as a decision aid for choosing a dialysis modality in patients with chronic kidney disease (CKD) and to assess the construct validity of the newly developed items.

Methods: Five focus group interviews were performed to extract specific self-assessment items regarding patient values in choosing a dialysis modality. After survey items were refined, a survey of 330 patients, consisting of 152 hemodialysis (HD) and 178 peritoneal dialysis (PD) patients, was performed to validate the self-assessment items.

Results: The self-assessment for the decision aid was refined to 35 items. The structure of the final items appeared to have three dimensions of factors; health, lifestyle, and dialysis environment. The health factor consisted of 12 subscales ($\alpha = 0.724$), the lifestyle factor contained 11 subscales ($\alpha = 0.624$), and the dialysis environment factor was represented by 12 subscales ($\alpha = 0.694$). A structural equation model analysis showed that the relationship between the decision aid factors (health, lifestyle, and dialysis environment), patients’ CKD perception, and cognition of shared decision-making differed between HD patients and PD patients.

Conclusion: We developed and validated self-assessment items as part of a decision aid to help patients with CKD. This attempt may assist CKD patients in making informed and shared decisions closely aligned with their values when considering dialysis modality.

Keywords: Decision support techniques, Perception, Self-assessment, Shared decision-making
Introduction

During the past three decades, the number of people undergoing maintenance dialysis globally has increased dramatically [1]. According to the Global Burden of Disease study, 697.5 million individuals worldwide had chronic kidney disease (CKD) in 2017, and 1.2 million of them died [2]. Korea is no exception; in 2019, the end-stage renal disease (ESRD) population was more than 100,000, doubling over a 10-year period [3].

CKD is not only a public health issue but also creates an economic burden. According to the 2014 National Health Insurance Statistical Yearbook (Korea), the number of hospital visits due to CKD increased from ~150,000 in 2013 to ~160,000 in 2014, and the corresponding medical expenses also increased [4]. CKD has the highest medical cost per person among chronic diseases, and hemodialysis (HD) and peritoneal dialysis (PD) cost 87 and 65 times more than hypertension treatment, respectively [5].

People with CKD and ESRD have a poorer health-related quality of life (HRQOL) than the general population [6,7]. In patients with ESRD, low HRQOL is associated with a higher risk of death and hospitalization, which affects morbidity and mortality in patients with ESRD [6-8]. However, little is known about the relationship between low HRQOL and adverse outcomes in patients with predialysis CKD.

Patients whose advanced CKD is approaching ESRD face complex medical decision-making regarding the type of medical therapy they wish to pursue. More than a decade ago, the Renal Physicians Association and the American Society of Nephrology recommended a shared approach to decision-making for all patients with ESRD [9], which is supported by evidence that shared decision-making can improve patient outcomes [10]. Despite shared decision-making emerging as a pillar of national and international quality of care standards and policies [11], evidence shows that people suffering from CKD still have limited involvement and participation in treatment decision-making [12,13].

Effective interventions to guide patients in decision-making include decision aids (DAs) and shared decision-making [14]. Patients exposed to DAs are more likely to be informed, have realistic expectations of option outcomes, participate actively in decision-making, and feel lower decisional conflict [15]. In this context, there is growing interest in developing, implementing, and further strengthening the quality of decision support provided to patients and families living with CKD. However, relatively little is known about how to achieve this goal.

The present research aims to develop self-assessment items for a DA by employing both qualitative and quantitative methods. We then seek to confirm the robustness of this study by examining the multifaceted validity of the newly developed scales for a DA.

Methods

Study 1: scale development

The aim of Study 1 was to develop DA scales for patients with CKD and to examine the content validity of the DA’s self-assessment items.

Study design

A flow chart of our study is shown in Fig. 1. First, we conducted five focus group interviews (FGIs) consisting of two groups undergoing HD, two groups undergoing PD, and one group of people facing a modality choice decision. Each group consisted of five patients, and interviewees volunteered to participate from two university medical centers; Ewha Womans University Medical Center and Severance Hospital. Based on the literature reviews of existing DA and communication expert consultations, 40 draft items were selected to undergo preliminary testing for further item selection and dimension exploration. Five nephrologists then reviewed the selected items, and two were excluded because they did not apply to the Korean population. Subsequently, items derived from the literature review and extracted from the FGIs were refined, and content validity was examined. Medically inappropriate items were deleted following content validity testing, and finally, 35 self-assessment items remained.

Procedure: item generation

A systematic literature review on international renal guidelines and other dialysis DA booklets was performed as the initial step in item procurement. Next, we solicited feedback from health communication experts regarding previously developed DA materials. Although there were many aspects that could be generally agreed upon from the review of existing DA materials, some elements did not fit the Korean
**Study 1: Scale development**

- **Literature review:** Decision aids algorithm and field leaflets for CKD patients

- **Item generation:** Items identified by 5 focus group interviews consisting of 5 patients in each group

- **Content validity:** Qualitative and quantitative content validity assessment conducted by 5 professionals

- **Item clarification:** 40 items were refined to 35 self-assessment items

**Study 2: Scale validation**

- **CKD patient survey (n = 330):**
  - Construct validity/reliability test
  - Exploratory factor analysis was conducted to verify the construct validity.
  - Reliability test was conducted by calculating Cronbach α coefficients.

- **Convergent validity:**
  - AVE and CR test by CFA

- **Discriminant validity:**
  - AVE and correlation coefficient analysis

- **Predictive validity:**
  - Analysis of structural equation model of HD patients and PD patients

- **Final items:**
  - Health value: 12 indicators
  - Life-style value: 11 indicators
  - Dialysis environment value: 12 indicators

**Figure 1.** Flow chart of the study.

AVE, average variance extracted; CFA, confirmatory factor analysis; CKD, chronic kidney disease; CR, composite reliability; HD, hemodialysis; PD, peritoneal dialysis.
context. Therefore, considering adequate self-assessment items for decision-making are culturally dependent, an
in-depth qualitative study was planned to fulfill the objective of extracting specialized items for CKD patients in Korea.
FGIs were conducted by a trained facilitator and a study team member using an interview guide developed by study team members with expertise in health communication. The interview questionnaire consisted of open questions not only relevant to health and lifestyle but also pertaining to other factors such as how patients think of the relative benefits and barriers of dialysis modality, dilemmas in undergoing the chosen treatment, satisfactory communication with attending doctors, and so on.

A qualitative interview study with five focus groups was performed from October 8, 2019 to October 31, 2019, at Ewha Womans University Medical Center and the dialysis center at Severance Hospital in Seoul. Interviews were conducted according to a semi-structured interview protocol that presented a series of questions designed to 1) identify interviewees’ demographic and cultural background, 2) articulate their illness perception and elicit ownership of their CKD management, and 3) explore the CKD patients’ communication traits and factors affecting doctor-patient communication. The interviews were recorded, and all interviewees gave consent to the analysis. The transcribed interviews were read repeatedly, and remarks that were determined to be relevant to each investigated phenomenon were recorded separately by each researcher. Through the interpretation and mutual exchange of opinions from the health communication researchers, the concept was refined, and the basis for deriving DA questions was formed.

Based on an extensive review of the DA materials in the field of CKD and the FGIs with patients, we generated an initial pool of 40 self-assessment items reflecting various aspects of personal orientation.

Study 2: scale evaluation

The aim of Study 2 was to evaluate the construct validity of the newly developed self-assessment DA items for patients with CKD. A sample of 330 participants was recruited from seven university hospitals to validate the properties of the items. Inclusion criteria were patients age 19 years or older who had undergone HD or PD for more than 3 months. Exclusion criteria were patients who were not able to participate in the survey due to cognitive impairment or psychological illness.

Procedure

An evaluation of the DA instrument was performed as follows. Patients with CKD undergoing dialysis at seven hospitals in Seoul were recruited from March 2020 to September 2020 to participate in preliminary testing of the DA instrument, containing 35 items. A total of 152 HD and 178 PD patients who met the eligibility criteria approved by institutional review board participated and completed the DA questionnaire.

Ethical considerations

This study was approved by each hospital’s Institutional Review Board (Ewha Womans University Seoul Hospital, No. 2020-03-018; Seoul National University Bundang Hospital, No. B-2004-604-307; Ulsan University Hospital, No. UUH 2020-06-009; Gil Medical Center, No. GFRIB2020-244; Seoul National University Boramae Medical Center, No. 06-2020-0036; Dongguk University Medical Center, No. DUIH 2020-05-011; and Severance Hospital, No. 4-2020-0422).

Statistical analysis

Statistical analyses were performed using IBM SPSS version 26.0 (IBM Corp., Armonk, NY, USA) and IBM SPSS AMOS version 21.0 (IBM Corp.). Exploratory factor analysis (EFA) was employed to identify the underlying relationships between measured variables (DA questions) and to extract their common dimensions. Based on the EFA results, confirmatory factor analysis (CFA) was performed to verify construct validity. Additional analysis was performed to examine the predictive validity of the newly developed scales using structural equation modeling (SEM).

Results

In total, 330 patients completed the instrument (DA questionnaire). Their mean age was 48.5 ± 12.8 years. The sociodemographic details of the study participants are summarized in Table 1.
Content validity

Content validity is usually qualitatively judged by experts; however, in this study, content validity was assessed by calculating the content validity index (CVI) for each item based on experts’ ratings of item relevance [16,17]. Here, CVI was assessed in terms of the item-level CVI (I-CVI), calculated as the proportion of experts assigning a rating of 3 (quite relevant) or 4 (highly relevant) among the total number of experts. In most cases, an I-CVI of 1.00 when there are five or fewer experts and an I-CVI greater than 0.78 otherwise are generally acceptable [16–18].

Out of 40 preliminary items, 37 were represented by I-CVI scores distributed between 0.80 and 1. Three items that did not meet the I-CVI criteria were deleted. The deleted items were “I am worried about the cost of dialysis,” “I am living with my elderly parents or in-laws,” and “I am so restless that I cannot lie still.” Two items that were not medically appropriate, “I want to be pregnant to be a mother” and “My sex life is important to me.” were also deleted. Through this refining process, 35 preliminary items were set up.

Exploratory factor analysis

Prior to conducting an EFA, we examined two indicators to determine whether the sample was appropriate for such an analysis. The Kaiser-Meyer-Olkin measure of sampling adequacy index was 0.62, and Bartlett’s test of sphericity was significant at χ² (degree of freedom [df] = 595, n = 330) = 2,821.37 (p < 0.001), indicating that the sample was appropriate for the analysis [19]. We performed an EFA using the principal components analysis extraction method with a varimax rotation because varimax rotation simplifies factor loadings by removing the middle ground and more specifically identifies the factor on which data load [20]. The EFA showed 13 factors, explaining 65.3% of the variance in the data; however, the number of factors retained from the EFA seemed to be too large and inadequate as the smallest number of possible factors. Thus, EFA by principal component analysis was performed again based on three fixed factors. Each factor consisted of 10 to 12 items with Cronbach alpha (α) values ranging from 0.62 to 0.72. Next, an independent t-test was conducted to determine the difference between the two groups, according to the dialysis modality, through the average difference for each item. Table 2 lists all scale

### Table 1. Participant demographics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>330</td>
</tr>
<tr>
<td>Age (yr)</td>
<td></td>
</tr>
<tr>
<td>20–29</td>
<td>17 (5.2)</td>
</tr>
<tr>
<td>30–39</td>
<td>30 (9.1)</td>
</tr>
<tr>
<td>40–49</td>
<td>83 (25.2)</td>
</tr>
<tr>
<td>50–59</td>
<td>82 (24.8)</td>
</tr>
<tr>
<td>60–69</td>
<td>92 (27.9)</td>
</tr>
<tr>
<td>≥70</td>
<td>26 (7.9)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>202 (61.2)</td>
</tr>
<tr>
<td>Female</td>
<td>128 (38.8)</td>
</tr>
<tr>
<td>Education</td>
<td></td>
</tr>
<tr>
<td>Elementary school</td>
<td>8 (2.4)</td>
</tr>
<tr>
<td>Middle school</td>
<td>24 (7.3)</td>
</tr>
<tr>
<td>High school</td>
<td>145 (43.9)</td>
</tr>
<tr>
<td>College/University</td>
<td>135 (40.9)</td>
</tr>
<tr>
<td>Graduate school</td>
<td>16 (4.8)</td>
</tr>
<tr>
<td>Others</td>
<td>2 (0.6)</td>
</tr>
<tr>
<td>Marital status</td>
<td></td>
</tr>
<tr>
<td>Married</td>
<td>218 (66.1)</td>
</tr>
<tr>
<td>Widowed</td>
<td>10 (3.0)</td>
</tr>
<tr>
<td>Separated</td>
<td>5 (1.5)</td>
</tr>
<tr>
<td>Divorced</td>
<td>27 (8.2)</td>
</tr>
<tr>
<td>Single</td>
<td>68 (20.6)</td>
</tr>
<tr>
<td>Others</td>
<td>2 (0.6)</td>
</tr>
<tr>
<td>Monthly income (Korean won)</td>
<td></td>
</tr>
<tr>
<td>&lt;1,000,000</td>
<td>107 (32.5)</td>
</tr>
<tr>
<td>1,000,000–2,000,000</td>
<td>39 (11.8)</td>
</tr>
<tr>
<td>2,000,000–3,000,000</td>
<td>30 (9.1)</td>
</tr>
<tr>
<td>3,000,000–4,000,000</td>
<td>32 (9.7)</td>
</tr>
<tr>
<td>4,000,000–5,000,000</td>
<td>14 (4.3)</td>
</tr>
<tr>
<td>5,000,000–6,000,000</td>
<td>2 (0.6)</td>
</tr>
<tr>
<td>6,000,000–7,000,000</td>
<td>4 (1.2)</td>
</tr>
<tr>
<td>≥7,000,000</td>
<td>6 (1.8)</td>
</tr>
<tr>
<td>Not available</td>
<td>96 (29.1)</td>
</tr>
<tr>
<td>Dialysis modality</td>
<td></td>
</tr>
<tr>
<td>Hemodialysis</td>
<td>152 (46.1)</td>
</tr>
<tr>
<td>Peritoneal dialysis</td>
<td>178 (53.9)</td>
</tr>
<tr>
<td>Treatment time (yr)</td>
<td></td>
</tr>
<tr>
<td>&lt;0.5</td>
<td>32 (9.7)</td>
</tr>
<tr>
<td>0.5–1</td>
<td>22 (6.7)</td>
</tr>
<tr>
<td>1–2</td>
<td>36 (10.9)</td>
</tr>
<tr>
<td>2–3</td>
<td>52 (15.8)</td>
</tr>
<tr>
<td>≥3</td>
<td>188 (57.0)</td>
</tr>
</tbody>
</table>

Data are expressed as number (%).
<table>
<thead>
<tr>
<th>Factor</th>
<th>Modality</th>
<th>No</th>
<th>Mean ± SD</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Health-related factors ( (\alpha = 0.724) )</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(1) I want to protect my bones, joints, and nerves</td>
<td>HD</td>
<td>152</td>
<td>4.36 ± 0.66</td>
<td>0.005</td>
</tr>
<tr>
<td></td>
<td>PD</td>
<td>178</td>
<td>4.15 ± 0.68</td>
<td></td>
</tr>
<tr>
<td>(2) I want to protect my heart</td>
<td>HD</td>
<td>152</td>
<td>4.33 ± 0.80</td>
<td>0.04</td>
</tr>
<tr>
<td></td>
<td>PD</td>
<td>178</td>
<td>4.16 ± 0.73</td>
<td></td>
</tr>
<tr>
<td>(3) I live a regular life</td>
<td>HD</td>
<td>152</td>
<td>3.43 ± 1.01</td>
<td>0.01</td>
</tr>
<tr>
<td></td>
<td>PD</td>
<td>178</td>
<td>3.17 ± 0.89</td>
<td></td>
</tr>
<tr>
<td>(4) I myself can control my daily routine</td>
<td>HD</td>
<td>152</td>
<td>3.78 ± 0.97</td>
<td>0.56</td>
</tr>
<tr>
<td></td>
<td>PD</td>
<td>178</td>
<td>3.72 ± 0.86</td>
<td></td>
</tr>
<tr>
<td>(5) I want regular check-ups with a doctor</td>
<td>HD</td>
<td>152</td>
<td>4.00 ± 0.85</td>
<td>0.25</td>
</tr>
<tr>
<td></td>
<td>PD</td>
<td>178</td>
<td>3.89 ± 0.90</td>
<td></td>
</tr>
<tr>
<td>(6) I want to live a high quality of life as much as I can</td>
<td>HD</td>
<td>152</td>
<td>3.82 ± 0.97</td>
<td>0.03</td>
</tr>
<tr>
<td></td>
<td>PD</td>
<td>178</td>
<td>4.04 ± 0.91</td>
<td></td>
</tr>
<tr>
<td>(7) I don’t want to be a burden on my family</td>
<td>HD</td>
<td>152</td>
<td>4.15 ± 0.99</td>
<td>0.95</td>
</tr>
<tr>
<td></td>
<td>PD</td>
<td>178</td>
<td>4.16 ± 0.87</td>
<td></td>
</tr>
<tr>
<td>(8) I want to be free from dialysis for at least one day</td>
<td>HD</td>
<td>152</td>
<td>4.34 ± 0.77</td>
<td>0.08</td>
</tr>
<tr>
<td></td>
<td>PD</td>
<td>178</td>
<td>4.17 ± 0.92</td>
<td></td>
</tr>
<tr>
<td>(9) I need to feel in control of my time and my life</td>
<td>HD</td>
<td>152</td>
<td>4.07 ± 0.77</td>
<td>0.10</td>
</tr>
<tr>
<td></td>
<td>PD</td>
<td>178</td>
<td>4.20 ± 0.72</td>
<td></td>
</tr>
<tr>
<td>(10) I make plans and act in daily life</td>
<td>HD</td>
<td>152</td>
<td>3.16 ± 1.01</td>
<td>0.29</td>
</tr>
<tr>
<td></td>
<td>PD</td>
<td>178</td>
<td>3.05 ± 0.93</td>
<td></td>
</tr>
<tr>
<td>(11) I like playing sports</td>
<td>HD</td>
<td>152</td>
<td>3.16 ± 0.99</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>PD</td>
<td>178</td>
<td>2.70 ± 0.98</td>
<td></td>
</tr>
<tr>
<td>(12) I don’t want to undergo dialysis everyday</td>
<td>HD</td>
<td>152</td>
<td>4.06 ± 1.04</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>PD</td>
<td>178</td>
<td>3.61 ± 1.11</td>
<td></td>
</tr>
<tr>
<td>Lifestyle-related factors ( (\alpha = 0.624) )</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(1) I need to be able to work or go to school</td>
<td>HD</td>
<td>152</td>
<td>2.36 ± 1.53</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>PD</td>
<td>178</td>
<td>3.06 ± 1.63</td>
<td></td>
</tr>
<tr>
<td>(2) I take care of a child or a disabled or elderly person</td>
<td>HD</td>
<td>152</td>
<td>2.10 ± 1.32</td>
<td>0.008</td>
</tr>
<tr>
<td></td>
<td>PD</td>
<td>178</td>
<td>2.53 ± 1.55</td>
<td></td>
</tr>
<tr>
<td>(3) I care about how I look</td>
<td>HD</td>
<td>152</td>
<td>2.87 ± 1.08</td>
<td>0.32</td>
</tr>
<tr>
<td></td>
<td>PD</td>
<td>178</td>
<td>2.98 ± 0.92</td>
<td></td>
</tr>
<tr>
<td>(4) I often travel abroad</td>
<td>HD</td>
<td>152</td>
<td>1.79 ± 1.03</td>
<td>0.47</td>
</tr>
<tr>
<td></td>
<td>PD</td>
<td>178</td>
<td>1.87 ± 1.02</td>
<td></td>
</tr>
<tr>
<td>(5) I love to travel and cannot give up traveling</td>
<td>HD</td>
<td>152</td>
<td>2.24 ± 1.21</td>
<td>0.44</td>
</tr>
<tr>
<td></td>
<td>PD</td>
<td>178</td>
<td>2.34 ± 1.13</td>
<td></td>
</tr>
<tr>
<td>(6) I want to be able to eat and drink what I like</td>
<td>HD</td>
<td>152</td>
<td>3.22 ± 1.12</td>
<td>0.87</td>
</tr>
<tr>
<td></td>
<td>PD</td>
<td>178</td>
<td>3.20 ± 1.06</td>
<td></td>
</tr>
<tr>
<td>(7) I am fostering a baby</td>
<td>HD</td>
<td>152</td>
<td>2.12 ± 1.43</td>
<td>0.40</td>
</tr>
<tr>
<td></td>
<td>PD</td>
<td>178</td>
<td>2.26 ± 1.54</td>
<td></td>
</tr>
<tr>
<td>(8) I want to spend as much time as I can with my family</td>
<td>HD</td>
<td>152</td>
<td>4.02 ± 0.90</td>
<td>0.60</td>
</tr>
<tr>
<td></td>
<td>PD</td>
<td>178</td>
<td>3.97 ± 0.91</td>
<td></td>
</tr>
<tr>
<td>(9) I like to take baths because I sweat a lot</td>
<td>HD</td>
<td>152</td>
<td>3.26 ± 1.03</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>PD</td>
<td>178</td>
<td>2.87 ± 0.98</td>
<td></td>
</tr>
<tr>
<td>(10) It takes me a long time to get used to something new</td>
<td>HD</td>
<td>152</td>
<td>3.09 ± 1.04</td>
<td>0.15</td>
</tr>
<tr>
<td></td>
<td>PD</td>
<td>178</td>
<td>2.93 ± 0.93</td>
<td></td>
</tr>
<tr>
<td>(11) I don’t have a care partner to help me</td>
<td>HD</td>
<td>152</td>
<td>2.59 ± 1.29</td>
<td>0.02</td>
</tr>
<tr>
<td></td>
<td>PD</td>
<td>178</td>
<td>2.26 ± 1.16</td>
<td></td>
</tr>
<tr>
<td>Dialysis environment-related factors ( (\alpha = 0.694) )</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(1) I don’t want a dialysis machine in my home</td>
<td>HD</td>
<td>152</td>
<td>3.26 ± 1.29</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>PD</td>
<td>178</td>
<td>2.48 ± 1.13</td>
<td></td>
</tr>
<tr>
<td>(2) I want professionals to take care of me</td>
<td>HD</td>
<td>152</td>
<td>4.11 ± 0.94</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>PD</td>
<td>178</td>
<td>2.38 ± 0.97</td>
<td></td>
</tr>
</tbody>
</table>
items and their properties.

**Confirmatory factor analysis**

CFA was performed on the 35 items based on the entire sample of 330 patients. Following the recommendations of Cole [21], Cuttance and Ecob [22], and Marsh and Bella [23], the DA scale’s goodness-of-fit was evaluated using multiple criteria: the goodness-of-fit index (GFI), the adjusted GFI, the root mean square error of approximation (RMSEA), the incremental fit index (IFI), the comparative fit index (CFI), and the Akaike information criterion [24]. Multiple criteria were used because each index has different strengths and weaknesses in assessing goodness-of-fit between a particular model and the observed data.

To assess the construct validity of the new scale, we estimated a series of CFA models using IBM SPSS AMOS [25]. The three-factor model identified via EFA initially consisted of three first-order latent variables, representing the following three scales; health-related values (12 indicators), lifestyle-related values (11 indicators), and dialysis environment-related values (12 indicators). In the first analysis of three first-order latent variables, model fit indices showed poor fitness; thus, we deleted some measured variables with low standardized path coefficients. Although the standardized estimate appeared low (>0.40), some measured variables were retained because they showed significance in the t-test, meaning that the item should be related to the decision-making choice for dialysis modality. This model was then refined to three scales with four indicators each.

Therefore, we performed CFA three times to obtain the best fit. A comparison of these alternate models revealed a significant difference in the fit indices, showing the best fit for the three-factor model, with a $\chi^2$ value (102.212, df = 51) significantly lower than those for the 13-factor ($\chi^2 = 946.551$, df = 417) and one-factor ($\chi^2 = 2,255.458$, df = 560) models. All the other fit indices (RMSEA = 0.05, GFI = 0.95, AGFI = 0.92, CFI = 0.91, IFI = 0.91, and $\chi^2$/df = 2.00) also showed good fit for the three-factor model based on the cut-off values recommended by Hu and Bentler [24], Kline [26], and Wheaton et al. [27]. The fitness changes of the alternative models, the best fit model, and the model fit of the HD and PD patient groups are shown in Table 3.

**Convergent and discriminant validity**

Construct validity was examined in terms of convergent and discriminant validity. Convergent validity is a subcategory

---

**Table 2. Continued**

<table>
<thead>
<tr>
<th>Factor</th>
<th>Modality</th>
<th>No</th>
<th>Mean ± SD</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>(3) I want to stay out of the hospital</td>
<td>HD</td>
<td>152</td>
<td>3.64 ± 1.17</td>
<td>0.19</td>
</tr>
<tr>
<td>PD</td>
<td>178</td>
<td>3.80 ± 0.97</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(4) It is hard for me to lie down for a long time</td>
<td>HD</td>
<td>152</td>
<td>3.29 ± 1.15</td>
<td>0.20</td>
</tr>
<tr>
<td>PD</td>
<td>178</td>
<td>3.13 ± 1.12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(5) I am terrified of needles</td>
<td>HD</td>
<td>152</td>
<td>2.68 ± 1.15</td>
<td>0.17</td>
</tr>
<tr>
<td>PD</td>
<td>178</td>
<td>2.51 ± 1.19</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(6) I want somebody to take care of me</td>
<td>HD</td>
<td>152</td>
<td>2.90 ± 1.12</td>
<td>0.01</td>
</tr>
<tr>
<td>PD</td>
<td>178</td>
<td>2.62 ± 0.95</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(7) I am quite conscious of others’ eyes on me</td>
<td>HD</td>
<td>152</td>
<td>2.76 ± 1.13</td>
<td>0.04</td>
</tr>
<tr>
<td>PD</td>
<td>178</td>
<td>3.00 ± 1.02</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(8) I love to experience new things</td>
<td>HD</td>
<td>152</td>
<td>3.08 ± 1.10</td>
<td>0.09</td>
</tr>
<tr>
<td>PD</td>
<td>178</td>
<td>3.28 ± 1.01</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(9) I tend to rely on my spouse a lot in my daily life</td>
<td>HD</td>
<td>152</td>
<td>2.71 ± 1.27</td>
<td>0.79</td>
</tr>
<tr>
<td>PD</td>
<td>178</td>
<td>2.67 ± 1.21</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(10) I like watching TV</td>
<td>HD</td>
<td>152</td>
<td>3.55 ± 0.99</td>
<td>0.59</td>
</tr>
<tr>
<td>PD</td>
<td>178</td>
<td>3.49 ± 0.97</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(11) I am comfortable with the familiar</td>
<td>HD</td>
<td>152</td>
<td>3.88 ± 0.86</td>
<td>0.91</td>
</tr>
<tr>
<td>PD</td>
<td>178</td>
<td>3.87 ± 0.71</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(12) I don’t like environmental changes</td>
<td>HD</td>
<td>152</td>
<td>3.44 ± 1.01</td>
<td>0.55</td>
</tr>
<tr>
<td>PD</td>
<td>178</td>
<td>3.38 ± 0.93</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

HD, hemodialysis; PD, peritoneal dialysis; SD, standard deviation.
of validity tests that can assist in establishing construct validity [28] and refers to the degree to which two measures of constructs, which theoretically should be related, are related. In contrast, discriminant validity tests whether concepts or measurements that are supposed to be unrelated are, in fact, unrelated [29].

The Fornell-Larcker [30] criterion has been commonly used to assess convergent and discriminant validity, and it can be assessed considering the average variance extracted (AVE) and composite reliability (CR). AVE measures the level of variance captured by a construct versus the level captured due to measurement error; values above 0.7 are considered very good, while a level of 0.5 is acceptable. CR is a less biased estimate of reliability than Cronbach’s α, and the acceptable values of CR are 0.7 and above. The AVE and CR can be calculated as follows:

$$\text{AVE} = \frac{\sum_{i=1}^{k} (\text{std.} \lambda_i^2)}{\sum_{i=1}^{k} (\text{std.} \lambda_i^2) + \sum_{i=1}^{k} (1-\text{std.} \lambda_i^2)}$$

$$\text{CR} = \frac{(\sum_{i=1}^{k} \text{std.} \lambda_i)^2}{(\sum_{i=1}^{k} \text{std.} \lambda_i)^2 + \sum_{i=1}^{k} (1-\text{std.} \lambda_i^2)}$$

Here, k is the number of items, and λ_i is the factor loading of item i.

As indicated in Fig. 1, four items have loaded onto each of the single latent factors, with standardized path coefficients ranging from 0.19 (item L2) to 0.90 (item H1) in the three-factor DA model. When evaluating the strength and adequacy of item loadings, some items and their expectedly related latent factors demonstrated poor convergent validity. For a more rigorous analysis of convergent and discriminant validity, the AVE and CR of each latent variable were calculated based on the formula given by Fornell and Larcker [30]. The AVE of health, lifestyle, and dialysis environment were found to be greater than 0.50, which is considered acceptable. The CR of each latent variable was also greater than 0.7, which can be said to signify convergent validity and internal consistency.

Discriminant validity was assessed by comparing the AVE and correlation coefficients. According to Fornell and Larcker [30], when the AVE is greater than the square of the correlation coefficient between each factor, discriminant validity is secured. As a result of the verification, the AVE obtained between each factor was greater than the square of the correlation coefficient between each factor; thus, discriminant validity was secured (Table 4).

### Predictive validity

A multigroup analysis of two patient groups was performed

<table>
<thead>
<tr>
<th>Table 3. Fit indices of competing models</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model fit</td>
</tr>
<tr>
<td>----------------------------------------</td>
</tr>
<tr>
<td>First-order 3-factor model</td>
</tr>
<tr>
<td>df = 51; p &lt; 0.001</td>
</tr>
<tr>
<td>Competing 13-factor model</td>
</tr>
<tr>
<td>df = 417; p &lt; 0.001</td>
</tr>
<tr>
<td>Competing 1-factor model</td>
</tr>
<tr>
<td>df = 560; p &lt; 0.001</td>
</tr>
<tr>
<td>Hemodialysis</td>
</tr>
<tr>
<td>df = 51; p &lt; 0.001</td>
</tr>
<tr>
<td>Peritoneal dialysis</td>
</tr>
<tr>
<td>df = 52; p &lt; 0.001</td>
</tr>
</tbody>
</table>

AGFI, adjusted goodness-of-fit index; AIC, Akaike information criterion; CFI, comparative fit index; df, degree of freedom; GFI, goodness-of-fit index; IFI, incremental fit index; RMSEA, root mean square error of approximation.
using SEM to determine whether the three decision support factors (health, lifestyle, and dialysis environment) could predict a patient’s choice of dialysis modality. Based on the literature on illness perception and dialysis modality decision-making, we hypothesized a causal relationship between decisional factors, CKD perception, and shared decision-making cognition \[31,32\]. More specifically, we forecasted differences in factors influencing decision-making between HD and PD patients, and we predicted these differences to be related to the perception of CKD as an illness and, ultimately, to affect the perception of shared decision-making processes.

As expected, a difference was found between the HD and PD patient groups. For the HD patient group, the dialysis decisional factor exhibited a positive association with illness perception \((\beta = 0.60, p < 0.01)\) and illness perception was positively associated with perceived shared decision-making \((\beta = 0.57, p < 0.05)\). However, the direct effect of decisional factors on perceived shared decision-making was not statistically significant. In the PD patient group, a positive relationship between the decisional factor \((\beta = 0.50, p < 0.01)\), illness perception \((\beta = 0.29, p < 0.05)\), and perceived shared decision-making \((\beta = 0.50, p < 0.01)\) was found. Through the path difference between the two groups, which was statistically significant, the self-assessment items developed through this study can be said to have predictive validity. The results of the HD patient group analysis and the PD patient group analysis are shown in Fig. 2 and 3, respectively. The final items that have been validated are shown in Table 5.

**Discussion**

A recent review of DA validation demonstrated an increase in patients selecting options related to their values and less decision-making passivity, as well as lower decisional con-

---

**Table 4. Validity and reliability of the decision aid self-assessment items**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Health</th>
<th>Lifestyle</th>
<th>Environment</th>
<th>AVE</th>
<th>CR</th>
<th>Cronbach α</th>
</tr>
</thead>
<tbody>
<tr>
<td>Health</td>
<td>1</td>
<td></td>
<td></td>
<td>0.53</td>
<td>0.75</td>
<td>0.72</td>
</tr>
<tr>
<td>Lifestyle</td>
<td>0.15**</td>
<td>1</td>
<td></td>
<td>0.53</td>
<td>0.74</td>
<td>0.62</td>
</tr>
<tr>
<td>Environment</td>
<td>0.21**</td>
<td>0.20**</td>
<td>1</td>
<td>0.50</td>
<td>0.80</td>
<td>0.69</td>
</tr>
</tbody>
</table>

AVE, average variance extracted; CR, composite reliability.

**Figure 2. The relationship between decisional factors, illness perception, and the cognition of SDM.**

CFI, comparative fit index; df, degree of freedom, IFI, incremental fit index; RMSEA, root mean square error of approximation; SDM, shared decision-making.
flict and increased knowledge levels [33]. In other words, DAs increase participation in shared decision-making. As proposed by the Kidney Disease Improving Global Outcomes guidelines, dialysis modality should be chosen with timely and shared decision-making among the healthcare team, patients, and their caregivers [34]. In particular, the decision to undergo dialysis depends on many abstract aspects, such as knowledge of dialysis; personal beliefs; and feelings toward life, suffering, death, and other patient experiences [13,32,35,36]. Moreover, how this specific illness is viewed and understood in any given society is crucial to medical decision-making because patients’ social and cultural backgrounds highly influence their decision-making.

In this study, we developed Korea-specific DA scales for ESRD by integrating both qualitative and quantitative research methods. Some noteworthy findings from this study are as follows.

First, the content of the DA questionnaire was classified into three dimensions; health, lifestyle, and dialysis environment. Though the correlations between these three dimensions were statistically significant, they were not robust in effect size. These results imply that factors influencing decision-making are sometimes unrelated to each other, existing as independent factors in many cases. In other words, since there are various factors that influence decision-making, the communication process for shared decision-mak-
ing should be set as specifically as possible and thoroughly include all possibilities regarding dialysis treatment.

Second, the difference between HD and PD patients in terms of health, lifestyle, and dialysis environmental factors was statistically significant. This implies that the importance of health and dialysis environmental factors is more emphasized in HD patients, while factors related to lifestyle may be considered more important to PD patients.

Third, in this study, we employed a multifaceted approach to testing the validity of the scales and examined the relationship between decisional factors, illness perception, and perceived shared decision-making. Interestingly, in HD patients, it was found that illness perception completely mediated the influence of decisional factors on shared decision-making. Meaning that the more the HD patient agrees with the decisional factor, the more negative the illness perception, and the more negative the illness perception, the more the patient recognizes shared decision-making. In the case of PD patients, illness perception partially mediated the relationship between decisional factors and perceived shared decision-making. Meaning that illness perception is not the only thing that affects perceived shared decision-making as is in HD patient group. Therefore, it is no doubt that patients’ decisional factors are crucial to such decision-making, but it can be equally said that decisional factors work somewhat differently between HD and PD patients.

Our study has several limitations. First, the design is that of a formative study, including both qualitative and quantitative methods. The qualitative study participants were all recruited from the university hospital medical center, while in-center dialysis patients were not included. Therefore, in a follow-up study, it is necessary to obtain cross validity of the newly developed DA items by examining whether there are any differences in decisional factors between patients taking HD at university medical centers versus other HD centers. Second, the DA items developed and validated in this study are indicators of a construct, which is an essential part of the complete DA. Therefore, further refinement and implementation will improve and contribute to shared decision-making using these DA items.

Nevertheless, this is the first attempt to develop and validate DA items, and the study results highlight a critical need for initiatives to encourage subsequent studies to improve shared decision-making.

Conflicts of interest

All authors have no conflicts of interest to declare.

Table 5. Final scales for the self-assessment items for the decision aid for chronic kidney disease patients

<table>
<thead>
<tr>
<th>Factor</th>
<th>No</th>
<th>Item</th>
</tr>
</thead>
<tbody>
<tr>
<td>Health</td>
<td>1</td>
<td>I want to protect my bones, joints, and nerves</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>I want to protect my heart</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>I live a regular life</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>I myself can control my daily routine</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>I want regular check-ups with a doctor</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>I want to live a high quality of life as much as I can</td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>I don’t want to be a burden on my family</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>I want to be free from dialysis for at least one day</td>
</tr>
<tr>
<td></td>
<td>9</td>
<td>I need to feel in control of my time and my life</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>I make plans and act in daily life</td>
</tr>
<tr>
<td></td>
<td>11</td>
<td>I like playing sports</td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>I don’t want to get dialysis everyday</td>
</tr>
<tr>
<td>Lifestyle</td>
<td>13</td>
<td>I need to be able to work or go to school</td>
</tr>
<tr>
<td></td>
<td>14</td>
<td>I take care of a child or a disabled or elderly person</td>
</tr>
<tr>
<td></td>
<td>15</td>
<td>I care about how I look</td>
</tr>
<tr>
<td></td>
<td>16</td>
<td>I often travel abroad</td>
</tr>
<tr>
<td></td>
<td>17</td>
<td>I love to travel and cannot give up traveling</td>
</tr>
<tr>
<td></td>
<td>18</td>
<td>I want to be able to eat and drink what I like</td>
</tr>
<tr>
<td></td>
<td>19</td>
<td>I am fostering a baby</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>I want to spend as much time as I can with my family</td>
</tr>
<tr>
<td></td>
<td>21</td>
<td>I like to take baths because I sweat a lot</td>
</tr>
<tr>
<td></td>
<td>22</td>
<td>It takes me a long time to get used to something new</td>
</tr>
<tr>
<td></td>
<td>23</td>
<td>I don’t have a care partner to help me</td>
</tr>
<tr>
<td></td>
<td>24</td>
<td>I don’t want a dialysis machine in my home</td>
</tr>
<tr>
<td>Dialysis environment</td>
<td>25</td>
<td>I want professionals to take care of me</td>
</tr>
<tr>
<td></td>
<td>26</td>
<td>I want to stay out of the hospital</td>
</tr>
<tr>
<td></td>
<td>27</td>
<td>It is hard for me to lie down for a long time</td>
</tr>
<tr>
<td></td>
<td>28</td>
<td>I am terrified of needles</td>
</tr>
<tr>
<td></td>
<td>29</td>
<td>I want somebody to take care of me</td>
</tr>
<tr>
<td></td>
<td>30</td>
<td>I am quite conscious of others’ eyes on me</td>
</tr>
<tr>
<td></td>
<td>31</td>
<td>I love to experience new things</td>
</tr>
<tr>
<td></td>
<td>32</td>
<td>I tend to rely on my spouse a lot in my daily life</td>
</tr>
<tr>
<td></td>
<td>33</td>
<td>I like watching TV</td>
</tr>
<tr>
<td></td>
<td>34</td>
<td>I am comfortable with the familiar</td>
</tr>
<tr>
<td></td>
<td>35</td>
<td>I don’t like environmental changes</td>
</tr>
</tbody>
</table>

Kim, et al. Decision aids: SDM for dialysis modality
**Funding**

This research was supported by a grant of Patient-Centered Clinical Research Coordinating Center (PACEN) funded by the Ministry of Health & Welfare, Republic of Korea (grant number: H119C0481, HC20C0054), and supported by a Cooperative Research Grant from the Korean Society of Nephrology.

**Acknowledgments**

The authors appreciate Dr. Sung Woo Lee (Uljeongbu Eullji Medical Center, Eulji University) and Dr. Seung Jun Kim (Catholic Kwandong University International St. Mary’s Hospital) for their interview support.

**Authors’ contributions**

Conceptualization: Sejoong K, DRR, SA  
Data curation: DRR, JHC, SJS, JPL, KDY, JTP , Sejoong K  
Formal analysis, Methodology: Soojin K  
Investigation, Project administration: Sejoong K, DRR  
Writing-original draft: Soojin K  
Writing-review & editing: Sejoong K  
All authors read and approved the final manuscript.

**ORCID**

Soojin Kim, https://orcid.org/0000-0002-3305-0712  
Jung Tak Park, https://orcid.org/0000-0002-2325-8982  
Sung Joon Shin, https://orcid.org/0000-0002-0777-9278  
Jae Hyun Chang, https://orcid.org/0000-0003-3947-0715  
Kyung Don Yoo, https://orcid.org/0000-0001-6545-6517  
Jung Pyo Lee, https://orcid.org/0000-0002-4714-1260  
Dong-Ryeol Ryu, https://orcid.org/0000-0002-5309-7606  
Soontae An, https://orcid.org/0000-0002-6016-8759  
Sejoong Kim, https://orcid.org/0000-0002-7238-9962

**References**


30. Fornell C, Larcker DF. Structural equation models with unobservable variables and measurement error: algebra and statistics. *J Mark Res* 1981;18:382–388.


Additive harmful effects of acute kidney injury and acute heart failure on mortality in hospitalized patients

Hyung Eun Son¹,², Jong Joo Moon³, Jeong-min Park², Ji Young Ryu¹,², Eunji Baek¹, Jong Cheol Jeong¹,², Ho Jun Chin¹,², Ki Young Na¹,², Dong-wan Chae¹,², Seung Seok Han²,³, Sejoong Kim¹,²,⁴

¹Department of Internal Medicine, Seoul National University Bundang Hospital, Seongnam, Republic of Korea
²Department of Internal Medicine, Seoul National University College of Medicine, Seoul, Republic of Korea
³Department of Internal Medicine, Seoul National University Hospital, Seoul, Republic of Korea
⁴Center for Artificial Intelligence in Healthcare, Seoul National University Bundang Hospital, Seongnam, Republic of Korea

Background: Organ crosstalk between the kidney and the heart has been suggested. Acute kidney injury (AKI) and acute heart failure (AHF) are well-known independent risk factors for mortality in hospitalized patients. This study aimed to investigate if these conditions have an additive effect on mortality in hospitalized patients, as this has not been explored in previous studies.

Methods: We retrospectively reviewed the records of 101,804 hospitalized patients who visited two tertiary hospitals in the Republic of Korea over a period of 5 years. AKI was diagnosed using serum creatinine-based criteria, and AHF was classified using International Classification of Diseases codes within 2 weeks after admission. Patients were divided into four groups according to the two conditions. The primary outcome was all-cause mortality.

Results: AKI occurred in 6.8% of all patients (n = 6,920) and AHF in 1.2% (n = 1,244). Three hundred thirty-one patients (0.3%) developed both conditions while AKI alone was present in 6,589 patients (6.5%) and AHF alone in 913 patients (0.9%). Among the 5,181 patients (5.1%) who died, 20.8% died within 1 month. The hazard ratio for 1-month mortality was 29.23 in patients with both conditions, 15.00 for AKI only, and 3.39 for AHF only. The relative excess risk of interaction was 11.85 (95% confidence interval, 2.43–21.27), and was more prominent in patients aged <75 years and those without chronic heart failure.

Conclusion: AKI and AHF have a detrimental additive effect on short-term mortality in hospitalized patients.

Keywords: Acute kidney injury, Cardiorenal syndrome, Heart failure, Risk factors

Introduction

Acute kidney injury (AKI) is an important clinical condition diagnosed in hospitalized patients over time that affects more than 20% of patients. It is consistently associated with high medical costs, prolonged hospital stay, and
increased mortality [1–3]. AKI also contributes to a higher risk of long-term poor renal outcomes and cardiovascular events [4]. However, little is known about comorbidities that develop as complications of AKI and their clinical consequences.

Cardiorenal syndrome is the term used to describe coexisting cardiac and renal dysfunction [5]. Acute heart failure (AHF) also contributes to short-term mortality risk and economic burden in hospitalized patients [6,7]. AKI is associated with 58% of congestive heart failure cases, and, in one study, the risk of congestive heart failure itself was higher with increasing AKI severity [8]. Although numerous attempts have been made to determine the prognoses of patients with cardiorenal syndrome, especially with respect to AKI and AHF; such reports have been limited to specific groups [9–11]. Epidemiological investigation of cardiorenal syndrome is challenging due to dynamic changes in renal function [12], heterogeneity of causes of AKI [13], difficulty in clarifying the temporal association between AKI and acute cardiac events, and lack of longitudinal follow-up data regarding coexisting conditions after AKI. In one previous study, the causes of death in hospitalized patients with AKI were reported. The results showed that 19.7% of all patients died from cardiovascular disease, and 3.1% of them from AKI [14]. Despite these limitations, there is a need for large epidemiological studies as some factors that influence AKI or AHF are potentially reversible.

Patients with coexisting AKI and AHF share many risk factors and medical treatments. This study aimed to investigate the interaction between AKI and AHF on death in hospitalized patients and find ways to improve mortality in this group of patients by focusing on reversible risk factors.

**Methods**

**Study population and data sources**

The study cohort was derived retrospectively from Seoul National University Hospital and Seoul National University Bundang Hospital in the Republic of Korea. We retrospectively collected data on the demographic and clinical characteristics of all patients over 18 years old who were admitted to either of the hospitals at least once from January 1, 2013 to December 31, 2017. Total follow-up time for all patients was about 7 years, from January 1, 2013 to October 30, 2019.

Patients with at least two serum creatinine measurements within 7 days of admission were considered eligible for inclusion in the study. Patients who started renal replacement therapy before the first admission were excluded. Clinical data collection was based on electronic medical record (EMR) system review. Information about the development of end-stage renal disease (ESRD) was obtained from the EMR system of each hospital and the ESRD registry of the Korea Society of Nephrology. Information about death was collected from the EMR system of each hospital and the Ministry of the Interior and Safety database by comparing the name and date of birth of each patient. Follow-up data were collected until October 30, 2019.

**Assessment of kidney function**

Definition of AKI was based on the Kidney Disease Improving Global Outcomes (KDIGO) criteria of creatinine measurement because urine output measurements were not available for all hospitalized patients. In more detail, AKI was diagnosed based on the change in serum creatinine concentration from the baseline value at the first measurement during admission to the peak level observed within 7 days after admission. The change in creatinine concentration was categorized according to the KDIGO criteria: AKI stage 1, ≥0.3 mg/dL absolute or 1.5- to 2.0-fold relative increase in serum creatinine; AKI stage 2, >2- to 3-fold increase in serum creatinine; AKI stage 3, >3-fold increase in serum creatinine or serum creatinine ≥4.0 mg/dL with an acute rise of >0.5 mg/dL. Initiation of renal replacement therapy was classified as stage 3 AKI.

**Outcomes**

The primary outcome was all-cause mortality within 1 month. Mortality data were collected from the EMR system of each hospital and the Ministry of the Interior and Safety database by comparing the name and date of birth of each patient. ESRD was also investigated as an outcome. The incidence of ESRD was obtained from the ESRD registry of the Korea Society of Nephrology.
**Exposure**

Exposure was defined as development of AKI, AHF, or both. We assigned patients into four groups: a) patients with neither AKI nor incident AHF during the observational period; b) patients with AHF during the observational period but without AKI; c) patients with AKI but without incident AHF; and d) patients with incident AHF and AKI. AHF was clinically diagnosed based on International Classification of Disease-10 (ICD-10) codes. Based on the ICD-10 codes for heart failure, we defined AHF as the first diagnosis of heart failure within 2 weeks after admission during the observational period. Patients with a diagnosis of heart failure based on ICD-10 codes before admission were classified as having chronic heart failure (CHF). We collected data for patients with ICD-10 codes I110, I119, I130, I500, I5000–5004, I5008, I501, I509, J81, J810, and R570, which included diagnosis of acute pulmonary edema, cardiogenic pulmonary edema, cardiogenic shock, chronic pulmonary edema, combined systolic and diastolic heart failure, congestive heart failure, diastolic, congestive heart failure, systolic dysfunction, diastolic heart failure, heart failure, hypertensive heart and renal disease with congestive heart failure, hypertensive heart disease, hypertensive heart failure with congestive heart failure, hypertensive heart failure, left ventricular dysfunction, left ventricular failure, right heart failure, right ventricular dysfunction, right ventricular failure, systolic heart failure, or ventricular dysfunction.

**Covariates**

The following data were obtained on the first day of admission during data collection; age, sex, body weight, body mass index (BMI), comorbidities (ischemic heart disease, hypertension, diabetes mellitus, heart failure, liver disease, cerebrovascular disease, chronic obstructive pulmonary disease, chronic kidney injury, and cancer), history of AKI, medications used in the last 6 months before admission (acyclovir, beta blockers, calcium-channel blockers, diuretics, nonsteroidal anti-inflammatory drugs [NSAIDs], renin-angiotensin system blockers, statins, vancomycin, vaspressors, cisplatin, cyclosporine, colistin, and amphotericin), Charlson comorbidity score, use of a mechanical ventilator, admission duration, laboratory results on the first day of admission (serum creatinine, hemoglobin, albumin, bilirubin, calcium, glucose, potassium, chloride, gamma-oxalate transaminase, gamma pyruvate transaminase, blood urea nitrogen, total carbon dioxide, platelet, and white blood cell counts), major operation, and minor operation. We classified surgery into two categories—1) over 1 hour as a major surgery and 2) less than 1 hour as a minor surgery—using operation names based on the expected time of each surgery. The expected time of each surgery was from the data used in previous study [15], which had developed postoperative AKI prediction score.

We used the abbreviated Modification of Diet in Renal Disease equation to estimate the glomerular filtration rate. The average serum creatinine on the first day of admission was used if serum creatinine was measured several times. Data about comorbid conditions were collected by reviewing the EMR system. Charlson comorbidity score was calculated using the name of the underlying disease based on the ICD-9-CM codes and corresponding ICD-10-AM codes [16].

**Statistical analysis**

Summary statistics are presented as percentages for categorical variables and means ± standard deviations for continuous variables. Each variable was compared between the two groups using Student t-test for continuous variables and the chi-square test for categorical variables. Survival curves were estimated using the Kaplan-Meier method and compared by log-rank tests among patients according to the development of AKI and AHF. We used time-dependent Cox proportional hazards model to determine the adjusted association between death and AKI. We considered backward stepwise variable selection with p < 0.05 and conventional risk factors associated with AKI, AHF, and death in hospitalized patients using collected sociodemographic variables to generate the final model. Thus, the final model was independent of demographic characteristics (age over 75 years, sex, and BMI), admission duration, comorbidities (hypertension, diabetes mellitus, chronic kidney disease [CKD], CHF, ischemic heart disease, liver disease, cerebrovascular disease, chronic obstructive pulmonary disease, and cancer), and medications used during the 6 months preceding admission (diuretics, renin-angiotensin system blockers, beta blockers, calcium-channel blockers,
Ethical approval

This study was performed in accordance with the Declaration of Helsinki. The study protocol was approved by the Institutional Review Boards of Seoul National University Bundang Hospital (B-1910/570-404) and Seoul National University Hospital (H-1909-079-1064). Informed consent was waived because of the retrospective nature of the study.

Results

Baseline characteristics

Among 101,804 patients included in the study, the mean age was 58 ± 16.7 years, and 53,119 patients (52.2%) were male (Table 1). Percentages of patients with comorbidities were as follows: diabetes mellitus, 9.6%; hypertension, 12.3%; ischemic heart disease, 9.0%; heart failure, 1.8%; CKD, 2.0%; cerebrovascular disease, 13.8%; and cancer, 26.4%. De novo heart failure or acute aggravation of CHF occurred in 4,070 patients (4.0%) during the observational period and 1,244 patients (1.2%) developed de novo heart failure or acute CHF aggravation within 2 weeks. Cancer was present in 26,898 (26.4%) patients, and 507 (0.5%) patients experienced AKI before admission.

Table 1. Baseline characteristics of the study participants

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total</th>
<th>No. of patients</th>
<th>Age (yr)</th>
<th>Male sex</th>
<th>Body mass index (kg/m²)</th>
<th>Admission period (day)</th>
<th>Comorbidity</th>
<th>Hypertension</th>
<th>Ischemic heart disease</th>
<th>Heart failure</th>
<th>Diabetes mellitus</th>
<th>Chronic kidney disease</th>
<th>Cerebrovascular disease</th>
<th>Liver disease</th>
<th>Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>59 ± 16.8</td>
<td>53,119</td>
<td>23.85 ± 3.44</td>
<td>6 (3–9)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>58 ± 16.7</td>
<td>93,971</td>
<td>23.87 ± 3.42</td>
<td>5 (3–9)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>71 ± 15.2</td>
<td>913</td>
<td>23.38 ± 3.86</td>
<td>6 (4–11)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>63 ± 16.2</td>
<td>6,589</td>
<td>23.72 ± 3.65</td>
<td>9 (5–15)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>73 ± 14.4</td>
<td>331</td>
<td>23.39 ± 4.00</td>
<td>9 (5–16)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
<td>0.009</td>
<td>&lt;0.001</td>
<td>0.03</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

(Continued to the next page)
### Table 1. Continued

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total</th>
<th>No AHF</th>
<th>AHF</th>
<th>p-value</th>
<th>No AHF</th>
<th>AHF</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous history of AKI</td>
<td>507 (0.5)</td>
<td>271 (0.3)</td>
<td>8 (0.9)</td>
<td>0.001</td>
<td>211 (3.2)</td>
<td>17 (5.1)</td>
<td>0.05</td>
</tr>
<tr>
<td>Baseline eGFR (mL/min/1.73 m²)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥90</td>
<td>53,171 (52.2)</td>
<td>50,299 (53.5)</td>
<td>202 (22.1)</td>
<td>2,627 (39.9)</td>
<td>43 (13.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>60–89</td>
<td>35,778 (35.1)</td>
<td>33,847 (36.0)</td>
<td>361 (39.5)</td>
<td>1,511 (22.9)</td>
<td>59 (17.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>30–59</td>
<td>9,879 (9.7)</td>
<td>8,448 (9.0)</td>
<td>269 (29.5)</td>
<td>1,067 (16.2)</td>
<td>95 (28.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>15–29</td>
<td>1,881 (1.8)</td>
<td>1,258 (1.3)</td>
<td>73 (8.0)</td>
<td>482 (7.3)</td>
<td>68 (20.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;15</td>
<td>1,095 (1.1)</td>
<td>119 (0.1)</td>
<td>8 (0.9)</td>
<td>902 (13.7)</td>
<td>66 (19.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Charlson comorbidity score</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
<td></td>
<td></td>
<td>0.16</td>
</tr>
<tr>
<td>0</td>
<td>52,773 (51.8)</td>
<td>49,567 (52.7)</td>
<td>387 (42.4)</td>
<td>2,699 (41.0)</td>
<td>120 (36.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1–2</td>
<td>39,607 (38.9)</td>
<td>36,257 (38.6)</td>
<td>446 (48.8)</td>
<td>2,763 (41.9)</td>
<td>141 (42.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3–4</td>
<td>6,911 (6.8)</td>
<td>6,027 (6.4)</td>
<td>69 (7.6)</td>
<td>765 (11.6)</td>
<td>50 (15.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥5</td>
<td>2,513 (2.5)</td>
<td>2,120 (2.3)</td>
<td>11 (1.2)</td>
<td>362 (5.5)</td>
<td>20 (6.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICU admission</td>
<td>5,695 (5.6)</td>
<td>4,194 (4.5)</td>
<td>289 (31.7)</td>
<td>&lt;0.001</td>
<td>1,044 (15.8)</td>
<td>168 (50.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Medication during the previous 6 mo</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beta blocker</td>
<td>4,740 (4.7)</td>
<td>4,079 (4.3)</td>
<td>78 (8.5)</td>
<td>&lt;0.001</td>
<td>549 (8.3)</td>
<td>34 (10.3)</td>
<td>0.22</td>
</tr>
<tr>
<td>RAS blocker</td>
<td>6,890 (6.8)</td>
<td>5,826 (6.2)</td>
<td>114 (12.5)</td>
<td>&lt;0.001</td>
<td>893 (13.6)</td>
<td>57 (17.2)</td>
<td>0.06</td>
</tr>
<tr>
<td>Diuretics</td>
<td>3,676 (3.6)</td>
<td>2,683 (2.9)</td>
<td>153 (16.8)</td>
<td>&lt;0.001</td>
<td>768 (11.7)</td>
<td>72 (21.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Calcium-channel blocker</td>
<td>7,410 (7.3)</td>
<td>6,323 (6.7)</td>
<td>110 (12.0)</td>
<td>&lt;0.001</td>
<td>920 (14.0)</td>
<td>57 (17.2)</td>
<td>0.10</td>
</tr>
<tr>
<td>Colistin</td>
<td>174 (0.2)</td>
<td>127 (0.1)</td>
<td>1 (0.1)</td>
<td>0.83</td>
<td>46 (0.7)</td>
<td>0 (0)</td>
<td>0.13</td>
</tr>
<tr>
<td>Acyclovir</td>
<td>107 (0.1)</td>
<td>82 (0.1)</td>
<td>0 (0)</td>
<td>0.37</td>
<td>25 (0.4)</td>
<td>0 (0)</td>
<td>0.26</td>
</tr>
<tr>
<td>Amphotericin</td>
<td>20 (0.02)</td>
<td>11 (0.01)</td>
<td>0 (0)</td>
<td>0.74</td>
<td>9 (0.1)</td>
<td>0 (0)</td>
<td>0.50</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>438 (0.4)</td>
<td>383 (0.4)</td>
<td>0 (0)</td>
<td>0.05</td>
<td>55 (0.8)</td>
<td>0 (0)</td>
<td>0.10</td>
</tr>
<tr>
<td>NSAID</td>
<td>20,290 (19.9)</td>
<td>18,468 (19.7)</td>
<td>114 (12.5)</td>
<td>&lt;0.001</td>
<td>1,657 (25.1)</td>
<td>51 (15.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Statin</td>
<td>7,540 (7.4)</td>
<td>6,759 (7.2)</td>
<td>81 (8.9)</td>
<td>0.05</td>
<td>660 (10.0)</td>
<td>40 (12.1)</td>
<td>0.22</td>
</tr>
<tr>
<td>Vasopressor</td>
<td>1,813 (1.8)</td>
<td>1,560 (1.7)</td>
<td>13 (1.4)</td>
<td>0.58</td>
<td>227 (3.4)</td>
<td>13 (3.9)</td>
<td>0.64</td>
</tr>
<tr>
<td>Use of a mechanical ventilator</td>
<td>63 (0.1)</td>
<td>39 (0.04)</td>
<td>4 (0.4)</td>
<td>&lt;0.001</td>
<td>20 (0.3)</td>
<td>0 (0)</td>
<td>0.34</td>
</tr>
</tbody>
</table>

**Admission laboratory parameter**

| Hemoglobin (g/dL)                     | 13.1 ± 2.07          | 13.2 ± 2.01 | 12.6 ± 2.33 | <0.001 | 12.2 ± 2.52 | 11.3 ± 2.45 | <0.001 |
| Albumin (g/dL)                        | 4.0 ± 0.60           | 4.1 ± 0.57  | 3.7 ± 0.58  | <0.001 | 3.7 ± 0.76  | 3.4 ± 0.60  | <0.001 |
| Sodium (mEq/L)                        | 139.1 ± 3.72         | 139.2 ± 3.57 | 137.9 ± 4.37 | <0.001 | 138.0 ± 5.11 | 137.4 ± 4.89 | 0.04     |
| Potassium (mEq/L)                     | 4.2 ± 0.46           | 4.2 ± 0.43  | 4.1 ± 0.57  | 0.25    | 4.3 ± 0.69  | 4.4 ± 0.79  | 0.001    |
| BUN (mg/dL)                           | 16.6 ± 10.49         | 15.7 ± 7.57 | 22.4 ± 12.42 | <0.001 | 28.7 ± 25.41 | 36.0 ± 22.64 | <0.001   |
| Total CO₂ (mEq/L)                     | 24.7 ± 3.39          | 24.9 ± 3.24 | 22.7 ± 3.33 | <0.001 | 22.6 ± 4.31 | 20.3 ± 4.02 | <0.001   |
| Platelet count (×10³/L)               | 235.4 ± 83.38        | 237.3 ± 82.40 | 209.4 ± 75.77 | <0.001 | 213.6 ± 93.35 | 205.26 ± 88.44 | 0.11     |
| WBC count (×10³/L)                    | 8.1 ± 7.08           | 7.9 ± 6.14  | 8.9 ± 4.26  | <0.001 | 10.1 ± 15.01 | 10.9 ± 6.46 | 0.35     |

**Operation type**

| Major operation                      | 34,262 (33.7)        | 31,695 (33.7) | 56 (6.1)   | <0.001 | 2,478 (37.6) | 33 (10.0) | <0.001 |
| Minor operation                      | 219 (0.2)            | 191 (0.2)     | 2 (0.2)    | 0.92    | 25 (0.4)    | 1 (0.3)  | 0.82    |

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

Operations were classified into two categories by expected surgery time: major operation defined as surgery duration ≥ 1 hour, and minor operation defined as surgery duration < 1 hour.

AHF, acute heart failure; AKI, acute kidney injury; BMI, body mass index; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate; ICU, intensive care unit; NSAID, nonsteroidal anti-inflammatory drug; RAS, renin-angiotensin system; WBC, white blood cell.
There were 6,589 patients (6.5%) with AKI only, 913 patients (0.9%) with AHF only, and 331 patients (0.3%) with both AKI and AHF. There were more elderly individuals among patients who developed AHF than patients without AHF, regardless of AKI. Patients with AHF had a higher proportion of underlying diseases, such as hypertension, ischemic heart disease, and CHF, and used diuretics more than those without AHF. Regardless of AKI, less than 20% of patients with AHF used NSAIDs compared to over 20% of those without AHF. Patients with AKI had longer hospital stays than those without AKI. In contrast, the presence of AHF did not significantly affect the length of hospital stay, even among patients who developed AKI. The percentages of patients with AKI who used beta blockers, renin-angiotensin system blockers, and calcium-channel blockers were similar regardless of the development of AHF. Usage proportion of vasopressors was higher among patients with AKI than those without AKI.

The highest proportion of CKD was found among patients who had both AKI and AHF (15.7%). One hundred sixty-eight patients (50.8%) with both AKI and AHF were admitted to the intensive care unit, and this proportion was higher than that of patients with either AKI or AHF. Serum potassium on the first day of admission was higher among patients with AKI than those without AKI, and it was highest in patients who developed both AKI and AHF.

**Additive effect of acute kidney injury and acute heart failure**

The overall death rate was 5.1% (5,181 patients), and 18.7% (121 patients) of patients who died developed both AKI and AHF. Among patients with AHF only, 350 (10.2%) died, while 933 patients (14.8%) with AKI only died (p < 0.001). Kaplan-Meier analysis showed a significant relationship between mortality and development of AKI or AHF based on a log-rank test (p < 0.001) (Fig. 1). As mortality rate was significantly higher early after enrollment, we further investigated 1-month mortality.

Within 1 month after admission, 1,076 patients (20.8%) died. Among these patients, 4.8% (52 patients) developed both AKI and AHF (Table 2). We compared the HRs of patients according to AKI or AHF to that of patients without AKI or AHF. The HR of 1-month mortality was 29.23 in patients with both AKI and AHF (95% confidence interval [CI],

![Figure 1. Kaplan-Meier curves for death by groups, based on the presence of AKI or AHF.](https://www.krcp-ksn.org)

AKI, acute kidney injury; AHF, acute heart failure.
Table 2. Results of analyses of interactions between AKI and AHF and mortality within 1 month of admission

<table>
<thead>
<tr>
<th>Variable</th>
<th>AKI absent</th>
<th>HR (95% CI)</th>
<th>No.</th>
<th>AKI present</th>
<th>HR (95% CI)</th>
<th>No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>AHF absent</td>
<td>494/93,971</td>
<td>1.00 (Ref)</td>
<td>509/6,589</td>
<td>15.00 (13.09–17.19)</td>
<td>50.00 (13.09–17.19)</td>
<td></td>
</tr>
<tr>
<td>AHF present</td>
<td>21/913</td>
<td>3.39 (2.10–5.5)</td>
<td>52/331</td>
<td>29.23 (20.83–41.03)</td>
<td>14.56 (12.75–16.64)</td>
<td></td>
</tr>
<tr>
<td>HR (95% CI) for AHF within strata of AKI</td>
<td>3.39 (2.10–5.5)</td>
<td>2.11 (1.65–2.96)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

RERI (95% CI), 11.846 (2.426–21.266); p = 0.014. AP (95% CI), 0.405 (0.211–0.600); p < 0.001. SI (95% CI), 1.723 (1.227–2.418); p = 0.002. RERI and AP were >0, and SI was >1 suggesting an additive interaction between AKI and AHF. Hazard ratio was adjusted for age over 75 years, sex, body mass index, admission duration in days, comorbidities (hypertension, diabetes mellitus, chronic kidney disease, chronic heart failure, ischemic heart disease, liver disease, cerebrovascular disease, chronic obstructive pulmonary disease, and cancer), and medications used in the past 6 months just before admission (diuretics, renin-angiotensin system blockers, beta blockers, calcium-channel blockers, nonsteroidal anti-inflammatory drugs, vancomycin, and vasopressors). AP, attributable proportion due to interaction; AKI, acute kidney injury; AHF, acute heart failure; CI, confidence interval; HR, hazard ratio; RERI, relative excess risk of interaction; SI, synergy index.

Table 3. Interaction between AKI and AHF and mortality within 1 month among patients aged ≤75 years

<table>
<thead>
<tr>
<th>Variable</th>
<th>AKI absent</th>
<th>HR (95% CI)</th>
<th>No.</th>
<th>AKI present</th>
<th>HR (95% CI)</th>
<th>No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>AHF absent</td>
<td>257/78,794</td>
<td>1.000 (Ref)</td>
<td>6/480</td>
<td>18.74 (15.62–22.47)</td>
<td>18.74 (15.62–22.47)</td>
<td></td>
</tr>
<tr>
<td>AHF present</td>
<td>294/4,951</td>
<td>5.63 (2.42–13.10)</td>
<td>21/151</td>
<td>70.40 (41.85–118.46)</td>
<td>18.50 (15.46–22.14)</td>
<td></td>
</tr>
<tr>
<td>HR (95% CI) for AHF within strata of AKI</td>
<td>5.63 (2.42–13.10)</td>
<td>4.02 (2.53–6.39)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Relative excess risk of interaction (95% CI), 47.042 (11.519–82.564); p = 0.009. Attributable proportion due to interaction (95% CI), 0.668 (0.496–0.840); p < 0.001. Synergy index (95% CI), 3.104 (1.831–5.260); p < 0.001. Hazard ratio was adjusted for sex, body mass index, admission days, comorbidities (hypertension, diabetes mellitus, chronic kidney disease, chronic heart failure, ischemic heart disease, liver disease, cerebrovascular disease, chronic obstructive pulmonary disease, and cancer), and medications used in the last 6 months just before admission (diuretics, renin-angiotensin system blockers, beta blockers, calcium-channel blockers, nonsteroidal anti-inflammatory drugs, vancomycin, and vasopressors).

AKI, acute kidney injury; AHF, acute heart failure; CI, confidence interval; HR, hazard ratio.

20.83–41.03), while it was 15.00 in patients with AKI only (95% CI, 13.09–17.19) and 3.39 in patients with AHF only (95% CI, 2.10–5.47). Within strata of AHF, the HRs of AKI to 1-month mortality did not differ substantially. Interaction indexes in RERI analysis suggested that AKI and AHF had an additive detrimental effect on 1-month mortality; RERI between AKI and AHF was 11.846 (p = 0.014), AP was 0.405 (p < 0.001), and SI was 1.723 (p = 0.002). After 1 month, the additive detrimental effect on mortality was not significant.

There were 1,031 patients (1.0%) who developed ESRD after the first admission within the observational period. Among them, 51 patients (4.9%) developed both AKI and AHF; 661 patients (64.1%) developed AKI only, and eight patients (0.8%) developed AHF only. AKI increased the risk of ESRD by 19.120-fold, and AHF increased the risk of ESRD by 1.560-fold. In RERI analysis, the HR of 1-month mortality was 28.599 in patients with both AKI and AHF (95% CI, 20.17–40.55). However, the additive effect of AKI and AHF on ESRD were not statistically significant (RERI: 8.057, p = 0.10; AP: 0.282, p = 0.022; S: 1.412, p = 0.05).

Subgroup analysis

In subgroup analysis, age was related to the adverse additive effect of AKI and AHF on short-term mortality. When patients were grouped by age, HRs in patients aged ≤75 years were higher than HRs in the total patient population (vs. patients without AKI or AHF: HR, 70.40 [95% CI, 41.85–118.46] in patients with AKI and AHF; HR, 18.74 [95% CI, 15.62–22.47] in patients with AKI only; and HR, 5.63 [95% CI, 2.42–13.11] in patients with AHF only) (Table 3). RERI was 47.042 (p = 0.009), and AP and SI were also significant (AP, 0.668 [p < 0.001]; SI, 3.104 [p < 0.001]). In contrast, in patients aged over 75 years, RERI was 2.428 (p = 0.43), AP was 0.170 (p = 0.35), and SI was 1.224 (p = 0.39), which were statistically insignificant (Table 4). In elderly patients, 1-month mortality was higher in patients with AKI and AHF, with AKI only, and with AHF only (vs. patients with...
out AKI or AHF: HR, 14.29 [95% CI, 9.16–22.29] in patients with AKI and AHF; HR, 10.76 [95% CI, 8.77–13.20] in patients with AKI only; and HR, 2.11 [95% CI, 1.18–3.77] in patients with AHF only).

CHF and renal dysfunction were related to the HRs of AKI and AHF to 1-month mortality in subgroup analysis. Patients without CHF had a 43.736-fold increased risk (95% CI, 30.06‒63.63) of 1-month mortality when both AKI and AHF developed (Fig. 2). Patients with CHF showed 10.031-fold increased 1-month mortality risk (95% CI, 4.75‒21.17) when both AKI and AHF developed, which was significantly lower than that in patients without CHF. Among patients with CHF, HR for patients with AKI only was higher than for patients who developed both AKI and AHF (HR, 10.66; 95% CI, 5.36–21.20). Patients with baseline eGFR over 60 mL/min/1.73 m² had a 26.756-fold risk of 1-month mortality (95% CI, 14.46–49.50), while patients with baseline eGFR under 60 mL/min/1.73 m² had a 17.115-fold risk (95% CI, 11.24–26.07).

Hazard ratios of confounders in multivariable Cox proportional hazard analysis

In multivariable analysis, HR of 1-month mortality was 2.56 (95% CI, 2.28–2.97) for patients aged ≥75 years compared with patients under 75 years (Fig. 3). Males had a 1.367-fold increased risk of 1-month mortality than women (HR, 1.37; 95% CI, 1.22–1.58). BMI was associated with 1-month mortality as well [HR, 0.87; 95% CI, 0.86–0.89]. Previous use of diuretics and vasopressor had HRs of 1.64 (95% CI, 1.31–2.05) and 2.52 (95% CI, 1.96–3.25), respectively. Previous use of beta blockers was also significant (HR, 0.63; 95% CI, 0.46–0.87). Comorbidities were associated with 1-month mortality as follows: HR, 2.00 (95% CI, 1.44–2.79) for liver disease; HR, 1.40 (95% CI, 1.18–1.66) for cerebrovascular disease; HR, 1.38 (95% CI, 1.21–1.59) for cancer; HR, 1.31 (95% CI, 1.07–1.60) for ischemic heart disease; HR, 0.77 (95% CI, 0.62–0.96) for diabetes mellitus; and HR, 0.541 (95% CI, 0.39–0.75) for CKD.

Discussion

This study demonstrated that AKI and AHF have additive harmful effects on 1-month mortality. The coexistence of AKI and AHF increased mortality risk more than isolated organ dysfunction in patients without CHF and CKD, especially non-elderly patients.

Four types of cardiorenal syndrome are currently recognized based on the primary organ defect detected first [19]. Coexisting AKI and AHF may complement each other and interact synergistically to produce other risk factors for mortality. Kidney dysfunction can induce heart apoptosis [20], and heart dysfunction can also change kidney structure [21]. Current temporal classification is not perfectly explained by our current pathophysiological understanding of the organ crosstalk between the heart and kidney. In this study, we investigated AKI and AHF that developed within a short period after admission without considering the temporal relationship between AKI and AHF and found that these two conditions had an additive detrimental effect on short-term mortality. A previous study of patients who started renal replacement therapy suggested that

<table>
<thead>
<tr>
<th>Variable</th>
<th>AKI absent</th>
<th>AKI present</th>
<th>HR (95% CI) for AKI within AHF strata</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>HR (95% CI)</td>
<td>No.</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>AHF absent</td>
<td>237/15,177</td>
<td>1.000 (Ref)</td>
<td>215/1,638</td>
</tr>
<tr>
<td>AHF present</td>
<td>15/433</td>
<td>2.11 (1.18–3.77)</td>
<td>31/180</td>
</tr>
<tr>
<td>HR (95% CI) for AHF within strata of AKI</td>
<td>2.11 (1.18–3.77)</td>
<td>1.51 (1.04–2.20)</td>
<td></td>
</tr>
</tbody>
</table>

RERI (95% CI), 2.428 (–3.626 to 8.482); p = 0.432. AP (95% CI), 0.170 (–0.187 to 0.526); p = 0.350. SI (95% CI), 1.224 (0.770–1.943); p = 0.393. RERI and AP were > 0 and SI was > 1 in patients who were ≤75 years old, while this was not the case in patients over 75 years old. AKI and AHF individually increased mortality within 1 month, regardless of age. Hazard ratio was adjusted for sex, body mass index, admission days, comorbidities (hypertension, diabetes mellitus, chronic kidney disease, chronic heart failure, ischemic heart disease, liver disease, cerebrovascular disease, chronic obstructive pulmonary disease, and cancer), and medications used in the last 6 months just before admission (diuretics, renin-angiotensin system blockers, beta blockers, calcium-channel blockers, nonsteroidal anti-inflammatory drugs, vancomycin, and vasopressors).

AP, attributable proportion due to interaction; AKI, acute kidney injury; AHF, acute heart failure; CI, confidence interval; HR, hazard ratio; RERI, relative excess risk of interaction; SI, synergy index.
heart failure impeded recovery from AKI [22]. Therefore, finding a way to detect dysfunction of these two organs is important.

In our study, the interactive effect of AHF and AKI on mortality lasted for a short period. A previous prospective cohort study reported that the association between AKI and mortality decreased after kidney function recovery and proteinuria at the three-month follow-up [23]. These results thus emphasize the need for early detection of and prompt intervention for AKI or AHF after admission, even in patients without previous chronic dysfunction of the heart or kidney. Availability of early diagnostic biomarkers of AKI that correlate with cardiovascular risk or mortality [24] and the development of predictive and prognostic algorithms by machine learning [25] will hopefully result in improved patient outcomes.

The causes of AKI are multifactorial and, similarly, AHF has a range of risk factors. This makes their relationship with acute mortality more challenging to discern, but it does not detract from their clinical significance during admission [26]. In patients older than 75 years in our study, there was an obscure interactive effect between AHF and AKI. We believe several other comorbidities that contribute to increased risk of mortality were present. A previous study suggested multiple organ dysfunction as a risk factor for mortality in elderly patients with AKI [27]. The results of our study also indicate that dysfunction of individual organs contributes to increased mortality.

Interestingly, the additive effect of AKI and AHF was more prominent in patients without CHF than in those with CHF. CHF was present in about 60% of patients who developed AKI and AHF. Patients with CHF who had either AKI or AHF had a lower HR of 1-month mortality than those without CHF. Management of CHF includes medical treatment with renin-angiotensin system blockers, beta blockers, and diuretics [28,29]. Because the pathophysiologic mechanisms of cardiorenal syndrome, involving AKI and AHF, are explained mostly by volume congestion [30–32], furosemide is

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>AKI/AHF</th>
<th>No. of patients (%)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>H</td>
<td>93,971 (92.3)</td>
<td>3.39 (2.10–5.47)</td>
</tr>
<tr>
<td></td>
<td>E</td>
<td>913 (0.9)</td>
<td>15.00 (13.07–17.19)</td>
</tr>
<tr>
<td></td>
<td>H</td>
<td>6,589 (6.5)</td>
<td>29.23 (20.83–41.03)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>H-H</td>
<td>48,516 (91.3)</td>
<td>(Ref)</td>
</tr>
<tr>
<td></td>
<td>H-E</td>
<td>432 (0.8)</td>
<td>2.28 (0.92–5.66)</td>
</tr>
<tr>
<td></td>
<td>E-H</td>
<td>4,024 (7.6)</td>
<td>12.48 (10.27–15.18)</td>
</tr>
<tr>
<td></td>
<td>E-E</td>
<td>147 (0.3)</td>
<td>13.31 (8.15–21.74)</td>
</tr>
<tr>
<td>Female</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>H-H</td>
<td>45,455 (93.4)</td>
<td>(Ref)</td>
</tr>
<tr>
<td></td>
<td>H-E</td>
<td>2,565 (5.3)</td>
<td>18.02 (14.39–22.57)</td>
</tr>
<tr>
<td></td>
<td>E-H</td>
<td>184 (0.4)</td>
<td>30.07 (18.10–49.96)</td>
</tr>
<tr>
<td>Chronic heart failure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>H-H</td>
<td>1,777 (64.7)</td>
<td>(Ref)</td>
</tr>
<tr>
<td></td>
<td>H-E</td>
<td>279 (10.2)</td>
<td>10.66 (5.36–21.20)</td>
</tr>
<tr>
<td></td>
<td>E-H</td>
<td>191 (7)</td>
<td>10.03 (4.75–21.17)</td>
</tr>
<tr>
<td>No</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>H-H</td>
<td>92,194 (93.1)</td>
<td>(Ref)</td>
</tr>
<tr>
<td></td>
<td>H-E</td>
<td>414 (0.4)</td>
<td>3.58 (1.84–6.95)</td>
</tr>
<tr>
<td></td>
<td>E-H</td>
<td>6,310 (6.4)</td>
<td>15.20 (13.23–17.46)</td>
</tr>
<tr>
<td></td>
<td>E-E</td>
<td>140 (0.1)</td>
<td>43.74 (30.06–63.63)</td>
</tr>
<tr>
<td>Baseline eGFR (mL/min/1.73 m²)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;60</td>
<td>H-H</td>
<td>84,138 (94.6)</td>
<td>(Ref)</td>
</tr>
<tr>
<td></td>
<td>H-E</td>
<td>563 (0.6)</td>
<td>3.14 (1.58–6.22)</td>
</tr>
<tr>
<td></td>
<td>E-H</td>
<td>4,196 (4.7)</td>
<td>11.13 (9.28–13.36)</td>
</tr>
<tr>
<td></td>
<td>E-E</td>
<td>102 (0.1)</td>
<td>26.76 (14.46–49.50)</td>
</tr>
<tr>
<td>≤60</td>
<td>H-H</td>
<td>9,833 (76.4)</td>
<td>(Ref)</td>
</tr>
<tr>
<td></td>
<td>H-E</td>
<td>350 (2.7)</td>
<td>2.13 (1.08–4.20)</td>
</tr>
<tr>
<td></td>
<td>E-H</td>
<td>2,453 (19.1)</td>
<td>11.82 (9.51–14.70)</td>
</tr>
<tr>
<td></td>
<td>E-E</td>
<td>229 (1.8)</td>
<td>17.12 (11.24–26.07)</td>
</tr>
</tbody>
</table>

**Figure 2.** HRs of death within 1 month in subgroups based on sex, underlying chronic heart disease, and baseline eGFR. eGFR, estimated glomerular filtration rate; HR, hazard ratio; CI, confidence interval.
one of the standard medications for managing volume congestion in AHF, and has been suggested to improve prognosis in AHF [33–35]. One study in patients with AKI suggested that furosemide reduced 2-month mortality when it was appropriately used for volume management [36]. Because de novo heart failure is usually associated with cardiogenic shock or severe hemodynamic alterations secondary to an insult, such as myocardial infarction (which is itself a risk factor for death [37]), usage of diuretics may be difficult. The consequent volume congestion would result in AKI and increased mortality [38].

We also found that the interactive effect of AKI and AHF was more prominent in patients without CKD than those with CKD. In our study, the proportion of patients with CKD among those who developed both AKI and AHF was 15.7%, while it was only 2.1% among patients who developed AHF. Progressive renal insufficiency might have led to acute decompensated heart failure and therefore admission to the hospital. However, the mortality of patients whose baseline eGFR was <60 mL/min/1.73 m² was less affected by the additive effect of AKI and AHF. Because of the prevalent use of renin-angiotensin system blockers and/or angiotensin-converting enzyme inhibitors in patients with CKD [39], these drugs may also have exerted protective effects in patients with an ischemic insult to the heart, as a previous study suggested [40].

The limitations of this study are as follows. First, we based our clinical diagnoses on ICD codes, and heart function was not objectively assessed. Because the diagnosis of AHF depends on clinical judgment, mostly based on fluid congestion, prospective studies that utilize objective measurements of heart function would be useful to develop treatments for cardiorenal syndrome [41]. Second, we did not know the cause of admission or the etiology of AKI in the study patients. Because data on the specific etiology of AKI were limited, pathophysiological links between AKI and AHF could not be determined. However, analyzing large numbers of hospitalized patients would be a good
starting point for studying cardiorenal syndrome and obtaining temporal evidence of organ crosstalk between AKI and AHF.

In conclusion, we studied the interaction between AKI combined with AHF and mortality. HRs of short-term mortality were elevated when AKI and AHF were both present. RERI suggested the possibility of a causal association of AKI and AHF with 1-month mortality, indicating the need for additional research. The coexistence of AKI and AHF in hospitalized patients was associated with increased mortality, even in patients whose renal function was near to normal. Great care must be taken to reverse fluid congestion and insults to the heart and kidney without causing additional renal impairment in these patients.

Conflicts of interest

All authors have no conflicts of interest to declare.

Authors’ contributions

Conceptualization: SK
Study design: JYR, EB
Data curation, Formal analysis: HES, SSH, SK
Investigation: SSH, JJM, JP, HES
Supervision: SK, SSH, JCJ, HJC, KYN, DC
Writing-original draft: HES
Writing-review & editing: HES, SSH, SK
All authors read and approved the final manuscript.

ORCID

Hyung Eun Son, https://orcid.org/0000-0002-8719-3823
Jong Joo Moon, https://orcid.org/0000-0003-1034-0837
Jeong-min Park, https://orcid.org/0000-0003-3493-8235
Ji Young Ryu, https://orcid.org/0000-0003-4134-1007
Eunji Baek, https://orcid.org/0000-0001-9226-7703
Jong Cheol Jeong, https://orcid.org/0000-0003-0301-7644
Ho Jun Chin, https://orcid.org/0000-0002-3710-0190
Ki Young Na, https://orcid.org/0000-0002-8872-8236
Dong-wan Chae, https://orcid.org/0000-0001-9401-892X
Seung Seok Han, https://orcid.org/0000-0003-0137-5261
Sejoong Kim, https://orcid.org/0000-0002-7238-9962

References

Association between serum osteoprotegerin level and renal prognosis in nondialysis patients with chronic kidney disease in the Korean Cohort Study for Outcomes in Patients with Chronic Kidney Disease (the KNOW-CKD Study)

Tae Ryom Oh¹, Chana Myeong¹, Su Hyun Song³, Hong Sang Choi¹, Sang Heon Suh¹, Chang Seong Kim¹, Eun Hui Bae¹, Wookyung Chung², Kyu Hun Choi³, Kook Hwan Oh⁴, Seong Kwon Ma¹, Soo Wan Kim²

¹Department of Internal Medicine, Chonnam National University Hospital, Chonnam National University Medical School, Gwangju, Republic of Korea
²Department of Internal Medicine, Gachon University Gil Medical Center, Gachon University College of Medicine, Incheon, Republic of Korea
³Department of Internal Medicine, Institute of Renal Failure Research, Yonsei University College of Medicine, Seoul, Republic of Korea
⁴Department of Internal Medicine, Seoul National University Hospital, Seoul, Republic of Korea

Background: Osteoprotegerin is an important regulator of bone metabolism and vascular calcification. The association between serum osteoprotegerin level and chronic kidney disease (CKD) progression has not been elucidated. We investigated the prognostic value of serum osteoprotegerin levels in nondialysis CKD patients.

Methods: We analyzed 2,082 patients enrolled in the Korean Cohort Study for Outcomes in Patients with CKD between 2011 and 2016. Patients were divided into quartiles by their serum osteoprotegerin levels. The primary outcome was the occurrence of ≥1 of the following: dialysis initiation, kidney transplantation, a two-fold increase in serum creatinine level from baseline, or a 50% decrease in the estimated glomerular filtration rate (eGFR). Cox proportional hazard regression models were used to investigate the prognostic value of the serum osteoprotegerin level to CKD progression.

Results: The median follow-up period was 48.9 months, and 641 patients (30.8%) experienced the primary outcome. The hazard ratio of serum osteoprotegerin for renal progression in the full extended Cox proportional hazard model was 1.064 (95% confidence interval, 1.041–1.088). Subgroup analyses by age, presence of diabetes, and eGFR showed significant results consistent with the overall analysis results.

Conclusion: Serum osteoprotegerin level is independently associated with renal prognosis and could have prognostic importance in CKD progression.

Keywords: Chronic kidney disease-mineral and bone disorder, Chronic renal insufficiency, Osteoprotegerin, Prognosis, Renal insufficiency
Introduction

Chronic kidney disease (CKD) is an emerging public health problem worldwide [1]. Patients with CKD have an increased risk of all-cause mortality, particularly from cardiovascular disease [2–4]. In addition, the progression of CKD to end-stage renal disease causes a considerable decrease in patient quality of life [5] and a high socioeconomic burden on society. Therefore, it is important to identify risk factors for the deterioration of kidney function and delay the progression to end-stage renal disease.

Osteoprotegerin (OPG) is an osteoclastic marker that is mainly secreted by osteoblasts and the vascular endothelium [6]. It is a cytokine receptor of the tumor necrosis factor (TNF) receptor superfamily that inhibits the downstream signaling of the receptor activator of nuclear factor-κB ligand (RANKL) [7] and TNF-related apoptosis-inducing ligands to their receptors [8]. OPG is a marker of bone turnover via RANKL and is also involved in vascular inflammation, endothelial dysfunction, and vascular calcification [9–11]. Recent studies have shown an association between elevated OPG levels and various patients’ outcomes in patients with type 1 diabetes mellitus [12], CKD [13], heart failure [14], and acute coronary syndrome [15].

Although it is clinically important to identify whether OPG is a risk factor for CKD progression, few studies to date have investigated the relationship between OPG levels and renal prognosis. Altinova et al. [16] reported that OPG levels are inversely correlated with renal function in patients with type 2 diabetes mellitus. Lewis et al. [17] showed the possibility of rapid renal decline and renal-disease-related hospitalization or death in older women with elevated OPG levels. However, both those studies were small crossover studies, so additional studies are needed to clarify the association between OPG levels and renal prognosis.

Our purpose in this study was to investigate the prognostic value of the serum OPG level for renal prognosis in nondialysis patients with CKD.

Methods

Study participants

The Korean Cohort Study for Outcomes in Patients with CKD (KNOW-CKD) was a nationwide prospective cohort study in Korea that included nondialysis patients with CKD stages 1–5 (NCT01630486, http://www.clinicaltrials.gov). A total of 2,238 patients were enrolled between 2011 and 2016. The detailed study design, methods, and protocols for KNOW-CKD have been described previously [18]. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or the national research committees of the institutions at which the studies were conducted (Seoul National University Hospital, No. 1104-089-359; Seoul National University Bundang Hospital, No. B-1106/129-008; Yonsei University Severance Hospital, No. 4-2011-0163; Kangbuk Samsung Medical Center, No. 2011-01-076; Seoul St. Mary’s Hospital, No. KC1101MI0441; Gachon University Gil Hospital, No. GIRBA2553; Eulji General Hospital, No. B-1105-01; Chonnam National University Hospital, No. CNUH-2011-092; and Pusan Paik Hospital, No. 11-091) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Written informed consent was obtained from all patients at each center before enrollment. Among the participants of KNOW-CKD, 156 patients were excluded from this study because they had missing data on serum OPG levels and unclear renal events. Therefore, the present analysis included 2,082 patients (Fig. 1).

Data collection, measurements, and definitions

The baseline demographic details and clinical data (age, sex, smoking history, cause of CKD, economic status, educational level, comorbidities, and medications) of all pa-
Patients were collected by a well-trained research coordinator. Anthropometric data (height, weight, and waist and hip circumferences) were also collected. Body mass index was calculated by dividing the initial body weight (kg) by the square of the height (m$^2$). Blood pressure was measured using an electronic sphygmomanometer in a clinic after 5 minutes of seated rest. Furthermore, all patients underwent collection of 10-mL blood samples for biochemical analyses, a first-voided urine sample, and a 24-hour urine sample. The collected samples were sent to a central laboratory (LabGenomics, Seongnam, Korea) for complete blood count and blood chemistry measurements. Serum creatinine levels were measured using the isotope dilution mass spectroscopy-traceable method. The estimated glomerular filtration rate (eGFR) was calculated using the four-variable CKD Epidemiology Collaboration equation [19]. Serum OPG and klotho levels were measured using an enzyme-linked immunosorbent assay kit (BioVendor R&D and IBL, Brno, Czech). Diabetes mellitus was defined as serum hemoglobin A1c of ≥6.5%, fasting glucose of ≥126 mg/dL, or a previous diagnosis of diabetes. CKD progression was defined as one or more of the following: initiation of dialysis, kidney transplantation, a two-fold increase in the serum creatinine level from baseline, or a 50% decrease in eGFR during the follow-up period.

Statistical analyses

Data are presented as the mean ± standard deviation for continuous variables with a normal distribution and as the median and interquartile range for continuous variables with nonnormal distribution. A Shapiro-Wilk normality test was used to test normality. Categorical variables are described as the number and percentage of patients. Continuous variables were compared using a one-way analysis of variance and the Kruskal-Wallis test. A Cochran-Armitage trend test was used to compare more than two categories. We applied a multiple imputation method for missing data using the “MICE” package [20] in R because missing values in clinical data are mostly missing at random [21]. Kaplan-Meier survival curves with the log-rank test and univariate Cox proportional hazard models were used to evaluate the association between serum OPG levels and CKD progression. We analyzed the mutual influence between variables using a collinearity test. The proportional hazard assumption of the Cox proportional hazard models was verified using a log-minus-log survival plot and the Schoenfeld residual test. If the proportional hazard assumption was violated, we could not estimate unbiased results using the Cox proportional hazard models. To solve that problem, we applied extended Cox proportional hazard models and measured the time-stratified effects of fixed baseline eGFR, which violated the proportional hazard assumption. We divided the entire follow-up duration into 150-day intervals. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated to estimate the risk of CKD progression and determine independent risk factors. Data were analyzed and plotted using R language (version 4.0.2; The R Foundation for Statistical Computing, Vienna, Austria) [22]. All statistical tests were two-tailed, and p-values of <0.05 were considered statistically significant.

Results

Clinical characteristics of study participants

Among the 2,082 total patients, the median follow-up period was 48.9 months, the mean age was 53.5 years, and the number of women was 814 (39.1%). The number of patients with diabetes mellitus was 701 (33.7%), and the median baseline eGFR was 46.2 mL/min per 1.73 m$^2$. The OPG levels measured at baseline were divided into quartiles (≤4.52, 4.52–6.02, 6.02–8.22, and ≥8.22 pmol/L). Significant differences in clinical characteristics were observed among the quartile groups. The highest quartile (Q4) was associated with older age and a higher prevalence of diabetes and hypertension compared with the others. Serum OPG level correlated inversely with baseline eGFR. Smoking history, body mass index, and serum klotho level showed no statistically significant differences among the OPG quartile groups. Serum albumin, total calcium, and low-density lipoprotein cholesterol levels were lower in patients in the highest quartile group than in the other groups, whereas the urine protein-to-creatinine ratio showed the opposite trend. The detailed results are summarized in Table 1. During the follow-up period, 641 patients experienced a renal event that was considered to indicate CKD progression. A significant difference was observed in the incidence of CKD progression according to serum OPG levels (Table 1): CKD progression occurred in 98 patients (18.8%) in the first...
quartile group, 120 (23.0%) in the second quartile group, 161 (30.9%) in the third quartile group, and 262 (50.3%) in the fourth quartile group (p < 0.001).

Association between serum osteoprotegerin levels and renal prognosis

Serum OPG levels increased with increasing CKD stages (Fig. 2). The Kaplan-Meier survival curves show statistically significant differences in renal event probability among the quartiles of serum OPG level (Fig. 3). The highest quartile showed the poorest prognosis among the groups. The extended Cox proportional hazard model was adjusted for serum OPG level, age, sex, presence of diabetes mellitus and hypertension, low-density lipoprotein level, calcium level, proteinuria (protein-to-creatinine ratio), C-reactive protein, serum klotho level, and time-stratified eGFR. Both listwise deletion and multiple imputations were used to minimize bias caused by missing values, and those results showed no significant differences. Serum OPG level was independently associated with CKD progression (HR, 1.064; 95% CI, 1.041–1.088; p < 0.001).

Subgroup analyses

We performed subgroup analyses by age, CKD stage, and the presence of diabetes mellitus (Table 2). Statistically significant associations between serum OPG level and CKD

---

### Table 1. Clinical characteristics of the study population

<table>
<thead>
<tr>
<th>Variable</th>
<th>Missing values</th>
<th>Total (n = 2,082)</th>
<th>Quartiles of serum osteoprotegerin</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Q1 (n = 521)</td>
<td>Q2 (n = 521)</td>
<td>Q3 (n = 520)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>0 (0)</td>
<td>53.5 ± 12.2</td>
<td>44.0 ± 10.9</td>
<td>51.3 ± 10.7</td>
</tr>
<tr>
<td>Sex (male)</td>
<td>0 (0)</td>
<td>1,268 (60.9)</td>
<td>335 (64.3)</td>
<td>300 (57.6)</td>
</tr>
<tr>
<td>Smoking history</td>
<td>0 (0)</td>
<td></td>
<td></td>
<td>1110 (53.3)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>0 (0)</td>
<td>701 (33.7)</td>
<td>56 (10.7)</td>
<td>131 (25.1)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0 (0)</td>
<td>2002 (96.2)</td>
<td>486 (93.3)</td>
<td>497 (95.4)</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>1 (0)</td>
<td>127.7 ± 16.1</td>
<td>124.3 ± 14.6</td>
<td>126.6 ± 14.3</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>1 (0)</td>
<td>77.0 ± 11.1</td>
<td>77.6 ± 10.8</td>
<td>78.2 ± 10.4</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>13 (0.6)</td>
<td>24.6 ± 3.4</td>
<td>24.6 ± 3.6</td>
<td>24.6 ± 3.5</td>
</tr>
<tr>
<td>Waist-to-hip ratio</td>
<td>137 (6.6)</td>
<td>0.89 ± 0.06</td>
<td>0.88 ± 0.06</td>
<td>0.89 ± 0.06</td>
</tr>
<tr>
<td>Serum osteoprotegerin (pmol/L)</td>
<td>0 (0)</td>
<td>6.0 (4.5–8.2)</td>
<td>3.7 (3.2–4.1)</td>
<td>5.3 (4.9–5.6)</td>
</tr>
<tr>
<td>Serum creatinine (mg/dL)</td>
<td>0 (0)</td>
<td>1.5 (1.1–2.2)</td>
<td>1.1 (0.8–1.6)</td>
<td>1.3 (0.9–1.9)</td>
</tr>
<tr>
<td>Estimated glomerular filtration rate (mL/min per 1.73 m²)</td>
<td>0 (0)</td>
<td>46.2 (28.4–73.0)</td>
<td>71.3 (48.3–100.3)</td>
<td>55.0 (34.8–81.4)</td>
</tr>
<tr>
<td>Low-density lipoprotein (mg/dL)</td>
<td>32 (1.5)</td>
<td>93.8 (73.0–116.0)</td>
<td>98.0 (76.0–116.0)</td>
<td>94.0 (75.0–118.0)</td>
</tr>
<tr>
<td>Serum albumin (g/dL)</td>
<td>13 (0.6)</td>
<td>4.2 ± 0.4</td>
<td>4.3 ± 0.3</td>
<td>4.2 ± 0.4</td>
</tr>
<tr>
<td>Calcium (mg/dL)</td>
<td>16 (0.8)</td>
<td>9.1 ± 0.5</td>
<td>9.2 ± 0.5</td>
<td>9.2 ± 0.5</td>
</tr>
<tr>
<td>Urine protein-to-creatinine ratio (g/g creatinine)</td>
<td>43 (2.1)</td>
<td>0.5 (0.1–1.5)</td>
<td>0.3 (0.1–0.8)</td>
<td>0.4 (0.1–1.0)</td>
</tr>
<tr>
<td>C-reactive protein (mg/dL)</td>
<td>135 (6.5)</td>
<td>0.6 (0.2–1.6)</td>
<td>0.5 (0.2–1.3)</td>
<td>0.7 (0.3–1.5)</td>
</tr>
<tr>
<td>Serum klotho (pmol/L)</td>
<td>12 (0.6)</td>
<td>536.0 (419.0–666.0)</td>
<td>543.0 (414.5–687.5)</td>
<td>528.5 (408.0–656.0)</td>
</tr>
<tr>
<td>Follow-up duration (mo)</td>
<td>0 (0)</td>
<td>48.9 (32.4–73.0)</td>
<td>60.8 (39.4–75.8)</td>
<td>54.0 (36.6–75.1)</td>
</tr>
</tbody>
</table>

Data are presented as mean ± standard deviation or median (interquartile range) for continuous variables and number (%) of patients for categorical variables.

Continuous variables were compared using a one-way analysis of variance and Kruskal-Wallis testing. A Cochran-Armitage trend test was used to compare more than two categories.

www.krcp-ksn.org 203
Figure 2. Changes in serum osteoprotegerin level according to CKD stage. The association between serum osteoprotegerin level and CKD stage. CKD, chronic kidney disease.

Figure 3. Kaplan-Meier curves for renal outcomes according to quartiles of serum osteoprotegerin level. Patients with the highest quartile of serum osteoprotegerin showed the poorest renal outcomes.
Table 2. Hazard ratios of the serum osteoprotegerin level in the Cox proportional hazard models

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard ratio (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum osteoprotegerin (pmol/L)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Missing values with listwise</td>
<td>1.07 (1.04–1.10)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>deletion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Missing values with multiple</td>
<td>1.06 (1.04–1.09)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>imputation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subgroup analyses</td>
<td></td>
<td></td>
</tr>
<tr>
<td>eGFR (mL/min per 1.73 m²)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;60</td>
<td>1.18 (1.02–1.37)</td>
<td>0.03</td>
</tr>
<tr>
<td>≥60</td>
<td>1.06 (1.03–1.09)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1.05 (1.02–1.09)</td>
<td>0.004</td>
</tr>
<tr>
<td>Yes</td>
<td>1.12 (1.06–1.18)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age (yr)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;60</td>
<td>1.05 (1.01–1.09)</td>
<td>0.01</td>
</tr>
<tr>
<td>≥60</td>
<td>1.06 (1.01–1.11)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

CI, confidence interval; eGFR, estimated glomerular filtration rate.

Cox proportional hazard models were adjusted for the serum osteoprotegerin level, age, sex, presence of diabetes mellitus and hypertension, low-density lipoprotein cholesterol, serum albumin, calcium, proteinuria (protein-to-creatinine ratio), C-reactive protein, serum klotho level, and time-stratified eGFR.

progression were observed in all subgroups. The HR (CI) values for serum OPG level were 1.062 (1.033–1.091) in the eGFR of ≥60 mL/min per 1.73 m² subgroup and 1.051 (1.011–1.093) in the age of <60 years subgroup. The results of all subgroup analyses were consistent with the overall results.

Discussion

In this study, serum OPG level was found to be a significant prognostic marker of CKD progression. Subgroup analyses also showed robust and consistent results. Most patients with CKD eventually develop bone mineral disorder, which is related to vascular calcification [23,24]. Vascular calcification is a common complication and an important risk factor for major cardiovascular events [25]. Numerous biomarkers related to vascular calcification have been studied, and serum OPG level has received attention as an osteoclastic marker. Because serum OPG level is a marker of vascular damage, many recent studies have focused on the relationship between it and cardiovascular outcomes, including coronary artery calcification and cardiovascular disease-related mortality [12,13,26,27]. This disorder of the kidney-vascular-bone axis can be related to mineral metabolism; however, it can also result from local inflammation [28]. OPG is expressed in various organs and cell types, including the heart, kidney, liver, osteoblasts, and vascular smooth muscle cells, and it is related to many cytokines and growth factors, such as interleukin (IL)-1, IL-6, IL-11, IL-17, TNF-α, transforming growth factor-β (TGF-β), and platelet-derived growth factor [29–32]. The multifaceted direct or indirect effects of OPG via molecular pathways are believed to affect renal prognosis. In addition, serum klotho is a biomarker that is recognized to be closely related to CKD progression, and it did not differ statistically according to the serum OPG quartiles in this study, which implies that serum OPG and serum klotho work in different ways. Further research is needed to elucidate the relationship between serum klotho and serum OPG.

Several studies have reported an inverse correlation between the serum OPG level and eGFR [33–35], and our study shows a similar result. Considering that the elevated serum OPG level in CKD patients decreases after transplantation [36], it is possible that serum OPG level is dependent on renal function. As age increases, atherosclerosis of the vessels progresses, which could explain why OPG levels increase with age [37,38]. That could also explain why high OPG levels are observed in patients with a history of cardiovascular disease [37]. A previous study observed considerable medial calcification in the aorta and renal arteries of OPG–/– mice [39]; however, the protective role of OPG has not been confirmed in human studies. The serum OPG level tends to be considered a risk marker rather than a risk factor for renal function deterioration because of that evidence.

Bernardi et al. [40] reported that OPG delivery not only upregulated the gene expression of IL-6 and TGF-β but also increased the amount of protein nitrosylation in kidney tissues in an experimental mouse model. Considering that previous studies have shown that TGF-β [41] is related to renal fibrosis and IL-6 [42] is upregulated in diabetic nephropathy, OPG might directly induce kidney injury. However, there is still no consensus about whether the OPG level is a true risk factor. Given the inconsistent results of previous studies, we performed subgroup analyses to identify the effects of the serum OPG level on renal prognosis. We divided patients into subgroups based on factors associated with the serum OPG level: old age [43], presence of diabe-
tes mellitus [43,44], and decreased eGFR [33–35]. Notably serum OPG level showed a statistically significant link with renal prognosis in all subgroups. The consistent and robust results of our study are important because they support the role of OPG as a risk factor for CKD progression.

Our study has many strengths, including its prospective observational design, robust data collection, large study population, minimization of omitted variable bias with the multiple imputation method, and nonviolation of the proportional hazard assumption, which make our results reliable. Despite those many strengths, our study also has a few limitations. First, we could not infer a causal relationship between the serum OPG level and CKD progression because of the inherent limitation of our observational design. However, observational studies are powerful tools for assessing epidemiologic relationships, and we used complementary analytic methods to robustly examine the effects of the serum OPG level on relevant clinical outcomes [45]. Second, despite the wide range of risk adjustments, the problems of hidden bias, confounders, and omitted variables cannot be completely solved. Third, because serum OPG levels were measured only at baseline, we could not assess the effect of variability in serum OPG levels.

In conclusion, our findings support the hypothesis that serum OPG level might be associated with renal prognosis and thus has prognostic value for the progression of CKD. Further studies are needed to determine causality between the serum OPG level and CKD progression.

Conflicts of interest

All authors have no conflicts of interest to declare.

Funding

This research was supported by the research program of the Korea Centers for Disease Control and Prevention (grants 2011E3300300, 2012E3301100, 2013E3301600, 2013E3301601, 2013E3301602, 2016E3300200, 2016E3300201, 2016E3300202, 2019E320100, 2019E320101, and 2019E320102), and a grant of the Korea Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI) funded by the Ministry of Health & Welfare, Republic of Korea (grant number: HR20C0021).

Authors’ contributions

Conceptualization: TRO, CM, SWK
Formal analysis: TRO, CM, SWK
Funding acquisition: KHO, SWK
Investigation: TRO, HSC, SH Song, EHB, WC, KHC, KHO, SWK
Writing–original draft: TRO, CM, SH Song, SH Suh
Writing–review & editing: TRO, CM, SH Song, SH Suh
All authors read and approved the final manuscript.

ORCID

Tae Ryom Oh, https://orcid.org/0000-0002-3713-0939
Chana Myeong, https://orcid.org/0000-0003-4535-7786
Su Hyun Song, https://orcid.org/0000-0003-3510-8655
Hong Sang Choi, https://orcid.org/0000-0001-8191-4071
Sang Heon Suh, https://orcid.org/0000-0003-3076-3466
Chang Seong Kim, https://orcid.org/0000-0001-8753-7641
Eun Hui Bae, https://orcid.org/0000-0003-1727-2822
Wooyung Chung, https://orcid.org/0000-0001-7657-130X
Kyu Hun Choi, https://orcid.org/0000-0003-0095-9011
Kook Hwan Oh, https://orcid.org/0000-0001-9525-2179
Seong Kwon Ma, https://orcid.org/0000-0002-5758-8189
Soo Wan Kim, https://orcid.org/0000-0002-3540-9004

References

6. Collin-Osdoby P. Regulation of vascular calcification by osteo-


Clinical features and outcomes of elderly patients with antineutrophil cytoplasmic antibody-positive vasculitis: a single-center retrospective study

Hyo Jin Kim\textsuperscript{1,2}, Miyeun Han\textsuperscript{3}, Sang Heon Song\textsuperscript{1,2}, Eun Young Seong\textsuperscript{1,2}

\textsuperscript{1}Department of Internal Medicine, Pusan National School of Medicine, Busan, Republic of Korea
\textsuperscript{2}Biomedical Research Institute, Pusan National University Hospital, Busan, Republic of Korea
\textsuperscript{3}Department of Internal Medicine, Hallym University Hangang Sacred Heart Hospital, Seoul, Republic of Korea

\textbf{Background:} We aimed to investigate the clinical characteristics and outcomes of patients aged ≥65 years with antineutrophil cytoplasmic autoantibody (ANCA)-positive ANCA-associated vasculitis (AAV) in Korea.

\textbf{Methods:} Seventy patients diagnosed with ANCA-positive AAV from 2006 to 2019 at a single center were analyzed and categorized into younger (aged <65 years) or elderly (aged ≥65 years) groups. Initial induction treatments were investigated according to age group. All-cause mortality and kidney outcomes were evaluated.

\textbf{Results:} After categorization by age, 34 (48.6\%) and 36 patients (51.4\%) were in the younger and elderly groups, respectively. In the elderly group, more patients were treated with oral cyclophosphamide (CYC) (30.6\%) than with intravenous CYC (19.4\%). During a median follow-up of 14.6 months (range, 3.0–53.1 months), 13 patients died (elderly group: 11 patients, 84.6\%). In the elderly group, older age (hazard ratio [HR], 1.44; 95\% confidence interval [CI], 1.09–1.90; \( p = 0.01 \)), lower hemoglobin (HR, 0.21; 95\% CI, 0.08–0.60; \( p = 0.003 \)), and higher serum creatinine level (HR 14.17; 95\% CI, 1.29–155.84; \( p = 0.03 \)) were significant risk factors for all-cause mortality after adjustment. Oral CYC + steroid treatment was associated with decreased all-cause mortality compared to untreated induction immunosuppressants (HR, 0.01; 95\% CI, 0.001–0.47; \( p = 0.02 \)). Kidney failure or kidney recovery outcomes were not significantly different between the younger and elderly groups.

\textbf{Conclusion:} Patients aged ≥65 years had higher mortality rates than younger patients, and mortality was associated with older age, lower hemoglobin, higher serum creatinine level, and nontreatment compared to oral CYC + steroids.

\textbf{Keywords:} Aged, Antineutrophil cytoplasmic antibodies, Antineutrophil cytoplasmic antibody-associated vasculitis, Mortality, Vasculitis

\section*{Introduction}

Antineutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis (AAV) comprises granulomatosis with polyangiitis (GPA, previously known as Wegener’s granulomatosis), microscopic polyangiitis (MPA), and eosinophilic GPA (EGPA, previously known as Churg-Strauss syndrome) \cite{1}. A reclassification of AAV into three categories, according to
the presence of ANCA, was recently suggested as follows: myeloperoxidase (MPO)-ANCA, proteinase 3 (PR3)-ANCA, and ANCA-negative vasculitis [2]. In patients with AAV, renal involvement can often present as rapidly progressive glomerulonephritis (GN), and the upper or lower respiratory tract and the peripheral nervous system may be involved as extrarenal manifestations. Although AAV also occurs in younger patients, it presents more commonly in elderly patients. The peak age of AAV incidence is between 65 and 74 years [3–6]. In a study of 430 Chinese patients aged ≥65 years who underwent renal biopsy, AAV (44%) was the leading cause of secondary GN [7]. In a recent study in Korea, AAV was more prevalent in those aged ≥65 years compared to those aged <65 years (3.9% vs. 0.3%) [8].

Substantial morbidity and mortality occur with AAV, especially in elderly patients. In addition, rapidly progressive GN requires prompt diagnosis and the early initiation of adequate treatment. Although AAV predominantly affects older patients, appropriate treatment strategies have not been established clearly, and it is unclear whether the benefits of immunosuppressants surpass the risks. The Kidney Disease: Improving Global Outcomes (KDIGO) guidelines recommend reducing the cyclophosphamide (CYC) dose in patients over 60 years old [9]. Data on the clinical characteristics and outcomes of elderly patients with AAV are scarce, especially in Asia. Therefore, this study aimed to investigate the demographic factors, treatments, and clinical outcomes of patients with AAV in Korea and to compare the characteristics of AAV among elderly and young patients.

Methods

Study design and subjects

The study reviewed patients that were ANCA-positive (MPO/P-ANCA or PR3/C-ANCA) at Pusan National University Hospital from 2006 to 2019. We excluded patients who were ANCA-positive because of non-vasculitis conditions, such as inflammatory bowel disease, primary sclerosing cholangitis, systemic lupus, idiopathic pulmonary fibrosis, and endocarditis. After excluding patients who were ANCA-positive due to non-vasculitis conditions, AAV was diagnosed with findings of necrotizing vasculitis in ANCA-positive patients who underwent biopsy. Patients who could not undergo a biopsy were diagnosed via physician judgment based on clinical characteristics, laboratory findings, and radiographic images. The AAV nomenclature was according to the Chapel Hill Consensus Conference 2012 revised nomenclature [1]. At the time of diagnosis, patients aged ≥65 years were defined as elderly patients with AAV.

The study was approved by the Institutional Review Board of Pusan National University Hospital (No. H-2008-002-093), which waived the requirement for informed patient consent because of the retrospective design of the study. All clinical investigations were in accordance with the Declaration of Helsinki.

Clinical data collection and laboratory measurements

The following data were retrospectively collected by reviewing the medical charts of patients: age, sex, ANCA specificity, diagnosis date, comorbidities, organ involvement, laboratory findings, induction treatment type, and initial dialysis dependency. ANCA was determined using an indirect immunofluorescence assay for P-ANCA and/or C-ANCA or enzyme-linked immunosorbent assay (ELISA) for MPO and/or PR3. ANCA testing was performed according to the manufacturer’s instructions. The indirect immunofluorescence assay was performed using an Immco ANCA kit (Immco Diagnostics, Inc., Buffalo, NY, USA). MPO and/or PR3 was measured using a ZEUS ELISA kit (ZEUS Scientific, Inc., Branchburg, NJ, USA) at the Seoul Clinical Laboratories (Yongin, Korea) until January 20, 2013. An ORGENTEC ELISA kit (ORGENTEC Diagnostika GmbH, Mainz, Germany) was used at our hospital after January 21, 2013. The date of AAV diagnosis was defined as the day of the first positive ANCA test result. Organ involvement, including the kidney, lung, skin, ear, nose, and throat (ENT), nerve, and gastrointestinal tract, was determined. Organ involvement was evaluated from the patients’ medical history, laboratory findings, radiographic images, and expert judgment. Kidney involvement was defined as urinary abnormalities, such as hematuria or proteinuria, or by kidney biopsy results that showed (1) no evidence of immune-complex deposition in immunofluorescence staining and electron microscopic examination, and (2) evidence of glomerular crescent but no other explainable pathologic diagnosis, such as lupus nephritis or immunoglobulin A nephropathy. Lung involvement was defined as a lung nodule, cavitation, lung fibrosis, pulmonary
hemorrhage, history of interstitial lung disease, and so on. Skin involvement was defined as purpura, skin ulcer, cutaneous nodule, and so on. ENT involvement was defined as rhinitis, sinusitis, septal perforation, nasal collapse, and so on. Nerve involvement was defined as peripheral neuropathy, mononeuritis multiplex, results of a nerve conduction study and electromyography, and so on. Gastrointestinal tract involvement was defined as bloody diarrhea, ischemic abdominal pain, and so on. The laboratory values reported closest to the date of AAV diagnosis were used for the analysis. Serum creatinine was measured using isotope dilution mass spectrometry (IDMS) reference method \[10\]. The estimated glomerular filtration rate at the time of AAV diagnosis was calculated using the abbreviated four-variable Modification of Diet in Renal Disease Study equation \[11\], using IDMS-traceable serum creatinine assay. Severe proteinuria and hematuria were defined as ≥3+ on the dipstick urine test and >100 red blood cells per high-power field in a urine microscopy examination, respectively. The protein quantitation values were investigated in patients with random urinary protein-to-creatinine ratio (UPCR) (g/g) values. Induction treatments were categorized as intravenous CYC + steroids, oral CYC + steroids, steroids only, others (rituximab or mycophenolate mofetil + steroids), or untreated. The usual induction treatment dose was as follows: intravenous CYC 500–750 mg/month, oral CYC 1.0-2.0 mg/kg/day with adjustment based on age and kidney function, starting with oral prednisolone 1 mg/kg/day and then taper down, rituximab 375 mg/m\(^2\), or mycophenolate mofetil 500 mg twice a day. Pulse steroids or plasma exchange treatment were also investigated. The pulse steroid dose was usually methylprednisolone 500–1,000 mg for 3 days. Dosage was adjusted according to the clinical judgment of the physician. Patients with severe kidney injury requiring dialysis at the time of AAV diagnosis were defined as having initial dialysis dependency.

Outcomes

Patients were followed up until April 2020. The primary outcome of the present study was all-cause death during the follow-up period. Causes of death were also investigated. The secondary outcome was kidney failure or kidney recovery. Kidney failure was defined as the need for maintenance dialysis in patients who did not require dialysis at the time of AAV diagnosis. In patients with initial dialysis dependency, kidney recovery with the cessation of dialysis was defined as a kidney outcome.

Statistical analyses

Continuous variables are presented as means ± standard deviations and were compared using t tests. Non-normally distributed variables are expressed as the medians (interquartile ranges) and were compared using the Mann-Whitney U test. Categorical variables were analyzed using the chi-square test or Fisher exact test, and the results are presented as frequencies and percentages. Log transformation was used to normalize variables with a skewed distribution. The Kaplan-Meier method was used to evaluate patient survival and kidney failure outcome, and statistical significance was determined using the log-rank test. Cox proportional hazards regression analyses were conducted. In the multivariable analysis, clinically relevant variables were chosen as covariates according to previous studies \[8,12,13\]. The logarithm of serum creatinine was used in the Cox regression analyses. The results are presented as hazard ratios (HRs) and 95% confidence intervals (CIs). The p-values of <0.05 were considered statistically significant. All analyses were conducted using SPSS version 20.0 (IBM Corp., Armonk, NY, USA).

Results

Baseline clinical characteristics of the patients

Seventy patients diagnosed with ANCA-positive AAV were analyzed. Table 1 presents the characteristics of all patients at baseline and after categorization by age. The mean age of patients was 62.8 ± 13.3 years and 64.3% were male. For ANCA-specific types, 52 (74.3%), 15 (21.4%), and three of the patients (4.3%) were MPO/P-ANCA, PR3/C-ANCA, and double-positive, respectively. The kidneys (70.0%) and lungs (70.0%) were the organs most commonly involved. The initial serum creatinine was 2.0 mg/dL (0.9–5.2 mg/dL). Eighteen (25.7%) and 25 patients (35.7%) had severe proteinuria and hematuria, respectively. The UPCR measured in 56 patients was 1.6 g/g (0.8–3.8 g/g). Among patients with renal involvement, 33 patients underwent kidney biopsy. The specific results of the kidney biopsy are...
Table 1. Baseline clinical characteristics and initial treatment of patients with ANCA-positive AAV

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total</th>
<th>Younger group</th>
<th>Elderly group</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>70</td>
<td>34</td>
<td>36</td>
<td></td>
</tr>
<tr>
<td>Age (yr)</td>
<td>62.8 ± 13.3</td>
<td>52.9 ± 12.0</td>
<td>72.2 ± 5.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male sex</td>
<td>45 (64.3)</td>
<td>23 (67.6)</td>
<td>22 (61.1)</td>
<td>0.57</td>
</tr>
<tr>
<td>Comorbidities</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>20 (28.6)</td>
<td>12 (35.3)</td>
<td>8 (22.2)</td>
<td>0.23</td>
</tr>
<tr>
<td>Hypertension</td>
<td>24 (34.3)</td>
<td>11 (32.4)</td>
<td>13 (36.1)</td>
<td>0.74</td>
</tr>
<tr>
<td>ANCA subtype</td>
<td></td>
<td></td>
<td></td>
<td>0.16</td>
</tr>
<tr>
<td>MPO/P-ANCA</td>
<td>52 (74.3)</td>
<td>23 (67.6)</td>
<td>29 (80.6)</td>
<td></td>
</tr>
<tr>
<td>PR3/C-ANCA</td>
<td>15 (21.4)</td>
<td>8 (23.5)</td>
<td>7 (19.4)</td>
<td></td>
</tr>
<tr>
<td>Double-positive</td>
<td>3 (4.3)</td>
<td>3 (8.8)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Organ involvement</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kidney</td>
<td>49 (70.0)</td>
<td>23 (63.6)</td>
<td>26 (72.2)</td>
<td>0.68</td>
</tr>
<tr>
<td>Lung</td>
<td>49 (70.0)</td>
<td>22 (64.7)</td>
<td>27 (75.0)</td>
<td>0.35</td>
</tr>
<tr>
<td>Skin</td>
<td>14 (20.0)</td>
<td>8 (23.5)</td>
<td>6 (16.7)</td>
<td>0.47</td>
</tr>
<tr>
<td>ENT</td>
<td>21 (30.0)</td>
<td>12 (35.3)</td>
<td>9 (25.0)</td>
<td>0.35</td>
</tr>
<tr>
<td>Nerve</td>
<td>22 (31.4)</td>
<td>11 (32.4)</td>
<td>11 (30.6)</td>
<td>0.87</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>2 (2.9)</td>
<td>1 (2.9)</td>
<td>1 (2.8)</td>
<td>0.97</td>
</tr>
<tr>
<td>Laboratory findings</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WBC (×10^3/mm^3)</td>
<td>11,759 ± 6,466</td>
<td>11,803 ± 7,147</td>
<td>11,718 ± 5,853</td>
<td>0.96</td>
</tr>
<tr>
<td>Platelet (×10^3/mm^3)</td>
<td>287 ± 120</td>
<td>293 ± 120</td>
<td>282 ± 122</td>
<td>0.73</td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>10.0 ± 2.1</td>
<td>10.6 ± 2.5</td>
<td>9.4 ± 1.6</td>
<td>0.02</td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>3.1 ± 0.7</td>
<td>3.3 ± 0.7</td>
<td>2.9 ± 0.6</td>
<td>0.02</td>
</tr>
<tr>
<td>Total cholesterol (mg/dL)</td>
<td>149.5 ± 51.5</td>
<td>161.3 ± 46.1</td>
<td>138.4 ± 54.5</td>
<td>0.08</td>
</tr>
<tr>
<td>CRP (mg/L)</td>
<td>3.3 (0.8–7.2)</td>
<td>1.3 (0.4–5.4)</td>
<td>4.8 (1.8–11.4)</td>
<td>0.004</td>
</tr>
<tr>
<td>BUN (mg/dL)</td>
<td>31.3 (16.9–56.3)</td>
<td>24.8 (13.1–50.0)</td>
<td>38.9 (19.5–62.7)</td>
<td>0.25</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>2.0 (0.9–5.2)</td>
<td>1.5 (0.8–5.1)</td>
<td>2.5 (0.9–5.2)</td>
<td>0.64</td>
</tr>
<tr>
<td>eGFR (mL/min/1.73 m²)</td>
<td>29.6 (10.6–88.0)</td>
<td>47.5 (12.3–107.7)</td>
<td>24.6 (10.1–73.2)</td>
<td>0.39</td>
</tr>
<tr>
<td>Severe proteinuria</td>
<td>18 (25.7)</td>
<td>10 (29.4)</td>
<td>8 (22.2)</td>
<td>0.49</td>
</tr>
<tr>
<td>Severe hematuria</td>
<td>25 (35.7)</td>
<td>10 (29.4)</td>
<td>15 (41.7)</td>
<td>0.29</td>
</tr>
<tr>
<td>UPCR (g/g)</td>
<td>1.6 (0.8–3.8)</td>
<td>1.4 (0.8–3.6)</td>
<td>1.7 (0.9–4.0)</td>
<td>0.85</td>
</tr>
<tr>
<td>Induction treatment</td>
<td></td>
<td></td>
<td></td>
<td>0.11</td>
</tr>
<tr>
<td>Intravenous CYC + steroids</td>
<td>19 (27.1)</td>
<td>12 (35.3)</td>
<td>7 (19.4)</td>
<td></td>
</tr>
<tr>
<td>Oral CYC + steroids</td>
<td>15 (21.4)</td>
<td>4 (11.8)</td>
<td>11 (30.6)</td>
<td></td>
</tr>
<tr>
<td>Steroids only</td>
<td>23 (32.9)</td>
<td>14 (41.2)</td>
<td>9 (25.0)</td>
<td></td>
</tr>
<tr>
<td>Others c</td>
<td>3 (4.3)</td>
<td>1 (2.9)</td>
<td>2 (5.6)</td>
<td></td>
</tr>
<tr>
<td>Untreated</td>
<td>10 (14.3)</td>
<td>3 (8.8)</td>
<td>7 (19.4)</td>
<td></td>
</tr>
<tr>
<td>Plasmapheresis</td>
<td>5 (7.1)</td>
<td>3 (8.8)</td>
<td>2 (5.6)</td>
<td>0.60</td>
</tr>
<tr>
<td>Pulse steroids</td>
<td>35 (50.0)</td>
<td>18 (52.9)</td>
<td>17 (47.2)</td>
<td>0.63</td>
</tr>
<tr>
<td>Initial dialysis dependency</td>
<td>22 (31.4)</td>
<td>9 (26.5)</td>
<td>13 (36.1)</td>
<td>0.39</td>
</tr>
</tbody>
</table>

Data are expressed as number only, mean ± standard deviation, number (%), or median (interquartile range). Younger group, aged <65 years; elderly group, aged ≥65 years.

AAV, ANCA-associated vasculitis; ANCA, antineutrophil cytoplasmic antibody; BUN, blood urea nitrogen; CRP, C-reactive protein; CYC, cyclophosphamide; eGFR, estimated glomerular filtration rate; ENT, ear, nose, and throat; MPO, myeloperoxidase; PR3, proteinase 3; UPCR, urinary protein-to-creatinine ratio; WBC, white blood cells.

aSevere proteinuria and hematuria were defined as dipstick urine protein ≥3+ and urine red blood cells ≥100/high-power field, respectively.
bMeasured only in 56 patients.
cRituximab or mycophenolate mofetil + steroids.
in Supplementary Table 1 (available online). After categorizing patients by age, 34 (48.6%) and 36 (51.4%) were in the younger and elderly groups, respectively. The number of patients by diagnosis year according to age groups is shown in Supplementary Fig. 1 (available online). More patients were diagnosed with AAV between 2013 and 2019 than between 2006 and 2012, and more of these patients were elderly. The mean age of the elderly group was 72.2 ± 5.4 years. Ten patients (14.3%) were above 75 years old, and the oldest patient was 83 years old. Comorbidities such as diabetes mellitus and hypertension were similar between the age groups. In the elderly group, MPO/P-ANCA was noted in 80.6% of patients. Hemoglobin (p = 0.015) and serum albumin (p = 0.019) were significantly lower and C-reactive protein (p = 0.004) was significantly higher in the elderly group compared with the younger group. The mean age of the elderly group was 72.2 ± 5.4 years. Ten patients (14.3%) were above 75 years old, and the oldest patient was 83 years old. Comorbidities such as diabetes mellitus and hypertension were similar between the age groups. In the elderly group, MPO/P-ANCA was noted in 80.6% of patients. Hemoglobin (p = 0.015) and serum albumin (p = 0.019) were significantly lower and C-reactive protein (p = 0.004) was significantly higher in the elderly group compared with the younger group. The baseline kidney function which was evaluated using serum creatinine values within 6 months was available only in 45 patients (64.3%), with 22 (64.7%) in the younger group and 23 (63.9%) in the elderly group. The baseline serum creatinine was 0.90 mg/dL (0.75–1.20 mg/dL), and the values were similar between the younger (0.93 mg/dL [0.75–1.21 mg/dL]) and elderly (0.90 mg/dL [0.70–1.20 mg/dL]) groups (p > 0.99). The changes in serum creatinine between baseline and the time of diagnosis are shown in Supplementary Fig. 2 (available online). Initial dialysis dependency was noted in 22 patients (31.4%) and was not significantly different between the younger (26.5%) and elderly (36.1%) groups (p = 0.39). Nineteen patients received conventional hemodialysis and three patients received continuous renal replacement therapy (CRRT). Two of three patients who received CRRT had lung hemorrhage. The cause of dialysis at the time of diagnosis included active AAV (n = 19) and infection (n = 3).

Initial induction treatment

Initial induction treatments were as follows: intravenous CYC + steroids (27.1%), oral CYC + steroids (21.4%), steroids only (32.9%), others (4.3%), and untreated (14.3%) (Table 1). Pulse steroid therapy was administered to 50% of patients. More patients were treated with intravenous CYC (35.3%) than with oral CYC (11.8%) in the younger group. In contrast, more patients were treated with oral CYC (30.6%) than with intravenous CYC (19.4%) in the elderly group. Overall, 19.4% of patients in the elderly group were untreated (vs. 8.8% in the younger group). In the elderly group, the untreated group tended to be slightly older than the treated group, but this was not statistically significant (74.1 ± 5.8 years vs. 71.7 ± 5.3 years, p = 0.23). The numbers of patients treated with plasmapheresis and pulse steroids were similar between the younger and elderly groups.

All-cause mortality

Mortality outcomes are shown in Table 2. The median follow-up duration was 14.6 months (3.0–53.1 months). During the follow-up period, 13 patients (18.6%) died: two (5.9%) in the younger group (follow-up duration, 28.5 months [6.9–92.3 months]) and 11 (30.6%) in the elderly group (follow-up duration, 6.0 months [1.6–23.3 months]). Infection (61.5%) was the major cause of death, and all the patients that died had pneumonia. The number of deaths was significantly higher in the elderly group than in the younger group, and the major cause of death in the elderly group was infection (54.5%). In the elderly group, three out of seven patients who did not receive initial induction treatment died, in all of these the cause was pneumonia and all died within 75 days. Fig. 1 presents the Kaplan-Meier curves for all-cause mortality according to age group. The elderly group showed a significantly lower survival rate than the younger group (p = 0.005). The 2-year survival rate was 94% in the younger group and 64% in the elderly group. The Cox regression analysis for all-cause mortality in all the patients and the elderly patients is presented in Table 3.

### Table 2. Mortality outcomes and cause of death according to age group

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Total</th>
<th>Younger group</th>
<th>Elderly group</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of participants</td>
<td>70</td>
<td>34</td>
<td>36</td>
<td></td>
</tr>
<tr>
<td>Death*</td>
<td>13 (18.6)</td>
<td>2 (5.9)</td>
<td>11 (30.6)</td>
<td>0.008</td>
</tr>
<tr>
<td>Cause of death*</td>
<td></td>
<td></td>
<td></td>
<td>0.69</td>
</tr>
<tr>
<td>Active vasculitis</td>
<td>1 (7.7)*</td>
<td>0 (0)</td>
<td>1 (9.1)</td>
<td></td>
</tr>
<tr>
<td>Infection</td>
<td>8 (61.5)*</td>
<td>2 (100)</td>
<td>6 (54.5)</td>
<td></td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>2 (15.4)</td>
<td>0 (0)</td>
<td>2 (18.2)</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>2 (15.4)*</td>
<td>0 (0)</td>
<td>2 (18.2)</td>
<td></td>
</tr>
</tbody>
</table>

Data are expressed as number only, *number (% of patients), or number (% of total deaths). Younger group, aged <65 years; elderly group, aged ≥65 years. Pulmonary hemorrhage. All patients had pneumonia. Gastrointestinal bleeding or cancer.
Figure 1. All-cause mortality according to age group. The younger group was aged <65 years and the elderly group was aged ≥65 years. Elderly patients exhibited a significantly lower survival rate than younger patients (p = 0.005).

Figure 2. Kidney failure outcomes rate according to age group. Forty-eight patients who did not require dialysis at the time of antineutrophil cytoplasmic antibody-associated vasculitis diagnosis were analyzed. The younger group was aged <65 years and the elderly group was aged ≥65 years. The cumulative kidney failure event rate was not significantly different according to age group (p = 0.201).

Table 3. Multivariable Cox regression analysis for all-cause mortality in the entire study population and elderly patients with ANCA-positive AAV

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total HR (95% CI)</th>
<th>p-value</th>
<th>Age ≥ 65 yr HR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>1.31 (1.12–1.52)</td>
<td>0.001</td>
<td>1.44 (1.09–1.90)</td>
<td>0.01</td>
</tr>
<tr>
<td>ANCA type</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MPO/P-ANCA</td>
<td>Reference</td>
<td>-</td>
<td>Reference</td>
<td>-</td>
</tr>
<tr>
<td>PR3/C-ANCA</td>
<td>2.44 (0.58–10.23)</td>
<td>0.22</td>
<td>3.02 (0.63–14.32)</td>
<td>0.17</td>
</tr>
<tr>
<td>Double-positive</td>
<td>15.72 (1.12–220.58)</td>
<td>0.04</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>0.31 (0.17–0.58)</td>
<td>&lt;0.001</td>
<td>0.21 (0.08–0.60)</td>
<td>0.003</td>
</tr>
<tr>
<td>Creatinine* (mg/dL)</td>
<td>3.75 (0.64–21.95)</td>
<td>0.14</td>
<td>14.17 (1.29–155.84)</td>
<td>0.03</td>
</tr>
<tr>
<td>Induction treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Untreated</td>
<td>Reference</td>
<td>-</td>
<td>Reference</td>
<td>-</td>
</tr>
<tr>
<td>Intravenous CYC + steroids</td>
<td>2.46 (0.43–14.20)</td>
<td>0.31</td>
<td>2.89 (0.30–28.05)</td>
<td>0.36</td>
</tr>
<tr>
<td>Oral CYC + steroids</td>
<td>0.05 (0.003–0.75)</td>
<td>0.03</td>
<td>0.01 (0.000–0.47)</td>
<td>0.02</td>
</tr>
<tr>
<td>Steroids only</td>
<td>0.60 (0.12–3.08)</td>
<td>0.54</td>
<td>0.21 (0.03–1.77)</td>
<td>0.15</td>
</tr>
<tr>
<td>Othersb</td>
<td>1.81 × 10⁻⁶ (0.00–NA)</td>
<td>0.99</td>
<td>4.08 × 10⁻⁷ (0.00–NA)</td>
<td>0.99</td>
</tr>
</tbody>
</table>

AAV, ANCA-associated vasculitis; ANCA, antineutrophil cytoplasmic antibody; CI, confidence interval; CYC, cyclophosphamide; HR, hazard ratio; MPO, myeloperoxidase; PR3, proteinase 3; NA, not available


In the multivariable Cox regression analysis, older age (HR, 1.31; 95% CI, 1.12–1.52; p = 0.001) and lower hemoglobin (HR, 0.31; 95% CI, 0.17–0.58; p < 0.001) were significant risk factors for all-cause mortality. ANCA double-positivity (HR, 15.72; 95% CI, 1.12–220.58; p = 0.04) was associated with increased all-cause mortality compared to MPO/P-ANCA positivity. Oral CYC + steroid treatment (HR, 0.05; 95% CI, 0.003–0.47; p = 0.02) was associated with decreased all-cause mortality compared to nontreatment. Similar results were noted in the elderly group. In the elderly group, older
Kidney outcomes

During the follow-up period, nine patients (18.8%) developed kidney failure among 48 patients who did not require dialysis at the time of AAV diagnosis. The cause of kidney failure development included active AAV (n = 3), infection (n = 1), and CKD progression after AAV (n = 5). The Kaplan-Meier curves for kidney failure events according to age group are presented in Fig. 2. The event rates for kidney failure were not significantly different between the younger and elderly groups (p = 0.20). Table 4 presents the Cox regression analysis for kidney failure outcomes. In the multivariable Cox regression analysis, higher serum creatinine (HR, 101.29; 95% CI, 3.25–3,159.70; p = 0.03) at the time of AAV diagnosis was a significant risk factor for kidney failure outcomes. In addition, oral CYC + steroid treatment (HR, 0.02; 95% CI, 0.0003–0.47; p = 0.02) was associated with decreased all-cause mortality with oral CYC + steroid treatment (HR, 0.02; 95% CI, 0.0003–0.47; p = 0.02) compared to nontreatment.

Discussion

In the present study, 36 elderly patients (51.4%) with ANCA-positive AAV were enrolled over 14 years. During the study period, more elderly patients were diagnosed with AAV between 2013 and 2019 than between 2006 and 2012. In the follow-up period, 13 patients died, and most of these patients (11, 84.6%) were in the elderly group. Older age, lower hemoglobin, and higher serum creatinine were significant risk factors for all-cause mortality in the elderly group. Similar to our study, previous studies have also demonstrated that advancing age and impaired renal function are significant risk factors for mortality [14,15]. Kidney outcomes were not significantly different between the younger and elderly groups in the present study.

In elderly patients, decreased immunity and the increased risk of infection are of great concern in immunosuppressant treatment. Elderly patients are particularly vulnerable to the adverse effects of disease and the immunosuppressants used for treatment. In the present study, there was decreased all-cause mortality in the oral CYC + steroids treatment group compared to the untreated group at all ages. This demonstrates the effect of immunosuppressants even in the elderly. In addition, the mortality rate may have been lower because the immunosuppressants were more likely to be used in stronger patients. Infection was the main cause of death, and six patients (54.5%) died of an infection in the elderly group, three of who were treated with immunosuppressants (1 patient each was treated with intravenous CYC + steroids, oral CYC + steroids, or steroids alone) and the other three underwent only supportive treatment. The three patients who received immunosuppressant treatment were relatively older compared to those who received supportive treatment (73, 83, and 83 years vs. 65, 73, and 73 years). In the present study,
there was no significant difference in mortality by infection in the elderly group, regardless of treatment with immuno-
suppressants. However, the small number of patients
precludes a definite conclusion regarding this finding. In a
previous retrospective study, patients that were older and
receiving immunosuppressants had an increased risk of
infection, particularly in the presence of leukopenia [3].
However, other studies have shown that elderly patients
with AAV receiving immunosuppressants had a better
prognosis (lower mortality and/or lower frequency of end-
stage renal disease [ESRD]) than those untreated or not
received via the standard method [16,17]. Overall, immu-
suppressants can be used with caution in elderly patients
with AAV, with careful monitoring for adverse events.

In our study, there were not many patients who under-
went rituximab induction treatment. In previous studies,
rituximab was not inferior compared to CYC as an induc-
tion treatment [18,19], and rituximab was more efficacious
than CYC in patients with relapsing disease [18]. Adverse
events were comparable between the two treatments and
there was no trend toward reduced infection rates [20].
However, rituximab induction may be preferred in frail old-
er adults according to the expert recommendation in the
draft of the 2020 KDIGO clinical guideline on glomerular
disease. Therefore, appropriate immunosuppressants in
elderly patients can improve the prognosis of the patient.
Further study is needed on the outcome of elderly AAV pa-
tients using rituximab.

In the present study, oral CYC was prescribed more of-
ten than intravenous CYC in older patients. The CYCLOPS
study showed that intravenous pulse and oral continuous
CYC were equally efficacious and pulse intravenous ther-
apy had lower side effects, including leukopenia [21]. The
long-term follow-up of the CYCLOPS study demonstrated
that pulse CYC was not associated with increased mortality
or long-term morbidity; however, it was associated with
a higher risk of relapse than oral CYC [22]. In the present
study, the reasons for the greater use of oral CYC compared
to intravenous CYC in the elderly could be the following.
First, patients from before the CYCLOPS study era were
also included in the study, and because of concerns about
relapse, which would have required repeat high-dose im-
munosuppressants, oral CYC may have been prescribed
more often than intravenous CYC. Furthermore, intrave-
nous CYC may have been less prescribed in the elderly
because the administration method is more cumbersome
than oral therapy and occasionally needs short-term ad-
mission. In a previous study, oral CYC was prescribed more
often than intravenous CYC in very elderly AAV patients
(oral vs. intravenous: 58% vs. 24%) [17]. In another obser-
vational study, patients receiving oral CYC were older than
those receiving intravenous CYC (72 years [65–78 years] vs.
55 years [44–68 years], p < 0.001) [23].

Lower hemoglobin was a significant risk factor for all-
cause mortality in the entire study population, including
the elderly group. Anemia-related markers, such as mean
corpuscular volume (MCV), mean corpuscular hemoglobin
concentration (MCHC), ferritin, iron, total-iron binding ca-
pacity (TIBC), and transferrin saturation (TSAT) were evalu-
ated. MCV was 88.6 ± 4.8 fl and MCHC was 33.4 ± 1.7 g/dL.
Serum ferritin, iron, TIBC, and TSAT values were available
only in 42 patients. Serum ferritin was 552.0 ng/mL (251.8–
837.3 ng/mL) and serum iron was 29.0 μg/dL (22.0–51.5 μg/
dL). Serum ferritin was significantly higher in the elderly
group than in the younger group (younger vs. elderly: 308.2
ng/mL [168.6–646.9 ng/mL] vs. 571.1 ng/mL [375.6–1,092.5
ng/mL]; p = 0.04). Iron (p = 0.428) and TSAT (p = 0.35) were
not significantly different between the younger and elderly
groups. The presence of anemia is known to increase with
age, and anemia is common in the elderly [24]. In one study,
anemia was prevalent in >10% of people aged ≥65 years and
in >20% of those aged ≥85 years in the United States [24]. In
a recent study, 13.8% of people aged ≥65 years who partic-
ipated in a Korean national survey had anemia [25]. Aging
is a proinflammatory condition that may cause altered iron
handling or the suppression of erythroid progenitors [26].
Anemia in the elderly is related to various adverse out-
comes, including hospitalization, morbidity, and mortality
[27]. In our study, ferritin was higher in the elderly, which
may reflect inflammatory conditions and lower hemoglobin
associated with patient death.

The presence of kidney involvement or impaired renal
function is a common negative prognostic factor for elderly
patients [14,15]. In the present study, higher serum crea-
tinine was a significant risk factor for all-cause mortality
in the elderly group. AAV-associated kidney involvement
often presents as rapidly progressive GN [28] and can
cause poor morbidities and mortality. Therefore, if elderly
patients with AAV have kidney involvement or impaired
renal function, meticulous care and close follow-up and
monitoring are needed.

In the present study, ANCA-positive AAV was not classified as GPA, MPA, or EGPA. AAV classification according to clinical phenotype, especially GPA or MPA, has significant overlap in clinical features and often ambiguous distinctions, adding to the controversial issues in AAV classification [29]. A classification system according to ANCA specificity (MPO-ANCA vs. PR3-ANCA disease) has been proposed. Relapse rates and clinical outcomes are better associated with ANCA specificity [29]. Therefore, in the present study, ANCA-positive AAV was classified as MPO/P-ANCA, PR3/C-ANCA, or double-positive AAV. In a previous study, there were no differences in mortality or time to remission between MPO-positive and PR3-positive patients, but PR3-positive patients had a higher rate of relapse and relapsed earlier than MPO-positive patients [30]. In the present study, there were no significant differences in mortality between MPO/P-ANCA and PR3/C-ANCA; however, further large-scale studies are needed to clarify our findings.

The strength of our study is that we investigated the outcomes of patients with AAV, especially elderly patients. In previous randomized controlled trials of induction immunosuppressant in AAV, the mean ages of patients were 57 years [10], 53 years [18], and 60 years [31], and in another study, elderly patients aged above 75 years were excluded [15]. In previous studies, similar responses to immunosuppressive treatment were found in elderly AAV patients compared to younger people [3], and one study found that they did not respond well [32]. Bomback et al. [17] showed that immunosuppressants were associated with a lower risk of ESRD or combined ESRD or death risk at 1 year in very elderly patients over 80 years of age. In a recent study, older age and infection were major risk factors for 1-year mortality in AAV patients over 65 years but failed to show a statistical significance between therapeutic strategy and mortality [33]. In our study, we investigated outcomes according to immunosuppressant use in elderly AAV patients and entire study patients, which is an advantage in our study. However, our study also has several limitations. First, we could not exclude the possibility of residual confounders because of the retrospective nature of the study. Moreover, we could not conduct a multivariable analysis for all-cause mortality in the younger group because mortality events (only two patients [2.9%]) were low during the follow-up period. In addition, this was a single-center study in Korea; thus, caution is required when generalizing our findings to other ethnicities.

In conclusion, patients aged 65 years or older had higher mortality rates than younger patients, which was associated with older age, lower hemoglobin, higher serum creatinine, and nontreatment compared to oral CYC + steroids.

Conflicts of interest

All authors have no conflicts of interest to declare.

Authors’ contributions

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

ORCID

Hyo Jin Kim, https://orcid.org/0000-0001-9289-9073
Miyeun Han, https://orcid.org/0000-0001-7304-2496
Sang Heon Song, https://orcid.org/0000-0002-8218-6974
Eun Young Seong, https://orcid.org/0000-0002-6006-0051

References


First snapshot on behavioral characteristics and related factors of patients with chronic kidney disease in South Korea during the COVID-19 pandemic (June to October 2020)

Yaerim Kim1, Inae Lee2, Jeonghwan Lee3, Jae Yoon Park4, Jung Nam An5, Kyung Don Yoo6, Yong Chul Kim7, Woo Yeong Park5, Kyubok Jin1, Younglim Kho8, Myoungsoon You2, Dong Ki Kim1, Kyungho Choi5, Jung Pyo Lee3

1Department of Internal Medicine, Keimyung University School of Medicine, Daegu, Republic of Korea
2Department of Environmental Health Sciences, School of Public Health, Seoul National University, Seoul, Republic of Korea
3Department of Internal Medicine, SMG-SNU Boramae Medical Center, Seoul, Republic of Korea
4Department of Internal Medicine, Dongguk University Ilsan Hospital, Goyang, Republic of Korea
5Department of Internal Medicine, Hallym University Sacred Heart Hospital, Anyang, Republic of Korea
6Department of Internal Medicine, Ulsan University Hospital, University of Ulsan College of Medicine, Ulsan, Republic of Korea
7Department of Internal Medicine, Seoul National University Hospital, Seoul, Republic of Korea
8Department of Health, Environment, and Safety, Eulji University, Seongnam, Republic of Korea

Background: The recent novel coronavirus disease 2019 (COVID-19) pandemic has led to unprecedented changes in behavior. We evaluated the current status of precautionary behavior and physical activity in chronic kidney disease (CKD) patients during the COVID-19 pandemic.

Methods: A population of CKD patients (n = 306) registered in the Study on Kidney Disease and Environmental Chemicals (SKETCH, Clinical Trial No. NCT04679168) cohort recruited from June 2020 to October 2020 was included in the study. We conducted a questionnaire survey related to risk perception of COVID-19, precautionary behavior, and physical activity.

Results: There were 187 patients (61.1%) with estimated glomerular filtration rate of <45 mL/min/1.73 m². This population showed a higher degree of risk perception for COVID-19 than the general population. Age was the most significant determinant of risk perception among CKD patients. During the pandemic, social distancing and hygiene-related behavior were significantly increased (p < 0.001). The frequency of exercise was decreased only in those who took regular exercise, without diabetes, or with a lower Charlson comorbidity index (CCI) (p < 0.001), with no change among the other groups. Socioeconomic status and comorbidities significantly af-
Introduction

The severe acute respiratory syndrome coronavirus 2 or coronavirus disease 2019 (COVID-19) pandemic has caused unprecedented threats to public health, disproportionally against the old and those with underlying health conditions. As the incidence rate of COVID-19 has increased exponentially, social distancing and the use of personal protective equipment (PPE) have been recommended and often enforced worldwide. Social distancing measures range from strict nationwide lockdown and/or curfew to more voluntary-based recommendations. In countries such as South Korea, varying stages of social (or physical) distancing measures were implemented depending on the extent of the viral spread in combination with rapid screening and efficient contact tracing without imposing draconian ‘stay-at-home’ restrictions [1-3]. Regardless of the extent of legal enforcement, the common factors in social distancing include avoidance of contact with other people, hygienic behavior, and the use of PPE.

Chronic kidney disease (CKD) is a common health problem worldwide, with a global prevalence reaching 29.3% in 2017 [4]. CKD is not only recognized as a risk factor for infectious diseases but may also aggravate their prognosis [5-7]. Indeed, CKD patients exhibit a significantly higher fatality rate following COVID-19 infection than the general population [8]. It is necessary to protect CKD patients from potential COVID-19 infection. Hence, health practitioners and clinicians need to understand the current status of compliance with precautionary recommendations among CKD patients, and the factors that influence their precautionary behaviors.

While active social distancing measures have contributed to a decrease in new cases by reducing the likelihood of transmitting COVID-19, these measures may lead to undesirable consequences, including physical inactivity. Recently, initial reports indicate that the stay-at-home orders in several countries caused significant decreases in physical activity not only among general or healthy populations but also among patients who require routine physical exercise [9,10]. Physical inactivity is responsible for approximately 3.2 million deaths per year [11]. Moreover, for CKD patients, a lack of physical activity has often been linked to adverse prognoses [12-14]. For this reason, we evaluate the impact of behavioral change on the physical activity of CKD patients.

This study was conducted to determine the current status of precautionary behaviors against the COVID-19 pandemic among CKD patients along with their physical activity during the first months of the pandemic. The observations made in this study can help to develop the most appropriate clinical recommendations in this vulnerable population to prevent COVID-19 infection and to promote healthy behavior that will improve the maintenance of underlying disease.

Methods

Study populations

This study was conducted with a cohort of CKD patients. The Study on Kidney Disease and Environmental Chemicals (SKETCH, Clinical Trial No. NCT04679168) aims to investigate the behavioral characteristics, chemical exposure, and clinical outcomes of CKD patients during and after the COVID-19 pandemic. We defined CKD as (1) estimated glomerular filtration rate (eGFR) of ≥15 and <60 mL/min/1.73 m^2 or (2) eGFR of ≥60 mL/min/1.73 m^2 and urine protein to creatinine ratio of >0.3 g/g. A total of 308 participants were recruited from five university hospitals located in Seoul, Ilsan, and Daegu, Korea between June and October 2020 (Supplementary Fig. 1, available online).

Contribution: CKD patients showed higher risk perception with active precautionary behavioral changes than the general population. Healthcare providers should be aware of the characteristics to comprise precautionary behavior without reducing physical activity.

Keywords: Chronic kidney disease, COVID-19, Exercise, Health behavior
Exclusion criteria included those who were followed up less than 3 months or with a recent history of acute kidney injury, progressive malignancy, cerebral infarction, cerebral hemorrhage, myocardial infarction, under hemodialysis, or immunosuppressant use.

The study protocol and consent to participate were approved by the Institutional Review Board in participating hospitals (Supplementary data 1, available online). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Questionnaire and clinical data

A questionnaire survey was conducted by trained surveyors for participating patients on their visit to the hospital. The questionnaire included questions related to 1) risk perception of COVID-19, 2) hygienic behavior, 3) social distancing, and 4) physical activity during the past year (before the pandemic) and the 1 month before the hospital visit (during the pandemic). Detailed information of the survey was described in Supplementary data 2 (available online). Perceived risk of COVID-19 infection was determined by a 5-point scale from ‘never’ (1) to ‘extremely high’ (5); items, marked 4 or 5 were grouped as high-risk perception or ‘high perceived risk.’ For evaluating the risk perception among the general population of Korea, the relevant data (i.e., the possibility of personal COVID-19 infection) was gleaned from Hankook Research (https://hrcopinion.co.kr/covid-19, accessed December 18, 2020) which collected data from 1,000 subjects through biweekly survey events. The statistics for the incidence of COVID-19 infection were obtained from the Korean Statistical Information Service (https://kosis.kr/covid/covid_index.do, accessed December 13, 2020).

Demographic data, anthropometric data, and clinical laboratory data related to CKD were obtained when the subject visited the hospital (Supplementary data 3, available online). Data on underlying comorbidities were collected via electronic medical records using prescription records and diagnostic codes according to the International Classification of Diseases 10th Revision (ICD-10).

Statistical analysis

The chi-square tests and Fisher exact tests for categorical variables were conducted to compare demographic and clinical parameters by CKD status. In addition, the Mann-Whitney U test and the Student t test were performed for continuous variables. Categorical variables were expressed as numerical with proportions (%), and continuous variables were expressed as mean ± standard deviation when distributed normally (as median with interquartile range otherwise).

To compare behaviors before and during the COVID-19 pandemic, the Wilcoxon signed-rank test was used. Logistic regression analysis was conducted to identify the relative factors related to risk recognition or behavior changes. Sensitivity analysis was conducted with age adjustment because the odds ratio (OR) of high-degree perception was greater than scale ‘3’ in the groups aged ≥60 years. First, we assessed the associations between possible demographic factors and risk recognition following stratification by age group (<60 years, ≥60 years). Second, the age group (1, <50 years; 2, 50–59 years; 3, 60–69 years; and 4: ≥70 years) was additionally adjusted as a covariate in logistic regression models. The p values of <0.05 were defined as significant when they were set to two-sided. Statistical analyses were performed using IBM SPSS version 23.0 (IBM Corp., Armonk, NY, USA) and SAS version 9.4 (SAS Institute, Cary, NC, USA). Spearman correlation was visualized by using the package corrplot (R 3.5.3; R Foundation for Statistical Computing, Vienna, Austria).

Results

Study populations

The mean age of the participating CKD patients (n = 306) was 61.0 ± 12.5 years, and 209 patients (68.3%) were male (Table 1). The mean serum creatinine and eGFR of the patients were 1.8 ± 0.7 mg/dL and 43.2 ± 20.7 mL/min/1.73 m², respectively. A total of 187 patients (61.1%) showed an eGFR less than 45 mL/min/1.73 m² and were regarded as the advanced CKD group. Advanced CKD was found more frequently among older and female patients; these patients tended to show lower serum hemoglobin, platelet, serum albumin, bilirubin, and a higher proportion of overt proteinuria (Table 1).

The majority of patients had completed a high school education (35.9%) or higher (29.2%). A total of 137 participants (44.8%) were working either full or part-time. There were 56
and 85 participants (27.8%) with current smoking and alcohol consumption, respectively. Most participating CKD patients stated their health status as ‘not good’ (43.1%) or ‘bad’ (46.7%).

**Risk perception**

At the time of the survey during the global pandemic of COVID-19, in general, most participating patients (89%) perceived the risk of infection as ‘serious.’ More people considered the general risk of infection nationwide (i.e., ‘nationwide in general’) as serious (76.1%) than the risk for their city of residence (55.4%) or the individual (45.6%) (Supplementary Fig. 2, available online).

In CKD patients, risk perception for the city of residence or the individual was also significantly correlated with trends of COVID-19 case reporting (Supplementary Table 1, available online). Based on this result, we used the risk perception variable as the risk on the individuals to evaluate the impact on behavior changes. The level of perceived risk in general populations appeared to be related to the trends in cases of COVID-19 infection (Fig. 1A). Most patients of the cohort were enrolled after the first peak of the pandemic. Compared to the general population of Korea (n = 1,000), CKD patients showed much greater levels of the perceived risk from COVID-19 infection (Fig. 1B).

Older patients with lower education and income were more likely to perceive a greater risk of infection. The stage of CKD, however, did not influence the risk perception (Table 2). When stratified by age group, the associations of education and income with risk perception disappeared (Supplementary Table 2, available online).

**Behavioral changes during the COVID-19 pandemic**

The frequencies of ‘public transport use’ and ‘public place visit’ were significantly decreased in all populations regardless of the frequency of such behaviors before the pandemic.
Figure 1. **Distribution of enrolled participants and risk cognition according to the pandemic.** (A) Number of participating chronic kidney disease patients recruited in the Study on Kidney Disease and Environmental Chemicals (SKETCH, Clinical Trial No. NCT04679168) cohort in comparison with the daily number of confirmed cases of coronavirus disease 2019 (COVID-19) nationwide (left Y-axis and red line). The proportion of people who answered ‘serious’ or ‘very serious’ for the possibility of infection by COVID-19 in the general population is shown by the blue dotted line (right Y-axis). (B) Comparison of risk perception between the general population of Korea (n = 1,000, left) and those who were participating in the SKETCH cohort (right) for given periods. Specific time periods were demonstrated under the graph, and **“*”** represented the period for chronic kidney disease (CKD) patients. Crimson red, gray, and blue colors indicate the proportion of the population who answered ‘high’ (‘4’ or ‘5’), ‘moderate’ (‘3’), and ‘low’ (‘1’ or ‘2’) levels of risk perception, respectively.

*The statistics for the incidence of COVID-19 represented with a black line were obtained from the Korean Statistical Information Service. The risk perception for COVID-19 in the general population was obtained from Hankook Research (https://hrcopinion.co.kr/covid-19, accessed December 18, 2020), which collected data from 1,000 subjects through biweekly survey events.*
The frequency of ‘private vehicle use’ tended to increase among those who seldom used private transport before the pandemic, but among those who frequently used private vehicles, the frequency of use decreased (Supplementary Fig. 3A, available online).

During the pandemic, CKD patients showed significant increases in several hygiene-related behaviors. The frequency of handwashing, showering, face mask use, and hand sanitizer use was significantly increased during the COVID-19 pandemic. In particular, there were no subjects who did not wear a face mask during the pandemic (p < 0.001). In addition, the frequencies of laundry and house cleaning were significantly increased (p < 0.001) (Supplementary Fig. 3B).

Regarding the frequency of exercise, i.e., physical activity over 30 minutes, no change was observed in general (n = 306) and in those who exercised on an irregular basis (n = 128). Among those who exercised regularly (n = 178) or in gyms (n = 28), however, the frequency of exercise significantly decreased.

Factors associated with social distancing behaviors

Several demographic and socioeconomic factors were associated with behaviors related to social distancing (Table 4). Younger patients (<50 years old) showed less frequent public place visits and more exercise. Patients with higher income showed >1.5 ORs for less frequent public place visits and longer stays-at-home (Supplementary Table 3, available online). The positive associations of stay-at-home with sex and income became stronger after age adjustment (Table 4).

Higher risk perception was significantly associated with decreased use of public transport (OR, 2.00; 95% CI, 1.09–3.66), and the association remained significant after adjustment for age (adjusted OR, 1.91; 95% CI, 1.01–3.60) (Table 4). Among patients with diabetes, the negative association with the frequency of public place visits was attenuated by age adjustment (adjusted OR, 0.66; 95% CI, 0.41–1.05). In addition, advanced CKD patients tended to stay-at-home for shorter times even after adjusting for age (adjusted OR, 0.54; 95% CI, 0.33–0.88) (Table 4).

Factors associated with hygiene-related behaviors

Behaviors related to personal hygiene were related to age, education, and CKD stage, even though clear linearities were often unseen (Supplementary Table 4, available online). Hand sanitizer use was more frequent among people with higher education and higher income (Table 5). In addition, patients with higher income tended to perform laundry and house cleaning more frequently. The positive association between income and frequency of laundry remained significant after age adjustment (Table 5). The frequencies of handwashing and face mask use, however, were not influenced by any factors assessed in the present study.

The level of risk perception was not related to hygiene-related behaviors. In addition, CCI status was not associated with hygienic behaviors except for hand sanitizer use (Table 5). However, among patients with diabetes, the use of hand sanitizer was significantly decreased (OR, 0.47; 95% CI, 0.23–0.99), and the number of clothes used between
Laundering was significantly increased (OR, 0.46; 95% CI, 0.21–0.97) compared to non-diabetes patients even after adjustment for age (Table 5). Advanced CKD status showed a significant association only with the decreased frequency of showering (OR, 0.52; 95% CI, 0.29–0.93).

Factors associated with physical activities

In general, exercise behavior among CKD patients was not affected during the COVID-19 pandemic. Among those who had exercised regularly, the frequency of exercise was negatively associated with age (OR, 0.26; 95% CI, 0.09–0.74). Among those who took regular exercise, education (OR, 5.47; 95% CI, 1.22–24.62) and income (OR, 6.59; 95% CI, 1.84–23.68) status were positively associated with exercise (Supplementary Table 5, available online). The positive association of income remained significant even after adjustment for age in patients who took regular exercise (Table 6).

Table 3. Behavioral changes related to social distancing, hygiene, and exercise during COVID-19 pandemic compared with before the pandemic

<table>
<thead>
<tr>
<th>Factor</th>
<th>Category</th>
<th>No</th>
<th>Before</th>
<th>After</th>
<th>% increase</th>
<th>% decrease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Social distancing</td>
<td>Public places (time/wk)</td>
<td>306</td>
<td>2.3 ± 2.7</td>
<td>1.1 ± 2.2***</td>
<td>1.6</td>
<td>42.8</td>
</tr>
<tr>
<td></td>
<td>Public transport (time/wk)</td>
<td>306</td>
<td>1.9 ± 3.2</td>
<td>1.4 ± 3.1***</td>
<td>2.6</td>
<td>17.0</td>
</tr>
<tr>
<td></td>
<td>Personal transport (time/wk)</td>
<td>304</td>
<td>1.1 ± 2.0</td>
<td>1.1 ± 2.0</td>
<td>6.9</td>
<td>5.3</td>
</tr>
<tr>
<td></td>
<td>Stay-at-home (hr/day)</td>
<td>306</td>
<td>12.0 ± 5.7</td>
<td>13.5 ± 5.7***</td>
<td>34.0</td>
<td>1.6</td>
</tr>
<tr>
<td>Hygiene</td>
<td>Mask (time/wk)</td>
<td>306</td>
<td>1.0 ± 2.2</td>
<td>6.2 ± 1.7***</td>
<td>85.0</td>
<td>0.3</td>
</tr>
<tr>
<td></td>
<td>Hand sanitizer (time/wk)</td>
<td>306</td>
<td>1.4 ± 4.9</td>
<td>8.4 ± 9.4***</td>
<td>87.3</td>
<td>0.3</td>
</tr>
<tr>
<td></td>
<td>Clothes (time before laundry)</td>
<td>306</td>
<td>1.9 ± 1.1</td>
<td>2.0 ± 1.4</td>
<td>15.0</td>
<td>11.1</td>
</tr>
<tr>
<td></td>
<td>Laundry (time/wk)</td>
<td>306</td>
<td>3.3 ± 2.1</td>
<td>3.7 ± 2.1***</td>
<td>23.5</td>
<td>0.7</td>
</tr>
<tr>
<td></td>
<td>Cleaning the house (time/wk)</td>
<td>306</td>
<td>4.6 ± 2.5</td>
<td>5.0 ± 2.6***</td>
<td>22.5</td>
<td>1.3</td>
</tr>
<tr>
<td></td>
<td>Soap (time/day)</td>
<td>306</td>
<td>3.3 ± 3.6</td>
<td>6.1 ± 5.0***</td>
<td>80.4</td>
<td>1.3</td>
</tr>
<tr>
<td></td>
<td>Shower (time/day)</td>
<td>306</td>
<td>1.1 ± 0.7</td>
<td>1.3 ± 0.8***</td>
<td>19.9</td>
<td>0.3</td>
</tr>
<tr>
<td>Exercise</td>
<td>Total exercise (time/wk)</td>
<td>306</td>
<td>2.7 ± 2.8</td>
<td>2.5 ± 2.7</td>
<td>12.4</td>
<td>14.7</td>
</tr>
<tr>
<td></td>
<td>Irregular exercise (time/wk)</td>
<td>128</td>
<td>0.7 ± 1.3</td>
<td>0.9 ± 1.5</td>
<td>15.6</td>
<td>7.0</td>
</tr>
<tr>
<td></td>
<td>Regular exercise (time/wk)</td>
<td>178</td>
<td>4.1 ± 2.7</td>
<td>3.7 ± 2.8**</td>
<td>10.1</td>
<td>20.2</td>
</tr>
<tr>
<td></td>
<td>Exercise at gym (time/wk)</td>
<td>28</td>
<td>3.6 ± 1.9</td>
<td>2.5 ± 2.1*</td>
<td>14.3</td>
<td>42.9</td>
</tr>
<tr>
<td></td>
<td>Without diabetes (time/wk)</td>
<td>140</td>
<td>2.4 ± 2.4</td>
<td>2.1 ± 2.3*</td>
<td>9.3</td>
<td>17.1</td>
</tr>
<tr>
<td></td>
<td>With diabetes (time/wk)</td>
<td>166</td>
<td>2.9 ± 3.1</td>
<td>2.9 ± 3.0</td>
<td>15.1</td>
<td>12.7</td>
</tr>
<tr>
<td></td>
<td>CCI &lt; 4 (time/wk)</td>
<td>142</td>
<td>2.4 ± 2.4</td>
<td>2.0 ± 2.2*</td>
<td>9.2</td>
<td>19.0</td>
</tr>
<tr>
<td></td>
<td>CCI ≥ 4 (time/wk)</td>
<td>164</td>
<td>3.0 ± 3.1</td>
<td>3.0 ± 3.0</td>
<td>14.0</td>
<td>9.8</td>
</tr>
<tr>
<td></td>
<td>Early CKD (time/wk)</td>
<td>116</td>
<td>2.6 ± 2.6</td>
<td>2.4 ± 2.4</td>
<td>13.8</td>
<td>18.1</td>
</tr>
<tr>
<td></td>
<td>Advanced CKD (time/wk)</td>
<td>190</td>
<td>2.7 ± 2.9</td>
<td>2.6 ± 2.9</td>
<td>11.6</td>
<td>12.6</td>
</tr>
</tbody>
</table>

Data are expressed as number only, mean ± standard deviation, or percentage only.
CCI, Charlson comorbidity index; CKD, chronic kidney disease; COVID-19, coronavirus disease 2019.
Wilcoxon signed-rank test was conducted; *p < 0.05, **p < 0.01, ***p < 0.001.

Discussion

Among the participating patients with CKD, the COVID-19 pandemic significantly altered behavioral characteristics related to social distancing, hygiene, and physical activity. Since the outbreak of the COVID-19 pandemic, several observations on behavioral changes among chronic disease patients have been reported [15,16]; however, no reports have been made on CKD patients. Because such behavioral changes may influence the progress or prognosis of underlying diseases, including CKD and also COVID-19 infection, characterizing behavioral changes in patients has important clinical implications [5,6,8].

The participating patients with CKD showed a greater level of risk perception toward COVID-19 infection, i.e., >2 times greater proportion of the SKETCH cohort answered ‘serious’ or ‘very serious’ for the possibility of COVID-19 infection risk, compared to the general population of Korea. Several hygienic behaviors were also more frequently
Table 4. Behavioral changes related to social distancing by demographic and socioeconomic characteristics and comorbidities after age adjustment

<table>
<thead>
<tr>
<th>Variable</th>
<th>Frequency</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Using public transport (decreased)</td>
<td>OR (95% CI)</td>
<td>p-value</td>
<td>OR (95% CI)</td>
<td>p-value</td>
</tr>
<tr>
<td>Sex (Ref, male)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>1.68 (0.90–3.14)</td>
<td>0.12</td>
<td></td>
<td>1.01 (0.39–2.60)</td>
<td>0.99</td>
</tr>
<tr>
<td>Education (Ref, ≤elementary school)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Middle school</td>
<td>0.76 (0.28–2.09)</td>
<td>0.60</td>
<td></td>
<td>2.55 (0.44–14.94)</td>
<td>0.30</td>
</tr>
<tr>
<td>High school</td>
<td>0.94 (0.39–2.26)</td>
<td>0.88</td>
<td></td>
<td>3.13 (0.61–16.01)</td>
<td>0.17</td>
</tr>
<tr>
<td>≥College</td>
<td>0.94 (0.36–2.47)</td>
<td>0.90</td>
<td></td>
<td>0.80 (0.11–5.57)</td>
<td>0.82</td>
</tr>
<tr>
<td>Income (Ref, &lt;$1,000)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1,000–2,000</td>
<td>1.40 (0.61–3.20)</td>
<td>0.43</td>
<td></td>
<td>0.45 (0.09–2.33)</td>
<td>0.34</td>
</tr>
<tr>
<td>2,000–3,000</td>
<td>0.96 (0.33–2.82)</td>
<td>0.95</td>
<td></td>
<td>1.02 (0.22–4.76)</td>
<td>0.98</td>
</tr>
<tr>
<td>3,000–5,000</td>
<td>1.02 (0.37–2.82)</td>
<td>0.98</td>
<td></td>
<td>1.74 (0.45–6.65)</td>
<td>0.42</td>
</tr>
<tr>
<td>≥5,000</td>
<td>0.68 (0.22–2.13)</td>
<td>0.51</td>
<td></td>
<td>0.16 (0.02–1.60)</td>
<td>0.12</td>
</tr>
<tr>
<td>Risk perception (Ref, &lt;3)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥4</td>
<td>1.91 (1.01–3.60)</td>
<td>0.046*</td>
<td></td>
<td>0.96 (0.38–2.42)</td>
<td>0.92</td>
</tr>
<tr>
<td>CCI (Ref, &lt;4)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥4</td>
<td>0.96 (0.52–1.79)</td>
<td>0.90</td>
<td></td>
<td>1.28 (0.51–3.21)</td>
<td>0.60</td>
</tr>
<tr>
<td>Diabetes</td>
<td>0.64 (0.35–1.19)</td>
<td>0.16</td>
<td></td>
<td>1.49 (0.59–3.78)</td>
<td>0.40</td>
</tr>
<tr>
<td>CKD stage (Ref, early CKD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Advanced CKD</td>
<td>1.62 (0.83–3.15)</td>
<td>0.16</td>
<td></td>
<td>1.56 (0.58–4.19)</td>
<td>0.38</td>
</tr>
</tbody>
</table>

CCI, Charlson comorbidity index; CI, confidence interval; CKD, chronic kidney disease; OR, odds ratio; Ref, reference.

*OR = 304 (personal transport). *n = 303 (personal transport).

*p < 0.05.

Adopted among CKD patients than the general Korean population, for example, the use of face masks (100% vs. 63.2% in the general population) and hand hygiene (93.7% vs. 67.8% in the general population) during the first wave of the pandemic (February 2020) [17]. Risk perception is generally considered to be related to culture, worldview, experience, and prosocial values and is often amplified through friends and family [18]. The higher perceived risk of infection among the participating CKD patients may be partly due to the underlying disease; comorbidities were suggested as one key indicator that could increase the perception of risk [19].

Socioeconomic status including education, income (higher), and sex (female) are negatively correlated with unhealthy behaviors [20,21]. In addition, the severity of comorbidities is closely related to the tendency toward healthy behavior. Patients with more comorbidities tend to engage in more conservative behaviors for the sake of their health [22]. In United States adults (n = 6,463) from March to April 2020, hygiene-related behaviors such as handwashing and surface disinfection were more common among females and those older patients with higher income, higher education, and self-rated good health [21]. Except for self-rated health status, these findings are generally comparable to the observations made for the present CKD patients. Longer stay-at-home behavior among CKD patients may reflect higher levels of risk perception among these patients in comparison to the general population of Korea (Fig. 1B). Although the stage of CKD was inversely associated with increased stay-at-home time, it might be related to a discrepancy between risk perception and behavior change due to the worse socioeconomic and education status in advanced CKD patients.

The lack of significant changes in the frequencies of handwashing and face mask use by key socioeconomic factors such as education and income warrant further discussion because these factors have been recognized as drivers of healthy or conservative behaviors. Null associations with
Table 5. Behavioral changes related to hygiene by demographic and socioeconomic characteristics and comorbidities after age adjustment

<table>
<thead>
<tr>
<th>Variable</th>
<th>Handwashing (increased)</th>
<th>Shower (increased)</th>
<th>Face mask (increased)</th>
<th>Hand sanitizer (increased)</th>
<th>No. of clothes use before laundry (decreased)</th>
<th>Laundry (increased)</th>
<th>Home cleaning (increased)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>p-value</td>
<td>OR (95% CI)</td>
<td>p-value</td>
<td>OR (95% CI)</td>
<td>p-value</td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td>Sex (Ref, male)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>0.97 (0.53–1.79)</td>
<td>0.93 (0.73–2.39)</td>
<td>1.61 (0.78–3.34)</td>
<td>1.09 (0.52–2.26)</td>
<td>1.68 (0.80–3.52)</td>
<td>1.65 (0.95–2.86)</td>
<td>1.19 (0.67–2.12)</td>
</tr>
<tr>
<td>Education (Ref, ≤elementary school)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Middle school</td>
<td>0.72 (0.29–1.82)</td>
<td>0.49 (0.43–2.86)</td>
<td>1.10 (0.25–1.76)</td>
<td>0.66 (0.32–2.37)</td>
<td>0.88 (0.13–2.58)</td>
<td>0.57 (0.33–2.24)</td>
<td>0.86 (0.38–2.74)</td>
</tr>
<tr>
<td>High school</td>
<td>0.96 (0.40–2.32)</td>
<td>0.93 (0.42–2.38)</td>
<td>&gt;0.99 (0.72–5.64)</td>
<td>2.01 (1.14–10.45)</td>
<td>3.45 (0.29–3.16)</td>
<td>0.96 (0.51–2.65)</td>
<td>1.16 (0.46–2.70)</td>
</tr>
<tr>
<td>≥College</td>
<td>1.01 (0.39–2.63)</td>
<td>0.99 (0.30–2.06)</td>
<td>0.79 (0.48–3.96)</td>
<td>1.37 (0.70–6.36)</td>
<td>2.10 (0.40–4.63)</td>
<td>1.36 (0.41–2.48)</td>
<td>1.01 (0.40–2.64)</td>
</tr>
<tr>
<td>Income (Ref, &lt;$1,000)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1,000–2,000</td>
<td>1.54 (0.65–3.70)</td>
<td>0.33 (0.50–2.56)</td>
<td>1.13 (0.38–2.41)</td>
<td>0.95 (0.66–4.76)</td>
<td>1.78 (0.33–5.18)</td>
<td>1.30 (0.48–2.41)</td>
<td>1.07 (0.87–4.75)</td>
</tr>
<tr>
<td>2,000–3,000</td>
<td>0.99 (0.39–2.53)</td>
<td>0.98 (0.27–2.06)</td>
<td>0.74 (0.31–2.56)</td>
<td>0.89 (0.49–4.46)</td>
<td>1.48 (1.22–15.11)</td>
<td>4.38 (1.40–2.62)</td>
<td>1.02 (0.99–6.48)</td>
</tr>
<tr>
<td>3,000–5,000</td>
<td>1.49 (0.56–3.93)</td>
<td>0.42 (0.37–2.37)</td>
<td>0.94 (0.43–3.58)</td>
<td>1.24 (1.21–15.88)</td>
<td>4.38 (1.22–15.11)</td>
<td>2.14 (0.30–1.95)</td>
<td>0.77 (0.55–3.63)</td>
</tr>
<tr>
<td>≥5,000</td>
<td>1.21 (0.45–3.22)</td>
<td>0.71 (0.19–1.47)</td>
<td>0.53 (0.48–4.54)</td>
<td>1.48 (1.10–12.91)</td>
<td>3.76 (0.87–12.18)</td>
<td>3.26 (0.60–3.53)</td>
<td>1.46 (0.50–3.48)</td>
</tr>
<tr>
<td>Risk perception (Ref, &lt;3)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥4</td>
<td>0.86 (0.48–1.55)</td>
<td>0.62 (0.58–1.87)</td>
<td>1.04 (0.47–1.73)</td>
<td>0.90 (0.55–2.23)</td>
<td>1.10 (0.24–1.18)</td>
<td>0.53 (0.85–2.56)</td>
<td>0.89 (0.51–1.57)</td>
</tr>
<tr>
<td>CCI (Ref, &lt;4)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥4</td>
<td>0.58 (0.32–1.07)</td>
<td>0.08 (0.53–1.67)</td>
<td>0.94 (0.33–1.23)</td>
<td>0.64 (0.15–0.72)</td>
<td>0.33 (0.30–1.34)</td>
<td>0.64 (0.36–1.08)</td>
<td>0.75 (0.43–1.31)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>0.71 (0.40–1.28)</td>
<td>0.26 (0.50–1.58)</td>
<td>0.89 (0.54–1.94)</td>
<td>1.02 (0.23–0.99)</td>
<td>0.47 (0.41–1.20)</td>
<td>0.46 (0.41–1.20)</td>
<td>0.70 (0.52–1.56)</td>
</tr>
<tr>
<td>CKD stage (Ref, early CKD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Advanced CKD</td>
<td>0.65 (0.35–1.20)</td>
<td>0.166 (0.29–0.93)</td>
<td>0.52 (0.39–1.51)</td>
<td>0.77 (0.34–1.49)</td>
<td>0.72 (0.26–1.13)</td>
<td>0.55 (0.48–1.42)</td>
<td>0.72 (0.41–1.25)</td>
</tr>
</tbody>
</table>

CCI, Charlson comorbidity index; CI, confidence interval; CKD, chronic kidney disease; OR, odds ratio; Ref, reference.

*p < 0.05.
handwashing and face mask use remained the same regardless of age adjustment (Table 5). These observations can be explained by the almost unanimous use of face masks (100%) and much greater frequency of handwashing (86.3% vs. 67.8% among the general population [17]) in the present CKD patients regardless of socioeconomic status or sex.

Stringent social distancing or self-isolation may produce side effects such as physical inactivity, which may lead to other health issues [23]. In the United Kingdom, the prevalence of physical activity was found to be substantially lower in general among adults than before the pandemic, and this change was attributed to the requirement for self-isolation and stay-at-home orders [24]. Moreover, patients with comorbidities tended to be less physically active during the pandemic than the matching healthy population [25,26]. Unlike previous studies that reported notable decreases in physical activity, our findings showed that the physical activity of CKD patients in Korea was generally unaffected during the COVID-19 pandemic (Supplementary Fig. 3C). These observations indicate the target population to whom clinical recommendations for exercise should be delivered.

Physical activity is an important component in the management of kidney disease; it helps to reduce inflammation, improve glomerular filtration rate, and reduce albuminuria [12–14] and is often related to the quality of life in CKD patients [27]. Guidelines for adequate levels of exercise are therefore warranted for CKD patients, especially during the pandemic, which has led to reduced physical activities. One survey of patients with kidney transplantation in Germany showed that a telemedicine-based aftercare program could efficiently increase overall activity during the COVID-19 pandemic, although sports activities decreased [28]. This interesting observation may be attributable not only to an effective follow-up care program but also to the less strict social distancing policy of Germany that allowed outdoor physical activity [28]. Follow-up and intervention programs designed specifically for CKD patients to maintain or enhance physical activity are recommended for this vulnerable population during the pandemic when self-isolation is involved.

This study is the first report of the behavioral characteristics and changes among CKD patients during the COVID-19 pandemic in Korea. As a cross-sectional study of a group of CKD patients recruited via convenience sampling, the observations of this study may not be generalizable. In addition, there are limitations for exact comparison to general populations because of the restriction on the population with CKD. Finally, because of the structural limitations for

<table>
<thead>
<tr>
<th>Variable</th>
<th>Increased frequency</th>
<th>OR (95% CI)</th>
<th>p-value</th>
<th>OR (95% CI)</th>
<th>p-value</th>
<th>OR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (Ref, male)</td>
<td>Overall</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>0.63 (0.29–1.40)</td>
<td>0.26</td>
<td></td>
<td>0.65 (0.22–1.93)</td>
<td>0.44</td>
<td>0.66 (0.20–2.16)</td>
<td>0.496</td>
</tr>
<tr>
<td>Education (Ref, ≤middle school)</td>
<td>Overall</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High school</td>
<td>1.51 (0.62–3.66)</td>
<td>0.37</td>
<td></td>
<td>0.88 (0.29–2.67)</td>
<td>0.82</td>
<td>3.41 (0.66–17.73)</td>
<td>0.15</td>
</tr>
<tr>
<td>Income (Ref, &lt;$2,000)</td>
<td>Overall</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥$2,000</td>
<td>1.72 (0.77–3.85)</td>
<td>0.19</td>
<td></td>
<td>0.78 (0.27–2.28)</td>
<td>0.65</td>
<td>4.76 (1.18–19.21)</td>
<td>0.03*</td>
</tr>
<tr>
<td>Risk perception (Ref, &lt;3)</td>
<td>Overall</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥4</td>
<td>0.58 (0.27–1.21)</td>
<td>0.15</td>
<td></td>
<td>1.01 (0.37–2.75)</td>
<td>0.99</td>
<td>0.32 (0.10–1.05)</td>
<td>0.06</td>
</tr>
<tr>
<td>CCI (Ref, &lt;4)</td>
<td>Overall</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥4</td>
<td>2.10 (1.01–4.38)</td>
<td>0.048*</td>
<td></td>
<td>3.31 (1.09–10.00)</td>
<td>0.03*</td>
<td>1.35 (0.49–3.75)</td>
<td>0.56</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Overall</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CKD stage</td>
<td>1.96 (0.95–4.06)</td>
<td>0.07</td>
<td></td>
<td>2.61 (0.92–7.38)</td>
<td>0.07</td>
<td>1.51 (0.54–4.25)</td>
<td>0.43</td>
</tr>
<tr>
<td>Advanced CKD</td>
<td>Overall</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.87 (0.43–1.74)</td>
<td>0.69</td>
<td></td>
<td>1.30 (0.47–3.57)</td>
<td>0.61</td>
<td>0.53 (0.19–1.43)</td>
<td>0.21</td>
</tr>
</tbody>
</table>

Due to no observations for explanatory variable (frequency of exercise) in some age, education, household income groups, the groups were redefined. CCI, Charlson comorbidity index; CI, confidence interval; CKD, chronic kidney disease; OR, odds ratio; Ref, reference. *p < 0.05.
reflecting the different baseline characteristics between the subgroups in the logistic regression analysis, ordinary concepts were not applicable in some of the results. Despite presenting only a snapshot observation on CKD patients during this global pandemic, the results of this study can help health practitioners design relevant recommendations for CKD patients not only to reduce the likelihood of COVID-19 infection but also to maintain health-related behaviors.

Conflicts of interest

All authors have no conflicts of interest to declare.

Funding

This work was supported by Seoul National University Research Grant in 2020 (SRnD 800-20200496).

Acknowledgments

The authors thank the participating patients and clinical research coordinators for their contribution.

Authors’ contributions

Conceptualization: YK, IL, KC, JPL
Investigation: YK, JL, JYP, JNA, KDY, YCK, WYP, KJ, DKK
Data curation and Formal analysis: IL, YK, MY
Funding acquisition: JPL
Project administration: KC, JPL
Writing–original draft: YK
Writing–review & editing: All authors
All authors read and approved the final manuscript.

ORCID

Yaerim Kim, https://orcid.org/0000-0003-1596-1528
Inae Lee, https://orcid.org/0000-0002-9946-8652
Jeonghwan Lee, https://orcid.org/0000-0003-3199-635X
Jae Yoon Park, https://orcid.org/0000-0001-8986-7492
Jung Nam An, https://orcid.org/0000-0001-5108-1005
Kyung Don Yoo, https://orcid.org/0000-0001-6545-6517
Yong Chul Kim, https://orcid.org/0000-0003-3215-8681
Woo Yeong Park, https://orcid.org/0000-0003-2662-2898
Kyubok Jin, https://orcid.org/0000-0002-7836-8863
Younglim Kho, https://orcid.org/0000-0002-2590-4722
Myoungsoon You, https://orcid.org/0000-0001-9869-014X
Dong Ki Kim, https://orcid.org/0000-0002-5195-7852
Kyungho Choi, https://orcid.org/0000-0001-7460-792X
Jung Pyo Lee, https://orcid.org/0000-0002-4714-1260

References


Background: The limited literature on mental illness in end-stage kidney disease (ESKD) patients suggests that this disease is common and burdensome but underrecognized in clinical practice. This study aimed to analyze the prevalence of mental illness in ESKD patients.

Methods: We assessed the prevalence and patterns of mental illnesses in a nationwide cohort of patients diagnosed with ESKD between January 1, 2008, and December 31, 2017. The risk of mental illness was evaluated using a multivariable Cox proportional hazards model.

Results: A total of 70,079 patients met all study inclusion criteria. A total of 28.3% of patients had mental illness, and the specific distribution was as follows: depression, 16.8%; anxiety, 20.0%; somatoform/conversion disorder, 0.9%; stress reaction/adjustment disorder, 2.5%; and substance abuse disorder, 0.6%. The frequency of mental illness was highest in patients on hemodialysis (HD), followed by patients on peritoneal dialysis (PD) and kidney transplant (KT) patients. The peak rate of mental illness in HD and PD patients was reached 1 to 2 years after renal replacement therapy initiation, but the peak rate of most mental illnesses in KT patients occurred before surgery. The prevalence of depression was 2.19 times higher in HD patients and 1.97 times higher in PD patients than in KT patients.

Conclusion: ESKD patients are at high risk of mental illness, and the prevalence of mental illness is highest in HD patients. Since the onset of mental illness occurs around the initiation of renal replacement therapy, clinicians need to pay attention to mental illness when treating ESKD patients.

Keywords: Anxiety, Chronic kidney failure, Depression, Mental disorders
**Introduction**

Patients with end-stage kidney disease (ESKD) experience a higher rate of mental illness than the general adult population [1,2]. Beyond depression, patients might experience a myriad of psychological distress symptoms including anxiety and fear of chronic kidney disease (CKD) progression (concerns about hopelessness, death, and dying). They also might experience recurrent psychological and physical trauma during the CKD course [3].

Previous large-scale studies have investigated the incidence and severity of psychiatric symptoms in ESKD patients [4,5]. A comprehensive analysis of psychiatric illnesses in a large, adult ESKD population found that 8.9% of patients on dialysis were hospitalized with a primary or secondary psychiatric diagnosis [4]. A systematic review and meta-analysis found a 1.4%–94.9% prevalence of depression in patients on dialysis, with a summary prevalence estimate of 39.3% when depression was assessed by questionnaire and 22.8% when assessed by interview [5]. Moreover, psychiatric information on ESKD patients remains underrecognized in clinical practice [6–8].

There are few studies on the prevalence of mental illness related to ESKD in Koreans. Since research on the relationship between ESKD and mental illness remains insufficient, we aimed to analyze the characteristics and prevalence of mental illness and psychiatric disorders in ESKD patients using data from the Health Insurance Review and Assessment (HIRA) service, a national registry including all patients in Korea.

**Methods**

The Republic of Korea public medical insurance system, the National Health Insurance Services (NHIS), includes the HIRA database of all health care claims for outpatient or inpatient visits to medical institutions and includes patient demographics, diagnoses, procedures, and prescriptions [9]. We retrospectively analyzed a nationwide cohort of patients diagnosed with ESKD between January 1, 2007, and December 31, 2017, from the HIRA database. This study was performed in accordance with the Declaration of Helsinki and the Institutional Review Board of Ajou University Hospital approved this study (No. AJIRB-MED-EXP-18-499), and the requirement for informed consent was waived as the NHIS database is anonymized according to strict confidentiality guidelines. Moreover, the attending government organization approved access to the HIRA database (HIRA No. M20181212478).

**Assessment of end-stage kidney disease population**

We collected the data of patients with at least one diagnosis code of CKD (International Classification of Diseases, 10th Revision [ICD-10], N18.0–18.6, 18.9) from 2007 to 2017, in Korea. We then selected ESKD patients who were newly diagnosed since 2008, so that we could observe them for at least 1 year before initiation of dialysis or transplant. The date of initial dialysis or transplant was defined as the index date. We hypothesized that anticipation regarding kidney replacement therapy (KRT) could affect the mental states of patients even before they actually started treatment. In addition, we wanted to observe changes in patient mental health when facing KRT initiation rather than the prevalence of newly developed mental illness after KRT initiation. Therefore, the observation period was defined as 1 year before the index date up to December 31, 2017. ESKD patients were confirmed by special exemption codes (V001: hemodialysis, HD; V003: peritoneal dialysis, PD; and V005: kidney transplant, KT) provided by the Korean government. Based on the special exemption codes and procedure codes (HD: O7020, O7021, O9991; PD: O707; and KT: R3280) on health claims, we classified patients into three KRT modality groups; HD, PD, and KT. Patients with less than 3 months of dialysis history and those who changed dialysis modality were excluded. For KT patients, preemptive KT cases were included in the KT group. Changes included: 1) change from PD to HD; 2) change to PD after being on HD for more than 3 months; 3) change from KT to HD or PD due to graft failure; or 4) transplantation surgery 1 year after the first dialysis initiation (for KT patients). Patients with no procedure codes related to KRT modalities or those younger than 18 years at the index date were excluded [10].

Baseline comorbidities, defined using ICD-10 codes, were observed in the year prior to the index date. The diagnostic codes of comorbidities were as follows: diabetes mellitus, E10–E14; hypertension, I10–I15; cardiovascular disease, I20–I25; cerebrovascular disease, I60–I69; chronic lung disease, J40–J47; and chronic liver disease, K70.3, K71.3.
K70.4, K72.1, K73, and K74.

Assessment of mental illnesses

We assessed five mental illnesses separately: i) depression, ii) anxiety, iii) somatoform/conversion disorder, iv) stress reaction/adjustment disorder, and v) substance abuse disorder. Each mental illness was identified by ICD-10 codes: F32 and F33 for depression, F40 and F41 for anxiety, F44 and F45 for somatoform/conversion disorder, F43 for stress reaction/adjustment, and F10–F19 for substance abuse disorder [11–13]. Some patients experience co-occurring mental illnesses, so we created independent subcohorts for each mental illness to include all cases in the analysis. We examined all visits with a diagnosis code during the observation period and analyzed trends of mental illness prevalence over time.

Statistical analysis

We performed the analysis of variance for continuous variables and the chi-square test of homogeneity for categorical variables to compare baseline characteristics and the overall prevalence of mental illness between groups. For each KRT modality, the prevalence of each mental illness was presented as a percentage. We conducted McNemar test to examine any psychiatric prevalence changes before and after the index date by KRT modality. Density plots were used to observe the distribution of psychiatric visits over time, and the peaks indicated the highest patient prevalence. We assessed the risk of each mental illness using the Cox proportional hazards model with adjustments for age group and sex. Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated for each covariate. All statistical analyses were two-sided and performed using SAS version 9.4 (SAS Institute, Cary, NC, USA). A p-value of <0.05 was considered statistically significant.

Results

Baseline characteristics of ESKD cohort

The study flowchart is presented in Fig. 1. The data of 813,907 patients with a diagnosis code of ESKD were extracted from the HIRA database. Of those, 108,264 ESKD patients registered between 2008 and 2017, were selected. After excluding 38,185 patients based on the exclusion criteria, the final ESKD cohort comprised 70,079 patients, including 61,497 (87.8%) in the HD group, 3,901 (5.6%) in the KT group, and 4,681 (6.7%) in the PD group. Fig. 1 shows the mental illness distribution according to KRT modality. The baseline characteristics of the study population are described in Table 1. Patients were followed for 4.3 ± 2.4 years. Overall, the mean age at the index date was 60.6 ± 14.2 years. The HD group was the oldest (mean age, 62.1 ± 13.7 years), and most KT and PD patients were aged 40 to 59 years. ESKD was more prevalent in males (59.6%) than in females. During the year before the index date, anxiety was the most prevalent disorder, with the KT group showing the highest prevalence. Comorbidities observed in the year before the index date were common, especially in the HD group, and the most prevalent comorbidities were hypertension (94.7%) and diabetes mellitus (74.4%).

Mental illness by kidney replacement therapy modality

Among all ESKD patients, 19,823 (28.3%) had at least one psychiatric diagnosis code during the observation period. The most frequent mental illness was anxiety (14,033, 20.0%), followed by depression (11,797, 16.8%), stress reaction/adjustment disorder (1,776, 2.5%), somatoform/conversion disorder (626, 0.9%), and substance abuse disorder (399, 0.6%). This order of frequency remained the same for all KRT modalities. Anxiety was still the most prevalent mental illness (HD, 12,721 [20.7%]; KT, 524 [13.4%]; and PD, 788 [16.8%]), followed by depression (HD, 11,797, 16.8%), stress reaction/adjustment disorder (1,776, 2.5%), somatoform/conversion disorder (626, 0.9%), and substance abuse disorder (399, 0.6%). The frequencies of all mental illnesses, except for somatoform/conversion disorder, were highest in the HD group, followed by the PD and KT groups. The prevalence of somatoform/conversion disorder was higher in the KT group than in other groups (Fig. 2).

Changes in mental illness before and after end-stage kidney disease diagnosis

We assessed whether a significant change in the prevalence of mental illness had occurred before and after the index date (Supplementary Table 1, available online). Overall, ESKD patients had more mental illnesses after the index date than before, with 4.9 times more depression, 4.0 times...
more anxiety, 3.5 times more somatoform/conversion disorder, 2.9 times more stress reaction/adjustment disorder, and 2.0 times more substance abuse disorder (all p < 0.001). However, the prevalence of somatoform/conversion disorders in the KT group and substance abuse disorders in the KT and PD groups did not show significant change after the index date. The KT group showed the smallest change after the index date, while the HD group showed the largest change; 3% of the patients in the HD group had depression before the index date, but 16.0% had depression after the index date (p < 0.001).

**Frequency density of mental illnesses**

The frequency density plot of mental illness among ESKD patients is shown in Fig. 3. The overall frequency of mental illness started to increase 1 year before the index date. There was a distinct difference in the distribution of mental illnesses (Fig. 3). The KT group, except for substance abuse disorder patients, had the highest number of psychiatric visits prior to KT. In the HD group, substance abuse disorders peaked around 5 months and other mental illnesses around 2 years after dialysis initiation. In the PD group, most of the peak times for mental illnesses, excluding stress...
Table 1. Baseline characteristics of the end-stage kidney disease cohort

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Overall (n = 70,079)</th>
<th>HD (n = 61,497)</th>
<th>KT (n = 3,901)</th>
<th>PD (n = 4,681)</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follow-up (yr)</td>
<td>4.3 ± 2.4</td>
<td>4.2 ± 2.4</td>
<td>4.4 ± 2.3</td>
<td>4.5 ± 2.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age at index date (yr)</td>
<td>60.6 ± 14.2</td>
<td>62.1 ± 13.7</td>
<td>45.0 ± 11.7</td>
<td>53.9 ± 13.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>18–39</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>40–59</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥60</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male sex</td>
<td>41,777 (59.6)</td>
<td>36,842 (59.9)</td>
<td>2,291 (58.7)</td>
<td>2,644 (56.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes</td>
<td>46,649 (66.6)</td>
<td>41,934 (68.2)</td>
<td>1,814 (46.5)</td>
<td>2,901 (62.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>64,299 (91.8)</td>
<td>56,258 (91.5)</td>
<td>3,722 (95.4)</td>
<td>4,319 (92.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>18,085 (25.8)</td>
<td>16,257 (26.4)</td>
<td>639 (16.4)</td>
<td>1,189 (25.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cerebrovascular</td>
<td>11,671 (16.7)</td>
<td>10,961 (17.8)</td>
<td>220 (5.6)</td>
<td>490 (10.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Chronic lung disease</td>
<td>15,937 (22.7)</td>
<td>14,594 (23.7)</td>
<td>594 (15.2)</td>
<td>749 (16.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Chronic liver disease</td>
<td>3,219 (4.6)</td>
<td>2,956 (4.8)</td>
<td>81 (2.1)</td>
<td>182 (3.9)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Comorbidities and psychiatric disorders observed during the observation period, which was 1 year before initiation of renal replacement therapy to December 31, 2017.

Data are expressed as mean ± standard deviation or number (%).
HD, hemodialysis; KT, kidney transplant; PD, peritoneal dialysis.

*p-value was based on the analysis of variance test; otherwise, the chi-square test was used.

Figure 2. Mental illnesses in end-stage kidney disease patients by kidney replacement therapy.
KRT, kidney replacement therapy; HD, hemodialysis; KT, kidney transplant; PD, peritoneal dialysis.
Figure 3. Frequency density of (A) all visits and (B) the first visit with mental illness by kidney replacement therapy in the end-stage kidney disease cohort.

KRT, kidney replacement therapy; HD, hemodialysis; KT, kidney transplant; PD, peritoneal dialysis.
reaction/adjustment disorder, were reached around 1 year after KRT initiation.

Frequency density plots were constructed from the frequency of the first onset of mental illnesses (Fig. 3B). The most common time to receive the first treatment for most mental illnesses was within 1 to 2 months before or after initiation of KRT, the transitional period. A higher frequency of depression, anxiety, and stress reaction/adjustment disorder around KRT initiation was noted. The computed peak time of each density plot is provided in Supplementary Table 2 (available online).

Hazard ratio of mental illnesses

The age- and sex-adjusted risk of depression was higher in the HD (adjusted HR [aHR], 2.19; 95% CI, 1.95–2.46; p < 0.001) and PD (aHR, 1.97; 95% CI, 1.73–2.26; p < 0.001) groups than in the KT group. With age, the risk of depression increased significantly, and patients older than 60 years had a 1.27-times higher risk than those younger than 40 years (p < 0.001). Depression was significantly more common in males than in females (aHR, 1.17; 95% CI, 1.128–1.216; p < 0.001). For anxiety, the HD (aHR, 1.64; 95% CI, 1.50–1.80; p < 0.001) and PD (aHR, 1.22; 95% CI, 1.09–1.35; p < 0.001) groups had a significantly higher risk than the KT group. Patients aged 40 to 59 years had a 1.11-times higher risk of anxiety than did younger patients (p = 0.002). Similar to depression, males had a higher risk of anxiety than females (aHR, 1.20; 95% CI, 1.16–1.24; p < 0.001). The HD group was at the highest risk for stress reaction/adjustment and substance abuse disorders. The KT group was at the lowest risk for most mental illnesses. However, the somatoform/conversion disorder risk was exceptionally high in the KT group, 1.7 times higher than that in the PD group (p = 0.04).

Discussion

In our study, the prevalence of mental illnesses was 28.3% in ESKD patients, with anxiety (20.0%) and depression (16.8%) being the most common. The prevalence of mental illness was highest in HD patients, followed by PD and KT patients. Since many ESKD patients seek mental illness-related treatment before and after initiation of KRT, it is necessary to pay attention to mental illnesses at the initiation of KRT. Diagnosis and treatment for ESKD can induce emotional stress, which can affect the prognosis of the disease [14,15]. Mental illness can be both a consequence of life on dialysis and a root cause of CKD and ESKD. The lack of self-care and energy that characterize depression has detrimental effects on patients’ ability to cope with the disease.

The prevalence of depression in a sampled population of one million individuals in South Korea, was 5.3% in 2013 [16], and the prevalence of depression was 6.7% from the 2014 Korea National Health and Nutrition Examination Survey [17]. However, previous studies of mental illness in ESKD patients showed a higher prevalence of mental illnesses. Chilcot et al. [18] reported that 20% to 30% of ESKD patients have significant depressive symptoms, which is higher than the lifetime prevalence of depression of approximately 6.9% observed in the general population and the mean prevalence of approximately 17% seen in cancer patients [19–21]. The prevalence of psychiatric morbidity in our ESKD cohort was 28.3%. Many previous studies have reported a higher prevalence of mental illness than ours. One Brazilian study reported a psychiatric morbidity rate of 46.4% in patients undergoing dialysis and demonstrated that psychiatric disorders can negatively impact the quality of life and treatment compliance [22]. Kim [23] reported in 2010, that the prevalence of depression, anxiety, and concomitant depression and anxiety was 58.5%, 27.9%, and 26.0%, respectively. In the HD group in our study, the anxiety and depression rates were 20.7% and 17.4%, respectively. In the previous studies [22,23], all patients underwent the Mini International Neuropsychiatric Interview or Hospital Anxiety and Depression Scale as a screening test at a single HD center to directly evaluate mental illness. In our study, we identified patients treated for mental illness using a claims database. Hence, mental illness is not difficult to recognize, and it is possible that treatment might have been insufficient compared to the actual prevalence.

The prevalence of mental illness differs according to KRT modality, and the timing at which it occurs also differs, particularly in the case of HD patients where the change in mental illness before and after dialysis was most obvious. Once ESKD is diagnosed, patients are subject to many stressors. They spend at least 3 days/week in a dialysis center or in a hospital for about 4 hours each session, they undergo dietary and lifestyle changes, and they need to manage their daily life on dialysis and a root cause of CKD and ESKD. The lack of self-care and energy that characterize depression has detrimental effects on patients’ ability to cope with the disease.
trips to the dialysis unit, in addition to considering possible family relocations and financial restrictions. Since HD patients visit the hospital three times a week and have higher contact with dialysis unit staff compared to patients on other KRT modalities, more active monitoring of HD patients by dialysis unit staff is required [24].

In this study, the prevalence of depression and anxiety was high within 1 to 2 years of dialysis, and the peak time of the first treatment was within 1 to 2 months of dialysis. Some patients undergo planned dialysis at KRT initiation, but others require urgent dialysis. In urgent cases, the stress of not only the patient, but also the medical staff is significant, and mental health aspects are likely to be overlooked. Therefore, nephrologists also need to pay more attention to the mental health aspects.

### Table 2. Hazard ratios of mental illnesses from the multivariable Cox proportional hazards model in the end-stage kidney disease cohort (n = 70,079)

<table>
<thead>
<tr>
<th>Psychiatric disorder</th>
<th>Parameter</th>
<th>HR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depression</td>
<td>KRT</td>
<td>2.19 (1.95–2.46)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>HD</td>
<td>1.97 (1.73–2.26)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>KT</td>
<td>1.27 (1.18–1.36)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Age group (yr)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>18–39</td>
<td>1.17 (1.09–1.26)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>40–59</td>
<td>1.17 (1.13–1.22)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>60+</td>
<td>1.17 (1.13–1.22)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Male sex</td>
<td>1.17 (1.13–1.22)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Anxiety</td>
<td>KRT</td>
<td>1.64 (1.50–1.80)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>HD</td>
<td>1.22 (1.09–1.35)</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>PD</td>
<td>1.22 (1.09–1.35)</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>KT</td>
<td>1.22 (1.09–1.35)</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>Age group (yr)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>18–39</td>
<td>1.11 (1.04–1.18)</td>
<td>0.002</td>
</tr>
<tr>
<td></td>
<td>40–59</td>
<td>1.11 (1.04–1.18)</td>
<td>0.002</td>
</tr>
<tr>
<td></td>
<td>60+</td>
<td>1.11 (1.04–1.18)</td>
<td>0.002</td>
</tr>
<tr>
<td></td>
<td>Male sex</td>
<td>1.11 (1.04–1.18)</td>
<td>0.002</td>
</tr>
<tr>
<td>Somatoform/conversion disorder</td>
<td>KRT</td>
<td>0.96 (0.70–1.32)</td>
<td>0.80</td>
</tr>
<tr>
<td></td>
<td>PD</td>
<td>0.60 (0.38–0.97)</td>
<td>0.04</td>
</tr>
<tr>
<td></td>
<td>KT</td>
<td>0.60 (0.38–0.97)</td>
<td>0.04</td>
</tr>
<tr>
<td></td>
<td>Age group (yr)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>18–39</td>
<td>0.98 (0.76–1.26)</td>
<td>0.87</td>
</tr>
<tr>
<td></td>
<td>40–59</td>
<td>0.98 (0.76–1.26)</td>
<td>0.87</td>
</tr>
<tr>
<td></td>
<td>60+</td>
<td>0.98 (0.76–1.26)</td>
<td>0.87</td>
</tr>
<tr>
<td></td>
<td>Male sex</td>
<td>0.98 (0.76–1.26)</td>
<td>0.87</td>
</tr>
<tr>
<td>Stress reaction/adjustment disorder</td>
<td>KRT</td>
<td>1.67 (1.29–2.15)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>PD</td>
<td>0.99 (0.72–1.39)</td>
<td>0.98</td>
</tr>
<tr>
<td></td>
<td>KT</td>
<td>0.99 (0.72–1.39)</td>
<td>0.98</td>
</tr>
<tr>
<td></td>
<td>Age group (yr)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>18–39</td>
<td>0.99 (0.76–1.06)</td>
<td>0.19</td>
</tr>
<tr>
<td></td>
<td>40–59</td>
<td>0.99 (0.76–1.06)</td>
<td>0.19</td>
</tr>
<tr>
<td></td>
<td>60+</td>
<td>0.99 (0.76–1.06)</td>
<td>0.19</td>
</tr>
<tr>
<td></td>
<td>Male sex</td>
<td>0.99 (0.76–1.06)</td>
<td>0.19</td>
</tr>
<tr>
<td>Substance abuse disorder</td>
<td>KRT</td>
<td>2.40 (1.31–4.38)</td>
<td>0.004</td>
</tr>
<tr>
<td></td>
<td>PD</td>
<td>1.84 (0.90–3.77)</td>
<td>0.10</td>
</tr>
<tr>
<td></td>
<td>KT</td>
<td>1.84 (0.90–3.77)</td>
<td>0.10</td>
</tr>
<tr>
<td></td>
<td>Age group (yr)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>18–39</td>
<td>1.22 (0.86–1.73)</td>
<td>0.28</td>
</tr>
<tr>
<td></td>
<td>40–59</td>
<td>1.22 (0.86–1.73)</td>
<td>0.28</td>
</tr>
<tr>
<td></td>
<td>60+</td>
<td>1.22 (0.86–1.73)</td>
<td>0.28</td>
</tr>
<tr>
<td></td>
<td>Male sex</td>
<td>1.22 (0.86–1.73)</td>
<td>0.28</td>
</tr>
</tbody>
</table>

HR, hazard ratio; CI, confidence interval; HD, hemodialysis; KT, kidney transplant; KRT, kidney replacement therapy; PD, peritoneal dialysis; Ref, reference group.
illness aspects around the timing of KRT initiation.

KT is considered the most effective treatment for ESKD patients. In addition to somatic benefits, such as reduced cardiovascular risk and overall mortality, patients also appear to benefit regarding individual health-related quality of life. However, transplantation is a very demanding and particularly stressful event that requires the patient to implement his biopsychosocial skills to accept and integrate the new organ physically and mentally. Therefore, KT involves numerous psychological, existential, affective, relational, and social changes for the patients and their families [25,26]. During the pre-evaluation prior to KT surgery, there is intervention with social work teams and psychiatrists. Therefore, it might be easier to assess mental illness in KT patients than in HD or PD patients. Among KT patients in our study, the depression and anxiety rates were 8.5% and 13.4%, respectively, representing the most common mental illnesses in this group. Other studies have reported anxiety and depression as the most likely disorders in KT recipients to influence disease process and graft survival [27]. To improve the quality of life of recipients, the management of mental illness is important because sufficient attention to treatment compliance, including drug compliance, is required.

One interesting result was that the prevalence of mental illnesses such as depression and anxiety, which usually is higher in women than in men in the general population [28–30], was higher in male ESKD patients in this study. Males had a 1.17 times higher risk of depression, 1.20 times higher risk of anxiety, and 3.3 times higher risk of substance abuse disorder than females. In another study of ESKD patients, there was no significant sex difference in the prevalence of mental illness [31]. In a United States ESKD study, the rates of depression and anxiety were higher in women than in men, although alcohol-related mental disorders were more prevalent in men than in women [32]. Compared to other studies, ours showed that Korean ESKD men have a higher prevalence of depression and anxiety than Korean women. This is probably because, in Korea, there is a more male-dependent home economic structure than in Western countries, so depression and anxiety occur due to physical and social constraints [33,34].

Although our study did not analyze mortality of ESKD patients, previous studies have reported that mental illness is associated with quality of life and/or mortality [35–39]. Patient nonadherence and psychological distress are highly prevalent among ESRD patients, and both contribute to greater morbidity and earlier mortality in this population. The number of patients with ESKD is increasing gradually [40,41]. Therefore, further studies should be conducted to evaluate more clearly the effectiveness of psychological interventions and to clarify the role of depression and social support on patient mortality.

There are a few limitations to this study. First, we examined mental illness cases using HIRA claims data, which offered only codes and demographic information. Clinical data (laboratory data), social data (educational data, marital status), and psychosocial factors were not available. Second, the disease code was based on claims data based on the treatment environment and was not created for a research setting. Moreover, the diagnostic accuracy of mental illness using ICD codes is not as high as that of structured clinical interviews using questionnaires. Furthermore, the diagnostic codes for mental illness can be influenced by medications, such as antidepressants prescribed for insomnia. Also, nephrologists tend to use psychiatric drugs frequently for controlling itching and pain in ESKD patients. However, in Korea, there is a tendency to refuse treatment for fear of being labeled mentally ill [42]. Therefore, diagnoses of mental illnesses are made very conservatively, which can compensate for the potential biases that would have arisen if patients had comorbid psychiatric disorders or symptoms. Third, the analysis was conducted under the assumption that the date of input of the diagnosis code was the actual diagnosis date of mental illness. Time discrepancies occur between diagnoses entered in the data and diseases that a patient has in reality, and this can be a source of limitation of HIRA data. Fourth, since the observation period was defined as 1 year before KRT initiation to December 31, 2017, there is a limitation in not considering the period of mental illness.

The strengths of our study are that it was a 10-year nationwide study of the entire population and an assessment of the prevalence of mental illness in ESKD patients according to KRT modality. To supplement the limited data of our study, further studies are needed to clarify mental illnesses based on the Diagnostic and Statistical Manual of Mental Disorders (DSM), prescribed psychiatric medications, and mortality. Furthermore, proper approaches for therapeutic interventions must be identified. Randomized,
controlled treatment trials in patients with ESKD are needed, as mental health is a modifiable risk factor for poor outcomes that nephrologists and mental health care workers can address.

In conclusion, ESKD patients have a high prevalence of mental illness, and HD patients have a higher prevalence of mental illness than do PD and KT patients. Furthermore, since there are many cases of mental illness-related treatment around KRT initiation, we must pay attention to mental illness as well as physical problems when treating ESKD patients.

Conflicts of interest

All authors have no conflicts of interest to declare.

Funding

This study was supported by research grants from Dae-won Pharmaceutical Company and the National Research Foundation of Korea (2019R1G1A1100671). The study sponsors had no role in study design, analysis, or interpretation of data.

Authors’ contributions

Conceptualization: PI, PB
Data curation: MJL
Formal analysis: EL
Funding acquisition: PI
Investigation: EL
Writing—original draft: MJL, EL
Writing—review & editing: PI, PB, MJL
All authors read and approved the final manuscript.

ORCID

Min-Jeong Lee, https://orcid.org/0000-0002-2611-7333
Eunyoung Lee, https://orcid.org/0000-0002-9440-9119
Bumhee Park, https://orcid.org/0000-0002-5271-1571
Inwhee Park, https://orcid.org/0000-0002-9912-5393

References


Effect of shared decision-making education on physicians’ perceptions and practices of end-of-life care in Korea

Byung Chul Yu¹, Miyeun Han², Gang-Jee Ko³, Jae Won Yang⁴, Soon Hyo Kwon⁵, Sungjin Chung⁶, Yu Ah Hong⁷, Young Youl Hyun⁸, Jang-Hee Cho⁹, Kyung Don Yoo¹⁰, Eunjin Bae¹¹, Woo Yeong Park¹², In O Sun¹³, Dongryul Kim¹⁴, Hyunsuk Kim¹⁵, Won Min Hwang¹⁶, Sang Heon Song¹⁷, Sung Joon Shin¹⁸

For further information for the authors' affiliations, see Additional information.

Background: Evidence of the ethical appropriateness and clinical benefits of shared decision-making (SDM) are accumulating. This study aimed to not only identify physicians’ perspectives on SDM, and practices related to end-of-life care in particular, but also to gauge the effect of SDM education on physicians in Korea.

Methods: A 14-item questionnaire survey using a modified Delphi process was delivered to nephrologists and internal medicine trainees at 17 university hospitals.

Results: A total of 309 physicians completed the survey. Although respondents reported that 69.9% of their practical decisions were made using SDM, 59.9% reported that it is not being applied appropriately. Only 12.3% of respondents had received education on SDM as part of their training. The main obstacles to appropriate SDM were identified as lack of time (46.0%), educational materials and tools (29.4%), and education on SDM (24.3%). Although only a few respondents had received training on SDM, the proportion of those who thought they were using SDM appropriately in actual practice was high; the proportion of those who chose lack of time and education as factors that hindered the proper application of SDM was low.

Conclusion: The majority of respondents believed that SDM was not being implemented properly in Korea, despite its use in actual practice. To improve the effectiveness of SDM in the Korean medical system, appropriate training programs and supplemental policies that guarantee sufficient application time are required.

Keywords: Clinical decision-making, End-of-life care, Life-sustaining treatment, Patient-centered care, Physician preference, Shared decision-making
**Introduction**

Shared decision-making (SDM) is a process by which patients and healthcare providers share the best available evidence and contribute to medical decisions under the mutual agreement [1]. Patients and physicians consider appropriate treatment options and make decisions together and share responsibility for the final decision [2,3].

Since Veatch [4] introduced the concept of “sharing of decision-making” in 1972, many studies on the efficacy of SDM in clinical practice have been conducted. Medical SDM is associated with improvement of treatment compliance, patient satisfaction, and patient quality of life [5–7]. In addition, SDM improves patients’ knowledge of treatment options and reduces conflict in the decision-making process related to uncertainty about their own values. Moreover, it encourages patients to play a more active role in the decision-making process and improve their awareness of associated risks [8–10]. Systematic reviews of SDM-related patient preferences and physicians’ perceptions have revealed that interest in SDM is increasing, with SDM now the preferred decision-making method of most patients and physicians [11,12]. As evidence of ethical adequacy and clinical effectiveness accumulates, many countries are policing the application of the SDM approach [13,14]. Various strategies for the effective adoption and application of SDM have been studied. Among these strategies, SDM education for health-care professionals has been the most studied and, although its effectiveness has shown heterogeneous results, is relatively effective [15,16].

Korea’s Act on Decisions on Life-Sustaining Treatment for Patients in Hospice and Palliative Care or at the End-of-Life came into effect in February 2018. The law allows life-sustaining treatment (LST) to be withdrawn or withheld based on the decision of the patient or his or her legal representative. However, the current law does not mention a specific decision-making method; its purpose is to respect and guarantee the patient’s right to make decisions about LST. A “good death,” based on the patient’s preferences, wishes, and needs, is the goal of the Act. It has been suggested that SDM is related strongly to “good death” in providing end-of-life care [17,18]. Because SDM can have an effect on the decision to withdraw or withhold LST, it has assumed importance in Korea.

SDM remains an unfamiliar concept in the Korean medical system. Although a few studies of the perspectives of nephrologists on decision-making about end-of-life care, including LST and palliative care, have been conducted [19,20], no nationwide survey of the perspectives of nephrologists regarding SDM and the effect of SDM education on decision-making regarding end-of-life care has been conducted in Korea. The purpose of this study is to identify clinical attitudes and experiences of nephrologists and internal medicine trainees related to SDM in decision-making—including decisions related to LST—and to determine the current status of and barriers to SDM, focusing on the effect of SDM education.

**Methods**

**Study population**

We conducted a cross-sectional survey of internal medicine residents, fellows, and professors in nephrology at 17 university hospitals. All participants were members of the Korean Society of Geriatric Nephrology. The survey period ranged from January 1 to August 31, 2020. The study was conducted in accordance with the principles of the Declaration of Helsinki, and clinical data from patients were obtained after approval of the Institutional Review Board of Daejeon St. Mary’s Hospital (No. DC19QEDI0085). As the residents and fellows were interacting with vulnerable participants who might have been concerned about the disadvantages of refusing to participate in the study, the current study was conducted with consent exemption. In addition, the following measures were performed to protect vulnerable participants: 1) the purpose and methods of the study were supplied to the survey participants at an open presentation; 2) the location of copies of the questionnaires was made known to the survey participants in advance; and 3) participants were given a one-week response time and advised of the location of the questionnaire collection box in advance.

**Questionnaire development process**

This study was designed as part of the project to identify the perspectives and attitudes of SDM among Korean physicians on end-of-life care. The other element of the study involved medical oncologists and residents of in-
ternal medicine (NECA-NA-19-008). The questionnaire development process is described elsewhere [21]. Briefly, it followed a three-round modified Delphi process, which is a well-known method for identifying collective opinions of experts [22]. The Delphi process is characterized by anonymity among participants, iterative feedback of group opinion, aggregation of group response, and expert input. A panel of six experts discussed survey items in round 1 after reviewing the relevant legislation on LST and published articles on the perspectives of physicians regarding SDM in various medical decisions, including LST. Selecting the questionnaire items related to attitudes toward SDM centered on the decision to withhold or withdraw of LST. Round 1 involved a panel of six experts discussing survey items. In rounds 2 and 3, researchers participated in online and offline meetings to modify and select appropriate questionnaire items through discussion and agreement. A final questionnaire item was adopted if the content validity index was deemed appropriate after an in-depth review of its clarity, accuracy, understandability, and suitability for research purposes by experts in law, medical ethics, and palliative care medicine [23].

**Questionnaire configuration items**

In the introduction on the first page of the questionnaire, an explanation of the purpose and method of the current study and a statement guaranteeing the confidentiality of respondents were supplied. The following virtual-patient example was provided before respondents chose the “usual” decision-making method: “A 40-year-old man is diagnosed with an illness and is going to be treated. There are two treatment options; both have the same survival rate but different benefits and harms. What is the best decision-making method from your perspective?” The decision-making methods from which respondents could choose are presented as detailed explanations of nameless concepts: paternalistic, informative, interpretative, and SDM. The paternalistic approach was defined as determining the patients’ clinical situation independent of their values and presenting them with evidence supporting the treatment decision. SDM was defined as discussing the patients’ health-related values with them and deliberating together using evidence-based information to decide on their treatment plan. The informative approach was defined as using evidence-based information to help the patients understand their health conditions and all possible treatment options so they can choose a treatment plan based on their values. The interpretative approach was defined as helping the patients understand their personal values and suggesting evidence-based treatment options that fit those values [1]. The survey comprised two sections: participant demographics (eight items and a total of 10 questions) and attitude toward SDM and a decision to withhold or withdraw of LST (seven items and a total 16 of questions including four open questions).

**Statistical analyses**

Descriptive characteristics of the study population were reported as means ± standard deviations and as frequency counts with percentages for categorical and binary variables. Comparisons of differences between groups were made using Mann-Whitney and Kruskal-Wallis tests for continuous variables and either chi-square tests or linear-by-linear association for categorical variables, as appropriate. The survey included some questions in which multiple options could be selected, and the number of answers to every item did not always sum to 100%. All statistical tests were two-sided, and the results were presented with 95% confidence intervals. We considered the p-values less than 0.05 to indicate statistical significance. All analyses were performed using IBM SPSS version 25 for Windows (IBM Corp., Armonk, NY, USA) or Graphpad Prism5 (GraphPad, Inc., La Jolla, CA, USA).

**Results**

**Study population**

Of the 342 questionnaires distributed, 321 were completed and returned, for a response rate of 93.9%. The authors reviewed missing data in detail and determined that each missing variable and the reason for absence were not related. The respondents with missing responses were excluded from the analysis, leaving 309 respondents in the final study group.

Of these respondents, 174 (56.3%) were male, and 178 (57.6%) were between 30 and 39 years of age. There were 226 residents (73.1%), followed by 51 professors (16.5%)
and 32 fellows (10.4%). Professors were grouped into neprologists (n = 51) and compared with trainees (fellows and residents, n = 258). When respondents were asked how many patients (both outpatients and inpatients) they treated in the week previous to filling out the questionnaire, most (46.6%) answered 20 to 49. When asked how many decisions they made for their patients according to the Act on Decisions on Life-Sustaining Treatment for Patients in Hospice and Palliative Care or at the End-of-Life in the last week, 67.0% answered fewer than 2 (Table 1). Respondents were divided into educated (n = 38) and non-educated (n = 271) groups based on whether they had received SDM education as part of their training. Those who reported that they did not receive SDM education or were not sure were assigned to the non-educated group. No differences in sex, age, and position were evident between the two groups, but the proportion of respondents who reported having received SDM was higher among trainees than among neprologists (p = 0.047) (Table 1).

Patterns in the decision-making process among physicians

After reading the virtual-patient example, the most “usual”

Table 1. Demographics of the questionnaire respondents

<table>
<thead>
<tr>
<th>Variable</th>
<th>Overall</th>
<th>Educated</th>
<th>Non-educated</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of respondents</td>
<td>309</td>
<td>38</td>
<td>271</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>174 (56.3)</td>
<td>26 (68.4)</td>
<td>148 (54.6)</td>
<td>0.12a</td>
</tr>
<tr>
<td>Female</td>
<td>135 (43.7)</td>
<td>12 (31.6)</td>
<td>123 (45.4)</td>
<td></td>
</tr>
<tr>
<td>Age (yr)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;30</td>
<td>90 (29.1)</td>
<td>14 (36.8)</td>
<td>76 (28.0)</td>
<td></td>
</tr>
<tr>
<td>30–39</td>
<td>178 (57.6)</td>
<td>22 (57.9)</td>
<td>156 (57.6)</td>
<td></td>
</tr>
<tr>
<td>40–49</td>
<td>26 (8.4)</td>
<td>1 (2.6)</td>
<td>25 (9.2)</td>
<td></td>
</tr>
<tr>
<td>50–59</td>
<td>9 (2.9)</td>
<td>1 (2.6)</td>
<td>8 (3.0)</td>
<td></td>
</tr>
<tr>
<td>60–65</td>
<td>6 (1.9)</td>
<td>0 (0)</td>
<td>6 (2.2)</td>
<td></td>
</tr>
<tr>
<td>Position</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Resident (1st/2nd grade)</td>
<td>148 (47.9)</td>
<td>16 (42.1)</td>
<td>132 (48.7)</td>
<td>0.41b</td>
</tr>
<tr>
<td>Resident (3rd/4th grade)</td>
<td>78 (25.2)</td>
<td>15 (39.5)</td>
<td>63 (23.2)</td>
<td></td>
</tr>
<tr>
<td>Fellow</td>
<td>32 (10.4)</td>
<td>5 (13.2)</td>
<td>27 (10.0)</td>
<td></td>
</tr>
<tr>
<td>Professor</td>
<td>51 (16.5)</td>
<td>2 (5.3)</td>
<td>49 (18.1)</td>
<td></td>
</tr>
<tr>
<td>Position group</td>
<td></td>
<td></td>
<td></td>
<td>0.047b</td>
</tr>
<tr>
<td>Trainee</td>
<td>258 (83.5)</td>
<td>36 (94.7)</td>
<td>222 (81.9)</td>
<td></td>
</tr>
<tr>
<td>Neprologist</td>
<td>51 (16.5)</td>
<td>2 (5.3)</td>
<td>49 (18.1)</td>
<td></td>
</tr>
<tr>
<td>No. of patients treated by respondent (/wk)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;20</td>
<td>53 (17.2)</td>
<td>7 (18.4)</td>
<td>46 (17.0)</td>
<td>0.54b</td>
</tr>
<tr>
<td>20–49</td>
<td>144 (46.6)</td>
<td>20 (52.6)</td>
<td>124 (45.8)</td>
<td></td>
</tr>
<tr>
<td>50–79</td>
<td>54 (17.5)</td>
<td>5 (13.2)</td>
<td>49 (18.1)</td>
<td></td>
</tr>
<tr>
<td>80–99</td>
<td>18 (5.8)</td>
<td>1 (2.6)</td>
<td>17 (6.3)</td>
<td></td>
</tr>
<tr>
<td>≥100</td>
<td>40 (12.9)</td>
<td>5 (13.2)</td>
<td>35 (12.9)</td>
<td></td>
</tr>
<tr>
<td>No. of patients who made decisionsc (/wk)</td>
<td></td>
<td></td>
<td></td>
<td>0.48b</td>
</tr>
<tr>
<td>&lt;2</td>
<td>207 (67.0)</td>
<td>28 (73.7)</td>
<td>179 (66.1)</td>
<td></td>
</tr>
<tr>
<td>2–5</td>
<td>92 (29.8)</td>
<td>9 (23.7)</td>
<td>83 (30.6)</td>
<td></td>
</tr>
<tr>
<td>5–7</td>
<td>5 (1.6)</td>
<td>0 (0)</td>
<td>5 (1.8)</td>
<td></td>
</tr>
<tr>
<td>7–10</td>
<td>4 (1.3)</td>
<td>1 (2.6)</td>
<td>3 (1.1)</td>
<td></td>
</tr>
<tr>
<td>≥10</td>
<td>1 (0.3)</td>
<td>0 (0)</td>
<td>1 (0.4)</td>
<td></td>
</tr>
</tbody>
</table>

Data are expressed as number only or number (%). Because of rounding, percentages might not sum to 100%.

The p-values obtained from "chi-square test or "linear-by-linear association test. According to the Act on Decisions on Life-Sustaining Treatment for Patients in Hospice and Palliative Care or at the End-of-Life.
decision-making method chosen by respondents was the informative approach (56.3%), followed by SDM (33.0%); while the paternalistic approach (3.2%) was the least-used method. The proportion of “usual” decision-making methods selected by respondents did not differ between the educated and non-educated groups (p = 0.83) (Fig 1; Supplementary Table 1, available online).

Shared decision-making application in decisions to withhold or withdraw life-sustaining treatment in clinical practice

Regarding the questionnaire items on the actual use of SDM, 64.3% of respondents reported its application in their usual practice (Supplementary Table 2, available online). Regarding whether respondents received SDM education as part of their undergraduate or postgraduate curriculum, 12.3% answered that they did receive it and 57.0% reported that they did not. The percentage of respondents who reported that they did not receive training on SDM was particularly high among professors and those in their 50s (96.1% and 90.7%, respectively) (Supplementary Table 3, available online). Only 2.3% of respondents reported being aware of the specific SDM model; the others were not aware or not sure. Regarding the questionnaire items seeking to determine whether SDM is implemented appropriately in decisions to withdraw or withhold LST in actual clinical practice, 40.1% reported that SDM was implemented properly, 16.2% reported it was not appropriate, while the rest answered that they were not sure (Fig 2). The proportion of respondents who used SDM for LST-related decisions tended to be higher (84.2% vs. 69.7%, p = 0.05) in the educated group compared with the non-educated group. More educated respondents and trainees indicated that SDM is being used appropriately in actual clinical practice compared with members of the non-educated group and nephrologists (63.2% vs. 36.9%, p = 0.002 and 43.8% vs. 21.6%, p = 0.003, respectively) (Supplementary Table 3, 4; available online). Respondents chose lack of time as the most common reason why SDM has not applied appropriately in actual clinical practice (46.0%). With regard to “patient aspects,” unrealistic needs of the family, high dependence on the physician, and ambiguous timing in the decision-making process were reported frequently (36.9%, 31.4%, and 28.8%, respectively). With regard to “physician aspects,” respondents frequently cited the lack of educational materials and tools and lack of training on the SDM method (29.4% and 24.3%, respectively) (Fig 2). With regard to the factors that hindered proper application of SDM, respondents in the educated and non-educated groups reported “insufficient time” (29.4% vs. 48.7%, p = 0.03) and “not trained in SDM” (7.9% vs. 26.6%, p = 0.02). A lower proportion of educated respondents compared with the non-educated reported “lack of educational materials and tools” (15.8% vs. 31.4%, p = 0.07; Supplementary Table 3). A higher proportion of nephrologists than trainees reported that the factors hindering proper application of SDM were “ambiguity of the timing of the decision” (43.1% vs. 26.0%, p = 0.02), “differences in patient preferences” (29.4% vs. 11.6%, p = 0.002), and “lack of educational materials and tools” (51.0% vs. 25.2%, p < 0.001; Supplementary Table 4).

Discussion

Previous studies on patient and caregiver satisfaction with SDM in various clinical situations have revealed that patients who experienced SDM were more likely to report a sense of well-being, greater satisfaction, and less regret compared with those without such experience [24,25]. One of the most critical topics in end-of-life care, including LST, in nephrology is the initiation, withholding, and withdrawal of dialysis; various studies have been conducted on this topic [26–29], including recent domestic research [19,20]. In dialysis treatment decision processes, sufficient information exchange and sharing of the decision-making process between the doctor and the patient are associated with less patient regret [27–29]. This is consistent with the current trajectory of the general approach to SDM and could be the reason for the need to establish appropriate SDM in the field of nephrology.

Respondents reported that the SDM approach was the most used decision-making method in actual clinical practice. However, most respondents reported that they did not receive adequate training on SDM and were not aware of a specific SDM model. Most also believed that SDM was not being applied appropriately in actual clinical practice, and lack of time, educational materials, and appropriate tools were the most cited reasons. The proportion of those who assumed they were using SDM appropriately in actual clinical practice was higher in the educated group compared...
“Usual” decision-making approach of respondents after reading a fictional example of a patient in the decision-making process and detailed explanations of each decision-making approach. (A) All respondents. (B) Educated group. (C) Non-educated group.

SDM, shared decision-making.

Appropriateness of SDM in actual clinical practice and factors that hinder its proper application. (A) Response to the question “Is SDM appropriately made in decision to withhold or withdraw of life-sustaining treatment in actual clinical practice?” (B) Patient aspects. (C) Medical system aspects. (D) Physician aspects.

SDM, shared decision-making.
with the non-educated group, while the proportion of those who chose lack of time and SDM education as factors hindering its proper application was lower.

Previous individual studies [30–32] and a meta-analysis [12] involving physicians have shown that, although their preference for SDM was consistently higher than other decision-making methods, the most preferred and most used methods differ in actual clinical practice. The current study results reflect those of previous studies in a larger context, but caution is needed when interpreting the results. In this study, the most used decision-making method in practice was the informative approach, including decisions to withhold or withdraw LST. This was based on respondents’ selection of the method after they were presented with a detailed explanation of the nameless concept of each method. However, respondents reported that 64.2% of the decisions they make in actual practice involved SDM. The reasons for these conflicting responses—despite having been given detailed definitions of each decision-making method—could be insufficient understanding of the conceptual difference between methods. In other words, lack of education might account for these conflicting answers. Another possible explanation could be that many physicians assume that they are already using SDM at the decision-making stage, while in actual clinical practice they often do not know that their general decision-making method does not reflect SDM [32,33].

When asked whether SDM is being applied properly in actual clinical practice, most physicians answered “no” or “unclear” and chose lack of time as the most common reason for not being able to apply it. Lack of time for physicians is a major obstacle to the SDM approach [34,35].

According to the Organisation for Economic Co-operation and Development (OECD) Health Statistics 2020, on the use of healthcare resources and utilization, number of annual outpatient visits per capita, average hospital stay per capita, and number of physicians per 1,000 population in Korea were the highest, second-highest, and third-lowest among OECD countries [36]. These data indicate that physicians in Korea have insufficient time to treat their patients compared with those in other OECD member countries. To overcome the lack of time, efforts to reduce time wasted due to improper SDM application by incorporating it into training curricula and providing sufficient education and continuous feedback from experts are needed. In this study, fewer respondents in the educated group chose “insufficient time” to explain the lack of proper application of SDM compared with the non-educated group. In the educated group, SDM was used more often in LST-related decisions, and the proportion of respondents who reported that SDM was used appropriately in actual clinical practice was higher compared with that in the non-educated group. A recent study also showed that, when a curriculum using standardized patients to teach the main concepts and techniques of SDM was applied to internal medicine residents, knowledge, attitude, and application ability of SDM were improved [37]. Considering that the respondents reported lack of education as the most common obstacle to proper application of SDM in “physicians’ aspects,” SDM education is essential to addressing the problems that hinder its proper application. A new scheduling algorithm that can allocate interview time for decision-making and an information system that actively supports physicians should be considered. Policy-makers should expend effort on developing policies that support allocating meaningful time for appropriate SDM [38].

Compared with trainees, nephrologists more frequently selected “ambiguity of the timing of the decision” and “differences in patient preferences” as factors that hinder proper SDM application. This can be attributed to two factors. First, nephrologists rather than trainees make the leading decisions as attending physicians. Second, based on their accumulated clinical experience, many nephrologists might believe that providing more objectified and diverse medical choices for patients in an appropriate doctor-patient relationship and allowing patients to make decisions that fit their values are superior options for achieving patient satisfaction and meeting physicians’ legal responsibilities.

There are several limitations to the current study. As with similar questionnaire surveys, limitations related to nonresponse bias and representativeness of participants exist. The response rate was comparable to or higher than that of similar studies [31,32]. As this study was conducted as a multiregional and multicenter study in Korea, it provides an opportunity to understand the perspectives of Korean internal medicine residents and nephrologists. However, the results cannot be generalized to other internal medicine specialists because the specialist-level participants consisted only of nephrologists. Moreover, trainees accounted for 83.5% of the total study population,
making it difficult to extrapolate their perception to that of all physicians. The results of this study showed a difference in the total number of patients treated by respondent per week between trainees and nephrologists. Trainees and nephrologists have different types and loads of tasks, making it unreasonable to generalize the results. To overcome this limitation, the authors divided the respondents into “trainees” and “nephrologists” and performed a subgroup analysis. Regarding the perception of SDM, the difference in perception between trainees and nephrologists was confirmed. However, because only 5.3% of the respondents had received SDM education, subgroup analysis according to position on importance and necessity of SDM education could not be performed. It is expected that further generalized results on the perception of and need for SDM education among physicians could be obtained if the results of the analysis were integrated with the aforementioned study results on medical oncologists and residents of internal medicine. Second, a discrepancy might exist between SDM perspectives and their actual application because physicians’ perspectives on SDM were determined based solely on the questionnaire without verification of their actual application. In a recent study that recorded and analyzed clinical decisions made in actual clinics, SDM often was incomplete [39]. In addition, the content and level of SDM training can differ by medical school. Even if the students of these schools received the same training, a difference can be expected in understanding the educational content and the ability to implement SDM in clinical practice. One of the major limitations of this study is that it divided the participants into groups based on SDM education: those who received SDM education and those who did not, with the latter only having memories of receiving SDM education. However, despite the expectation that the content of training and the ability to apply SDM after training would vary among respondents, the group that reported having received training on SDM was more likely to report a higher rate of appropriate use of SDM in actual clinical practice. In addition, a lower proportion of respondents who chose lack of time and SDM education as a hindrance factor of SDM could be seen as disproving the importance of education for the proper settlement of SDM. To clarify this, we recommend an additional comparative study of groups who received or did not receive the same SDM education curriculum that includes verification of practical application ability. Third, there might be a desirability bias to meet social expectations because this study relied on physicians’ self-reported knowledge. Physicians could have been reluctant to present opinions contrary to the social climate that encourages providing extensive medical information to patients and caregivers and engaging them in the decision-making process. Fourth, interpretation of the respondents’ responses to questions about factors that hinder proper application of SDM was problematic because respondents were allowed to supply multiple answers. To overcome this, two independent researchers analyzed these data separately. Finally, the fidelity of each research subject’s questionnaire was not evaluated by an objective method. Prior to administering the survey, we explained the purpose of the study in detail and asked the respondents to answer sincerely to produce accurate study results. We explained the survey questions in detail to prevent any missing values from respondents, and a sufficient question and answer session was conducted with the respondents who did not understand the survey questions. Considering that 3.7% missing data occurred despite these measures, we should have reviewed the fidelity of each research subject’s questionnaire.

In conclusion, the majority of nephrologists and internal medicine trainees believed that SDM was not being implemented properly in Korea. Respondents cited a lack of time and education on SDM as the major obstacle to its proper application. Considering that dramatic changes to the medical system, including adjustments of health insurance fees, are needed to resolve this lack of time, appropriate training programs for SDM appear to be a realistic and feasible solution to properly strengthen SDM in the Korean medical system. The perceptions about SDM of nephrologists and internal medicine trainees and the findings of this study can be used to develop an appropriate SDM model in Korea.

**Additional information**

1. *Division of Nephrology, Department of Internal Medicine, Soonchunhyang University Bucheon Hospital, Bucheon, Republic of Korea*
2. *Division of Nephrology, Department of Internal Medicine, Hallym University Hangang Sacred Heart Hospital, Hallym University College of Medicine, Seoul, Republic of Korea*
3. *Division of Nephrology, Department of Internal Medicine, Korea University Guro Hospital, Korea University College of Medicine,*
Conflicts of interest

All authors have no conflicts of interest to declare.

Funding

This work was supported in part by a Cooperative Research Grant 2019 from the Korean Society of Nephrology and the Soonchunhyang University Research Fund.

Authors’ contributions

Conceptualization: BCY, MH, JYW, SHK, SC, YAH, YYH, DK, WMH, SJS

Data curation, Formal analysis, Investigation: All authors

Funding acquisition: YAH, BCY

Project administration: SJS

Writing–original draft: BCY, MH, SJS

Writing–review & editing: GJK, SHS, JHC, KDY, EB, WYP, IOS, HK, BCY, MH, SJS

All authors read and approved the final manuscript.

ORCID

Byung Chul Yu, https://orcid.org/0000-0002-2686-1904

Miyeun Han, https://orcid.org/0000-0001-7304-2496

Gang-Jee Ko, https://orcid.org/0000-0001-8355-1083

Jae Won Yang, https://orcid.org/0000-0003-3689-5865

Soon Hyo Kwon, https://orcid.org/0000-0002-4114-4196

Sungjin Chung, https://orcid.org/0000-0002-9886-8339

Yu Ah Hong, https://orcid.org/0000-0001-7856-4955

Young Youl Hyun, https://orcid.org/0000-0002-4204-9908

Jang-Hee Cho, https://orcid.org/0000-0002-7031-5214

Kyung Don Yoo, https://orcid.org/0000-0001-6545-6517

Eunjin Bae, https://orcid.org/0000-0001-6890-4725

Woo Yeong Park, https://orcid.org/0000-0003-2662-2898

In O Sun, https://orcid.org/0000-0001-7245-3736

Dongryul Kim, https://orcid.org/0000-0002-1322-1887

Hyunsuk Kim, https://orcid.org/0000-0003-1889-253X

Won Min Hwang, https://orcid.org/0000-0001-7548-6111

Sang Heon Song, https://orcid.org/0000-0002-8218-6974

Sung Joon Shin, https://orcid.org/0000-0002-0777-9278

References


Stacey D, Légaré F, Col NF, et al. Decision aids for people facing
Siu HYH, Elston D, Arora N, et al. The impact of prior advance
Witkamp FE, van Zuylen L, Borsboom G, van der Rijt CC, van
decision making about life-sustaining treatment and palliative
2021;24:527–535.
20. Yun YS, Kwon SH, Jung JM, Jeon JS, Noh HJ, Han DC. Attitudes


Background: Patients on dialysis have numerous gastrointestinal problems related to uremia, which may represent concealed cholecystitis. We investigated the incidence and risk of acute cholecystitis in dialysis patients and used national health insurance data to identify acute cholecystitis in Korea.

Methods: The Korean National Health Insurance Database was used, with excerpted data from the insurance claim of the International Classification of Diseases code of dialysis and acute cholecystitis treated with cholecystectomy. We included all patients who commenced dialysis between 2004 and 2013 and selected the same number of controls via propensity score matching.

Results: A total of 59,999 dialysis and control patients were analyzed; of these, 3,940 dialysis patients (6.6%) and 647 controls (1.1%) developed acute cholecystitis. The overall incidence of acute cholecystitis was 8.04-fold higher in dialysis patients than in controls (95% confidence interval, 7.40–8.76). The acute cholecystitis incidence rate (incidence rate ratio, 23.13) was especially high in the oldest group of dialysis patients (aged ≥80 years) compared with that of controls. Dialysis was a significant risk factor for acute cholecystitis (adjusted hazard ratio, 8.94; 95% confidence interval, 8.19–9.76). Acute cholecystitis developed in 3,558 of 54,103 hemodialysis patients (6.6%) and in 382 of 5,896 patients (6.5%) undergoing peritoneal dialysis.

Conclusion: Patients undergoing dialysis had a higher incidence and risk of acute cholecystitis than the general population. The possibility of a gallbladder disorder developing in patients with gastrointestinal problems should be considered in the dialysis clinic.

Keywords: Acute cholecystitis, Epidemiology, Population, Renal dialysis
treatment. The most common symptom is upper abdominal pain, which usually begins in the epigastric region and is then localized to the right upper quadrant. Nausea, vomiting, and fever are generally significant [1]. The prevalence of acute cholecystitis among individuals with abdominal pain is 3% to 8%, and its incidence is markedly increased after the age of 50 years in the general population [2]. The 30-day mortality was 1.1% in a Japanese-Taiwanese study with similar ethnic characteristics as that of the Korean population [3].

As life expectancy increases, the number of patients with diabetes and hypertension increases globally. The increased number of chronic kidney disease cases correspondingly increases the dialysis population [4], and improved cardiovascular outcomes in the dialysis population result in prolonged dialysis duration and enhanced long-term survival [5]. However, elderly patients demonstrated a relatively decreased survival gain because of multiple medical problems [6]. Therefore, general medical care with superior quality has become important for dialysis patients.

Patients with end-stage renal disease (ESRD) have multiple problems associated with uremia. They have more common nonspecific gastrointestinal problems such as abdominal pain, constipation, dyspepsia, nausea, and irritable bowel syndrome than controls without renal impairment [7]. Although uremia is thought to cause nonspecific gastrointestinal problems, it could mimic specific gastrointestinal illnesses that could result in the misdiagnosis of an important disease. Furthermore, dialysis patients have a higher incidence of gastrointestinal disease than the general population [8]. However, the incidence of acute cholecystitis, its clinical characteristics, and treatment outcomes in dialysis patients are still not fully understood.

This study aimed to determine the incidence and risk of acute cholecystitis in the dialysis population and to investigate the differences among the dialysis modalities in patients with ESRD. We designed a propensity score-matched cohort study using the Korean National Health Insurance Service (KNHIS) data.

Methods

Database

Data on patients undergoing dialysis were obtained from the Korean National Health Information database. The KNHIS, a single national insurance provider, covers almost the entire Korean population. This database, which contains reimbursement records from all medical facilities across the country, was used to develop an exposure cohort. We previously reported the incidence of active tuberculosis and cancer in dialysis patients using KNHIS data [9,10].

Definition and selection of cohort

All incidental patients with ESRD who underwent dialysis for more than 3 months and were diagnosed between 2004 and 2013 in Korea were selected from the database to establish the exposure cohort. The dialysis cohort included patients who claimed insurance for any procedures or services for both hemodialysis and peritoneal dialysis, based on the Korean electronic data interchange codes (O7020, O7021, O9991 for hemodialysis; E6593, O7061, O7062, O7074, O7075, O7080 for peritoneal dialysis) combined with the International Classification of Diseases (ICD) code of chronic kidney disease (N18.**) [10]. Patients who underwent dialysis for more than 3 months were defined by a dialysis code that appeared again within 3 months after the initial dialysis code appeared. In the peritoneal dialysis patient group, codes (O7061 and O7062) were used to find new patients receiving peritoneal dialysis. The date these codes appeared was the first peritoneal dialysis date, and the cases where the peritoneal dialysis code reappeared after 3 months was the peritoneal dialysis patient group.

Patients with a diagnosis of ESRD who were provided with medical services in 2003 and received kidney transplantation were excluded from this cohort to rule out chronic ESRD (Fig. 1).

The control cohort was selected from the KNHIS National Sample Cohort (NSC) from the National Health Information database established by the KNHIS in 2011 [11]. These cohort data covered 1,125,691 Korean individuals and represented 2.2% of all Korean population disease entities. We excluded patients with dialysis, diagnosed with cholecystitis and/or cholecystectomy, or kidney transplantation (Fig. 1).

Definition of acute cholecystitis and covariables

The incidence of acute cholecystitis was investigated using ICD 10th Revision (ICD-10) codes. Acute cholecystitis was
defined as follows; admission to an acute care hospital with diagnostic codes of acute or other cholecystitis regardless of calculus (ICD-10 K80, K81, K82) with confirmed cholecystitis by pathology after performing cholecystectomy (Q7380) [12]. We excluded patients who were diagnosed with cholecystitis and/or cholecystectomy before the start of dialysis. The factors associated with the incidence of acute cholecystitis, such as age, sex, income level, Charlson comorbidity index (CCI), and comorbidities, were used as independent variables. The comorbidities for covariates, such as diabetes mellitus, hypertension, hyperlipidemia, connective tissue disease, myocardial infarction, heart failure, peripheral vascular disease, severe liver disease, dementia, and atrial fibrillation, were selected based on a previous Taiwanese nationwide study [13,14] (Supplementary Material, available online). Income level was categorized into three groups after it was scored on a scale of 0 to 10.

**Propensity score matching**

We included patients who began dialysis before their diagnosis of acute cholecystitis based on the visit date. Dialysis cohort data between 2014 and 2015 were excluded because in the KNHIS-NSC database only data up to 2013 was available. The eligible patients, who started dialysis between 2004 and 2013 (dialysis cohort), were identified after excluding potentially preexisting cases of dialysis or acute cholecystitis. We identified individuals without ESRD from the KNHIS-NSC database, who were propensity score-matched to an equal number of ESRD cases. Propensity score matching using the nearest neighbor method was performed to identify similar individuals in the dialysis and

---

**Figure 1. Patient and control enrollment flowchart showing the selection from the database.** We evaluated 59,999 patients and compared them with 59,999 non-dialysis subjects selected from the National Sample Cohort of 1,125,691 Koreans via propensity score matching.

CCT, acute cholecystitis patients who underwent cholecystectomy.
control cohorts [15]. Logistic regression was used to obtain propensity scores for each patient based on their age, sex, income level, and CCI as well as comorbidities. Individuals in both cohorts were randomly ordered and matched 1:1 using the nearest neighbor method (Fig. 1).

**Statistical analysis**

Proportional differences in independent variables between the dialysis and control cohorts were analyzed using the Wald chi-square test. The acute cholecystitis incidence rate was expressed as the number of newly diagnosed acute cholecystitis cases per 10,000 person-years from the database. The incidence rate ratio (IRR) of dialysis cohorts, relative to the controls, was calculated with a 95% confidence interval (CI). The cumulative incidence of acute cholecystitis was calculated by using the Kaplan-Meier method and analyzed by the log-rank test. We applied the multivariate Cox proportional hazards model to all independent variables after combining the two cohorts to determine the dialysis-associated risk of developing acute cholecystitis, which was described as hazard ratio (HR). The follow-up period started on the first date of dialysis for the cases and on randomly selected visit dates for the controls, which occurred in years that matched the start of dialysis for the cases. The follow-up period ended on the first date of acute cholecystitis diagnosis or the last follow-up date. Analyses were performed using the statistical package SAS version 9.4 (SAS Institute, Cary, NC, USA) and R version 3.4.3 (R Foundation for Statistical Computing, Vienna, Austria). A statistical significance level of 0.05 was established.

**Ethics statement**

The retrospective protocol of this study was performed in accordance with the Declaration of Helsinki and approved by the Institutional Review Board (IRB) of Chungbuk National University Hospital in Cheongju, Republic of Korea (No. 2016-11-009). We used encrypted national insurance data. The IRB exempted our study from informed consent. All encrypted patients’ records from the KNHIS were anonymized to ensure patient confidentiality.

**Results**

**Baseline characteristics of the dialysis and control cohort**

A total of 208,512 patients who were newly diagnosed with ESRD were selected from the KNHIS database. Patients who had undergone dialysis before 2003 (24,329), with a dialysis duration of less than 3 months (88,532), without a dialysis deductible code (4,149), who had incorrect or missing value (308), and who had kidney transplantation (9,440) were excluded. Patients who underwent cholecystectomy before the initiation of dialysis (7,159) were also excluded. A total of 59,999 patients were included in the patient arm, and 59,999 patients from the NSC of the 1,125,691 Korean population were included in the propensity score-matched group (Fig. 1).

The baseline characteristics and comorbidities between the dialysis and control cohorts are summarized in Table 1. In the dialysis cohort, 34,772 patients (58.0%) were men, and the mean duration of dialysis was 2.76 ± 2.76 years. The dialysis patients commonly commenced at 50 to 79 years of age (43,346, 72.0%) in comparison with a similar number of patients in the matched control cohort. In total, 54,103 patients underwent hemodialysis (90.2%), whereas 5,896 underwent peritoneal dialysis (9.8%).

**Comparison of acute cholecystitis in the dialysis and control cohort**

Among the 59,999 dialysis patients and 59,999 controls, 3,940 dialysis patients (6.6%) developed acute cholecystitis, and 647 controls (1.1%) developed cholecystitis (Table 2). The overall incidence of acute cholecystitis was remarkably higher in the dialysis patients than controls (IRR, 8.04; 95% CI, 7.40–8.76). The cumulative incidence of acute cholecystitis was significantly higher in dialysis patients than controls (p < 0.001), the result is illustrated in Fig. 2. In the subgroup analysis, the incidence of acute cholecystitis was similarly elevated in the dialysis group (Table 2). Because the variables were different between dialysis and the control group, we analyzed the HR by multivariate analysis. Multivariate Cox proportional hazards analysis revealed that dialysis was a significant risk factor for acute cholecystitis with an HR of 8.94 (95% CI, 8.19–9.76) (Table 3).

In the subgroup of dialysis modality, acute cholecystitis
occurred in 3,558 of 54,103 hemodialysis patients (6.6%) and in 382 of 5,896 peritoneal dialysis patients (6.5%). After variables were adjusted, hemodialysis patients were at a lower risk of acute cholecystitis than peritoneal dialysis patients (adjusted HRs, 0.84; 95% CI, 0.76–0.94; p < 0.01), and a significant difference was observed (Table 4, Fig. 3).

Discussion

This nationwide cohort study found that patients with ESRD undergoing dialysis were associated with an 8.94-fold higher risk of acute cholecystitis than the matched control group. This is the largest cohort study to investigate the incidence and risk factors of acute cholecystitis after the initiation of dialysis for ESRD in the Korean population. A recent Taiwanese nationwide cohort study that consisted of 54,065 patients with new-onset ESRD reported that the incidence of acute cholecystitis was 5.8/1,000 patient-years. In addition, patients with ESRD were associated with a 6.83-fold higher risk of developing acute cholecystitis [13].

Acute cholecystitis is commonly associated with inflammation caused by prolonged obstruction of the cystic duct with gallstones [16]. Even though gallstones are the most important factor in the pathogenesis of acute cholecystitis, there are also many other investigated factors for developing gallstones [17,18]. Although many studies have investigated the relationship between gallstones and ESRD, it remains to be clarified whether gallstones are more common in patients with ESRD [16–18]. Some studies report that the incidence of gallstones in patients on hemodialysis was not different from that in controls [19–24], whereas others have reported a higher incidence of gallstones in patients on hemodialysis than in the control group [25–30]. In this study, both hemodialysis and peritoneal dialysis were associated with an increased risk of developing acute cholecystitis. In terms of dialysis modality, hemodialysis patients were at a lower risk of acute cholecystitis than peritoneal dialysis patients.

In patients on hemodialysis, hemodynamic fluctuations cause hypoperfusion to organs. The resulting frequent mesenteric ischemia leads to disruption of the gut mucosal structure with increased gut permeability, and chronic malnutrition causing a higher incidence of peptic ulcer disease. Dialysis patients with poor nutrition have a higher incidence of peptic ulcer disease [31]. This could occur in the gallbladder. The ischemia and reperfusion injury leads to epithelial damage of the gallbladder. Additionally, increased circulating uremic toxin levels in hemodialysis patients cause systemic inflammation. Moreover, increased leukocyte margination and focal lymphatic dilation with interstitial edema are associated with local microvascular occlusion [32–34]. In peritoneal dialysis patients, acute

---

**Table 1. Baseline characteristics of the dialysis patients and controls**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Dialysis</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>59,999</td>
<td>59,999</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>34,772 (58.0)</td>
<td>31,838 (53.1)</td>
</tr>
<tr>
<td>Female</td>
<td>25,227 (42.0)</td>
<td>28,161 (46.9)</td>
</tr>
<tr>
<td>Age (yr)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–29</td>
<td>1,083 (1.8)</td>
<td>874 (1.5)</td>
</tr>
<tr>
<td>30–39</td>
<td>3,408 (5.7)</td>
<td>2,630 (4.4)</td>
</tr>
<tr>
<td>40–49</td>
<td>8,849 (14.7)</td>
<td>7,225 (12.0)</td>
</tr>
<tr>
<td>50–59</td>
<td>14,086 (23.5)</td>
<td>13,090 (21.8)</td>
</tr>
<tr>
<td>60–69</td>
<td>16,317 (27.2)</td>
<td>16,943 (28.2)</td>
</tr>
<tr>
<td>70–79</td>
<td>12,943 (21.6)</td>
<td>14,815 (24.7)</td>
</tr>
<tr>
<td>≥80</td>
<td>3,313 (5.5)</td>
<td>4,422 (7.4)</td>
</tr>
<tr>
<td>Income level</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>23,301 (38.8)</td>
<td>17,210 (28.7)</td>
</tr>
<tr>
<td>Middle</td>
<td>18,446 (30.7)</td>
<td>21,472 (35.8)</td>
</tr>
<tr>
<td>High</td>
<td>18,252 (30.4)</td>
<td>21,317 (35.5)</td>
</tr>
<tr>
<td>CCI score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤1</td>
<td>6,400 (10.7)</td>
<td>5,326 (8.9)</td>
</tr>
<tr>
<td>2</td>
<td>6,332 (10.6)</td>
<td>5,611 (9.4)</td>
</tr>
<tr>
<td>≥3</td>
<td>47,267 (78.8)</td>
<td>49,062 (81.8)</td>
</tr>
<tr>
<td>Comorbidity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>43,591 (72.7)</td>
<td>43,062 (71.8)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>53,253 (88.8)</td>
<td>55,006 (91.7)</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>40,773 (68.0)</td>
<td>42,083 (70.1)</td>
</tr>
<tr>
<td>Connective tissue disease</td>
<td>5,304 (8.8)</td>
<td>10,172 (17.0)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>6,877 (11.5)</td>
<td>6,211 (10.4)</td>
</tr>
<tr>
<td>Heart failure</td>
<td>19,470 (32.5)</td>
<td>15,240 (25.4)</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>18,687 (31.1)</td>
<td>27,393 (45.7)</td>
</tr>
<tr>
<td>Severe liver disease</td>
<td>2,016 (3.4)</td>
<td>2,424 (4.0)</td>
</tr>
<tr>
<td>Dementia</td>
<td>3,495 (5.8)</td>
<td>9,591 (16.0)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>3,637 (6.1)</td>
<td>4,685 (7.8)</td>
</tr>
</tbody>
</table>

**Discussion**

This nationwide cohort study found that patients with ESRD undergoing dialysis were associated with an 8.94-fold higher risk of acute cholecystitis than the matched control group. This is the largest cohort study to investigate the incidence and risk factors of acute cholecystitis after the initiation of dialysis for ESRD in the Korean population. A recent Taiwanese nationwide cohort study that consisted of 54,065 patients with new-onset ESRD reported that the incidence of acute cholecystitis was 5.8/1,000 patient-years. In addition, patients with ESRD were associated with a 6.83-fold higher risk of developing acute cholecystitis [13].

Acute cholecystitis is commonly associated with inflammation caused by prolonged obstruction of the cystic duct with gallstones [16]. Even though gallstones are the most important factor in the pathogenesis of acute cholecystitis, there are also many other investigated factors for developing gallstones [17,18]. Although many studies have investigated the relationship between gallstones and ESRD, it remains to be clarified whether gallstones are more common in patients with ESRD [16–18]. Some studies report that the incidence of gallstones in patients on hemodialysis was not different from that in controls [19–24], whereas others have reported a higher incidence of gallstones in patients on hemodialysis than in the control group [25–30]. In this study, both hemodialysis and peritoneal dialysis were associated with an increased risk of developing acute cholecystitis. In terms of dialysis modality, hemodialysis patients were at a lower risk of acute cholecystitis than peritoneal dialysis patients.

In patients on hemodialysis, hemodynamic fluctuations cause hypoperfusion to organs. The resulting frequent mesenteric ischemia leads to disruption of the gut mucosal structure with increased gut permeability, and chronic malnutrition causing a higher incidence of peptic ulcer disease. Dialysis patients with poor nutrition have a higher incidence of peptic ulcer disease [31]. This could occur in the gallbladder. The ischemia and reperfusion injury leads to epithelial damage of the gallbladder. Additionally, increased circulating uremic toxin levels in hemodialysis patients cause systemic inflammation. Moreover, increased leukocyte margination and focal lymphatic dilation with interstitial edema are associated with local microvascular occlusion [32–34]. In peritoneal dialysis patients, acute
Cholecystitis is caused by chronic active inflammation of the peritoneum and endotoxemia [35,36]. We hypothesize that chronic inflammation of the gallbladder and decreased gallbladder motility due to uremia caused the increased incidence of cholecystitis.

In the management of acute cholecystitis, laparoscopic cholecystectomy is recommended as a first-line treatment in the general population [37]. However, previous studies on the outcomes of patients with ESRD undergoing cholecystectomy have reported that ESRD is an independent risk factor for postoperative morbidity [38,39]. Although patients on dialysis are at risk of postoperative complications, laparoscopic cholecystectomy is recommended as a first-line treatment for acute cholecystitis even in patients undergoing peritoneal dialysis [40–44]. In severe acute cholecystitis, operative management increased morbidity and mortality. Chung et al. [45] reported that emergent laparoscopic cholecystectomy for acute cholecystitis in patients with ESRD was an independent risk factor for mortality. Therefore, patients with acute cholecystitis must be treated before exacerbation of the inflammation. To avoid operative complications, Gunay et al. [46] suggested percutaneous

### Table 2. The incidence of acute cholecystitis according to baseline characteristics among dialysis patients and controls

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Dialysis (n = 59,999)</th>
<th>Control (n = 59,999)</th>
<th>IRR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. (%)</td>
<td>PY</td>
<td>IR/1,000 PY</td>
</tr>
<tr>
<td>Case</td>
<td>3,940 (6.6)</td>
<td>205,456</td>
<td>19</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>2,298 (3.8)</td>
<td>117,146</td>
<td>20</td>
</tr>
<tr>
<td>Female</td>
<td>1,642 (2.7)</td>
<td>88,310</td>
<td>19</td>
</tr>
<tr>
<td>Age (yr)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–29</td>
<td>36 (0.1)</td>
<td>4,979</td>
<td>7</td>
</tr>
<tr>
<td>30–39</td>
<td>182 (0.3)</td>
<td>15,882</td>
<td>11</td>
</tr>
<tr>
<td>40–49</td>
<td>569 (0.9)</td>
<td>38,692</td>
<td>15</td>
</tr>
<tr>
<td>50–59</td>
<td>955 (1.6)</td>
<td>53,090</td>
<td>18</td>
</tr>
<tr>
<td>60–69</td>
<td>1,165 (1.9)</td>
<td>54,258</td>
<td>21</td>
</tr>
<tr>
<td>70–79</td>
<td>846 (1.4)</td>
<td>32,456</td>
<td>26</td>
</tr>
<tr>
<td>≥80</td>
<td>187 (0.3)</td>
<td>6,100</td>
<td>31</td>
</tr>
<tr>
<td>Income level</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>1,745 (2.9)</td>
<td>91,795</td>
<td>19</td>
</tr>
<tr>
<td>Middle</td>
<td>1,067 (1.8)</td>
<td>59,791</td>
<td>18</td>
</tr>
<tr>
<td>High</td>
<td>1,128 (1.9)</td>
<td>53,870</td>
<td>21</td>
</tr>
<tr>
<td>CCI score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤1</td>
<td>508 (0.8)</td>
<td>35,361</td>
<td>14</td>
</tr>
<tr>
<td>2</td>
<td>447 (0.7)</td>
<td>27,335</td>
<td>16</td>
</tr>
<tr>
<td>≥3</td>
<td>2,985 (5.0)</td>
<td>142,760</td>
<td>21</td>
</tr>
<tr>
<td>Comorbidity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>2,670 (4.5)</td>
<td>129,602</td>
<td>21</td>
</tr>
<tr>
<td>Hypertension</td>
<td>3,310 (5.5)</td>
<td>167,101</td>
<td>20</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>2,430 (4.1)</td>
<td>118,317</td>
<td>21</td>
</tr>
<tr>
<td>Connective tissue disease</td>
<td>313 (0.5)</td>
<td>14,118</td>
<td>22</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>476 (0.8)</td>
<td>18,478</td>
<td>26</td>
</tr>
<tr>
<td>Heart failure</td>
<td>1,252 (2.1)</td>
<td>52,671</td>
<td>24</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>1,067 (1.8)</td>
<td>46,129</td>
<td>23</td>
</tr>
<tr>
<td>Severe liver disease</td>
<td>163 (0.3)</td>
<td>5,161</td>
<td>32</td>
</tr>
<tr>
<td>Dementia</td>
<td>184 (0.3)</td>
<td>6,255</td>
<td>29</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>227 (0.4)</td>
<td>9,075</td>
<td>25</td>
</tr>
</tbody>
</table>

CCI, Charlson comorbidity index; CI, confidence interval; IR, incidence rate; IRR, incidence rate ratio; PY, person-years.
of acute cholecystitis (i.e., emphysematous cholecystitis, acalculous cholecystitis) in our dataset, we could not find a relationship between ESRD and gallstone disease. Second, it is possible that a case diagnosed with cholecystitis, but not having surgery or having undergone gallbladder drainage, may have been excluded from both groups. Since 2003, the code for cholecystectomy can be confirmed in the data, so patients in the dialysis group and the control group belong to the definition of cholecystitis in this study. “Cholecystectomy with cholecystitis and histologically confirmed” were identified and excluded, and many dialysis patients underwent percutaneous cholecystostomy due to poor medical conditions with a high rate of readmission [46]. Because we used a cholecystectomy code for specifying acute cholecystitis, we did not include a cholecystostomy code at initiation, which might be an important limitation in our study. Third, we used a general Cox model to control the selected covariates. After the ‘proportional hazards’ assumption is confirmed, stratified Cox analysis should be performed rather than general Cox analysis for propensity score matching data. However, in the matching, the HR of the general Cox analysis is smaller than that of the stratified Cox analysis, and the HR is underestimated. Therefore, the result does not change even if the analysis method is dif-
Table 3. Univariate and multivariate analysis of risk factors for acute cholecystitis

<table>
<thead>
<tr>
<th>Variable</th>
<th>Crude HR (95% CI)</th>
<th>Adjusted HR (^a) (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dialysis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Yes</td>
<td>8.10 (7.46–8.81)</td>
<td>8.94 (8.19–9.76)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>0.85 (0.8–0.9)</td>
<td>0.90 (0.84–0.95)</td>
</tr>
<tr>
<td>Age (yr)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–29</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>30–39</td>
<td>1.74 (1.24–2.43)</td>
<td>1.64 (1.17–2.29)</td>
</tr>
<tr>
<td>40–49</td>
<td>2.05 (1.49–2.82)</td>
<td>1.94 (1.41–2.67)</td>
</tr>
<tr>
<td>50–59</td>
<td>2.30 (1.68–3.15)</td>
<td>2.36 (1.72–3.24)</td>
</tr>
<tr>
<td>60–69</td>
<td>2.49 (1.82–3.41)</td>
<td>2.80 (2.04–3.84)</td>
</tr>
<tr>
<td>70–79</td>
<td>2.66 (1.94–3.65)</td>
<td>3.26 (2.37–4.49)</td>
</tr>
<tr>
<td>≥80</td>
<td>2.57 (1.83–3.61)</td>
<td>3.38 (2.40–4.76)</td>
</tr>
<tr>
<td>Income level</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Middle</td>
<td>0.78 (0.73–0.84)</td>
<td>0.87 (0.81–0.94)</td>
</tr>
<tr>
<td>High</td>
<td>0.87 (0.81–0.93)</td>
<td>0.90 (0.84–0.97)</td>
</tr>
<tr>
<td>CCI score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤1</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>2</td>
<td>1.15 (1.02–1.29)</td>
<td>1.20 (1.06–1.36)</td>
</tr>
<tr>
<td>≥3</td>
<td>1.26 (1.15–1.38)</td>
<td>1.30 (1.15–1.47)</td>
</tr>
<tr>
<td>Comorbidity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1.17 (1.10–1.24)</td>
<td>1.00 (0.92–1.08)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.02 (0.94–1.11)</td>
<td>0.89 (0.80–1.00)</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>1.04 (0.98–1.10)</td>
<td>1.06 (0.99–1.14)</td>
</tr>
<tr>
<td>Connective tissue disease</td>
<td>0.68 (0.61–0.75)</td>
<td>1.02 (0.92–1.12)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>1.34 (1.23–1.46)</td>
<td>1.19 (1.09–1.31)</td>
</tr>
<tr>
<td>Heart failure</td>
<td>1.36 (1.28–1.45)</td>
<td>1.16 (1.08–1.24)</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>0.77 (0.72–0.82)</td>
<td>1.08 (1.01–1.16)</td>
</tr>
<tr>
<td>Severe liver disease</td>
<td>1.52 (1.32–1.74)</td>
<td>1.66 (1.45–1.90)</td>
</tr>
<tr>
<td>Dementia</td>
<td>0.60 (0.54–0.68)</td>
<td>1.04 (0.92–1.18)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>1.07 (0.95–1.20)</td>
<td>1.12 (1.00–1.27)</td>
</tr>
</tbody>
</table>

CI, confidence interval; CCI, Charlson comorbidity index; HR, hazard ratio.
\(^a\)Adjusted for sex, age, income level, diabetes mellitus, hypertension, hyperlipidemia, connective tissue disease, myocardial infarction, heart failure, peripheral vascular disease, severe liver disease, dementia, atrial fibrillation, and CCI.

In conclusion, we found that patients undergoing dialysis have a higher incidence and risk of acute cholecystitis compared to the general population. As acute cholecystitis in a patient with dialysis is associated with high mobility and mortality rates, the possibility of developing a gallbladder disorder in patients with gastrointestinal problems should be considered in the dialysis clinic. Further investigations are required to explore the development of acute cholecystitis and gallstones in patients with ESRD.

Conflicts of interest

All authors have no conflicts of interest to declare.

Funding

This work was supported by a research grant from the Chungbuk National University in 2020.

Authors’ contributions

Conceptualization: HC, SKK, JHH, GK
Data curation: MK
Formal analysis: HC, SKK, GK, MK
Funding acquisition: JHH
Writing – original draft: HC, SKK, JHH, JSL, GK
Writing–review & editing: HC, SKK, JHH
All authors read and approved the final manuscript.
References

27. Li Vecchi M, Soresi M, Cusimano R, et al. Prevalence of biliary...


Focal segmental glomerulosclerosis following the Pfizer-BioNTech COVID-19 vaccine

Cho A Lim¹, Hyun Soon Lee², Songuk Yoon³, Eun Jung Kim¹, Jang Won Seo⁴, Ja-Ryong Koo¹, Seon Ha Baek¹

¹Division of Nephrology, Department of Internal Medicine, Hallym University Dongtan Sacred Heart Hospital, Hwaseong, Republic of Korea
²Hankook Renal Pathology Lab, Seoul, Republic of Korea

Correspondence
Kidney Res Clin Pract 2022;41(2):263-266
pISSN: 2211-9132 • eISSN: 2211-9140
https://doi.org/10.23876/j.krcp.21.308

Received: December 24, 2021; Revised: January 4, 2022; Accepted: January 13, 2022

Correspondence: Seon Ha Baek
Division of Nephrology, Department of Internal Medicine, Hallym University Dongtan Sacred Heart Hospital, 7 Keunjaebong-gil, Hwaseong 18450, Republic of Korea. E-mail: seohnabaek@hallym.or.kr, haya2001@hanmail.net
ORCID: https://orcid.org/0000-0002-4751-9817

Copyright © 2022 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.

Coronavirus disease 2019 (COVID-19) vaccines have shown excellent safety profiles. The most common short-term side effects are injection site reactions, fever, fatigue, and headache, while severe adverse reactions have rarely been reported [1]. However, since mass-scale vaccination began, several immune-mediated reactions (including myocarditis and de novo or relapsed glomerulonephritis [GN]) have been reported [1]. COVID-19 vaccines have also been reported to induce T-cell activation [2]. In this regard, the occurrence of kidney disease following administration of a COVID-19 vaccine can be related to the T-cell–mediated immune response it generates to viral messenger RNA (mRNA), which can trigger podocyte injury [2]. Herein, we report a case of focal segmental glomerulosclerosis (FSGS) with segmental lobular collapse and podocyte proliferation following vaccination with the first dose of the Pfizer-BioNTech COVID-19 vaccine that mimicked the cellular lesions of FSGS.

A previously healthy 29-year-old man visited our hospital with complaints of edema and decreased urine output that had occurred 7 days previously. He had received a COVID-19 vaccine 2 weeks prior (Fig. 1). He had also undergone a health checkup 3 months before the visit, including urinalysis and renal function testing, which showed no abnormalities.

Upon physical examination, the patient was afebrile with a blood pressure of 140/80 mmHg, and there was noticeable edema. He had gained 10 kg (from 83 kg to 93 kg) within 1 week. Urinalysis showed the following results: protein, 4+; glucose, negative; red blood cells (RBCs), 10 to 19 per high-power field; and white blood cell (WBC) count, 1 to 4 per high-power field. Further evaluation showed WBC count, 6,800/mm³; hemoglobin, 15.6 g/dL; platelet count, 277,000/mm³; serum creatinine, 1.24 mg/dL; total protein, 4.7 g/dL; albumin, 2.5 g/dL; total cholesterol, 351 mg/dL; spot urine protein-to-creatinine ratio, 6.12 g/g; serum kappa-to-lambda light chain ratio, 0.79; serum complement C3, 144 mg/dL; and serum complement C4, 65 mg/dL. Additionally, the patient had negative serologic testing results for hepatitis B, hepatitis C, human immunodeficiency virus, anti-glomerular basement membrane antibody, rheumatoid factor, fluorescent antinuclear antibody, antineutrophil cytoplasmic antibody, anti-phospholipase A2 receptor-immunoglobulin G, and lupus anticoagulant. The screening test for COVID-19 was also negative.

A kidney biopsy was performed 31 days after the patient received his COVID-19 vaccination. Under light microscopy, the glomeruli were diffusely enlarged and hypercellular into the mesangium. Of the 20 glomeruli submitted, one...
(5.0%) exhibited FSGS with overlying podocyte proliferation (Fig. 2A). Electron microscopy revealed aggregates of RBCs in the capillary lumen with platelets and fibrin fibrils attached, which was suggestive of imminent microthrombus formation. The foot processes of the podocytes were diffusely effaced (Fig. 2B).

Based on these findings, we initiated treatment for FSGS with prednisolone (1 mg/kg daily), diuretics, angiotensin receptor blocker, and statin. Ten weeks after steroid treatment, the patient had no appreciable symptoms, and his laboratory results had normalized (serum albumin, 4.4 g/dL and creatinine, 1.03 mg/dL). The urine protein-to-creatinine ratio was 0.10 g/g.

Most cases of GN following COVID-19 vaccine have been associated with administration of an mRNA vaccine [1]. Foreign mRNA can induce strong innate and adaptive immune responses [2,3]. Among these responses, the T-cell response provokes swift production of cytokines (such as interferon-gamma, tumor necrosis factor-alpha, and interleukin-2), which could trigger podocytopathies and GN [3].

To the best of our knowledge, this is the first report of *de novo* FSGS following COVID-19 mRNA vaccine. Although we could not demonstrate definitive causality, we believe that the FSGS in this case might have been caused by a COVID-19 mRNA vaccine for the following reasons. First, a healthy patient suddenly developed nephrotic syndrome 7 days after vaccination. The onset of disease at this time point was compatible with that mentioned in previous reports of COVID-19 mRNA vaccine triggering enhanced T follicular helper cell (Tfh) responses that peak 7 days after vaccination [2]. The mRNA vaccine-induced Tfh population and the associated cytokine system in susceptible patients can promote podocyte injury [2]. Second, previous reports [4,5] have shown the development of recurrent FSGS lesions as early as 1 to 2 months after renal transplantation, which further support that the sclerotic lesions visible in this case could be a consequence of rapidly progressive podocytopathy triggered by a COVID-19 mRNA vaccine. Third, many viral infections, including COVID-19, are well-known triggers for glomerular lesions and stimulate the onset of *de novo* and relapsing GN [2,6]. Because mRNA itself can be highly immunogenic, like an intact mRNA virus,
COVID-19 mRNA vaccine-induced immune responses are analogous to COVID-19 virus-induced immune responses, both resulting in de novo and relapsing GN \cite{2,7}. It is noteworthy that the FSGS in our case was a non-collapsing cellular variant, while COVID-19-induced FSGS is most commonly the collapsing type \cite{7}.

Our patient with no apparent underlying disease presented with FSGS after vaccination. We also acknowledge that increased patient awareness of symptoms after vaccination might lead to the recognition of previously undiagnosed kidney disease \cite{2}. Although these associations do not prove causation, we believe that the abrupt onset of nephrotic syndrome following vaccination and the consistent time course of events indicate a direct role of mRNA vaccines \cite{2,6}. Therefore, physicians should be aware of the possibility of FSGS development associated with vaccination. Further studies are needed to verify the cause of FSGS related to administration of COVID-19 vaccine and to study the risk factors for FSGS after COVID-19 immunization.

Conflicts of interest

The authors declare that there are no competing interests.

Authors’ contributions

Conceptualization: JRK, SHB
Data curation: CAL, SY
Investigation: CAL, SY, EJK, JWS
Methodology: HSL, EJK, JWS
Visualization: CAL, HSL
Writing–original draft: CAL, HSL, JRK, SHB
Writing–review & editing: CAL, HSL, JRK, SHB
All authors read and approved the final manuscript.

ORCID

Cho A Lim, https://orcid.org/0000-0002-3434-8801
Hyun Soon Lee, https://orcid.org/0000-0003-0682-3115
Songuk Yoon, https://orcid.org/0000-0002-9029-1918
Eun Jung Kim, https://orcid.org/0000-0002-4033-2769
Jang Won Seo, https://orcid.org/0000-0002-3495-5388
Ja-Ryong Koo, https://orcid.org/0000-0003-4245-2569
Seon Ha Baek, https://orcid.org/0000-0002-4751-9817

Figure 2. Kidney biopsy findings. (A) A periodic acid-Schiff-stained glomerulus showing a segmental area of sclerosis (arrow) with overlying podocyte proliferation. Scale bar = 25 μm. (B) An electron micrograph of a glomerulus showing aggregates of red blood cells (RBCs) in the capillary lumen with a platelet (black arrow) and fibrin fibrils (white arrows) attached. The foot processes of the podocyte are diffusely effaced. Scale bar = 2 μm.
References

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 resubmit 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. If the submission of visual abstract is delayed, there is inevitable delay in publication. Please submit it within the specified time.

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 papers as follows:

- Original Article, Review Article, Special Article, and Study Protocol: KRW 1,000,000 (Korea) / USD 1,000 (rest of world)
- Correspondence, Image in Practice: KRW 300,000 (Korea) / USD 300 (rest of world).

There are no additional charges based on color, length, figures or other elements. The publication costs for invited papers such as editorials, some reviews and special articles 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.
OPTIMIZE TROUGH LEVEL
START LIFE—LONG JOURNEY
INDICATIONS
1. Renal anemia
2. Chronic kidney disease with dialysis

DOSE AND ADMINISTRATION
- For adult patients:
  - Initial dose: The usual dose of NESP in adult patients is 20 μg to be administered as a single intravenous injection once weekly.
  - Maintenance dose: When correction of anemia is achieved, the usual dose of NESP in adult patients is 30–120 μg as darbepoetin alfa (pegylated recombinant), to be administered as a single injection once every two weeks subcutaneously or intravenously. If a decrease in hemoglobin concentration is observed, the frequency of administration can be increased to once every four weeks. The dose should be adjusted by the healthcare provider according to the patient's response.

- For pediatric patients:
  - Initial dose: The usual dose of NESP in pediatric patients is 15–40 μg as darbepoetin alfa (pegylated recombinant), to be administered as a single injection once weekly. The dose should be titrated to achieve the desired hemoglobin concentration.

- For patients with chronic kidney disease:
  - Initial dose: The initial dose of NESP in patients with chronic kidney disease is 100 μg to be administered as a single injection once every two weeks subcutaneously or intravenously.

- Initial dose at the switching from erythropoiesis-stimulating agents:
  - The initial dose of NESP should be titrated based on the patient's response and the desired hemoglobin concentration.

PRECAUTIONS
- See the package insert.

STORAGE
Store in a lightproof container at 2–8°C and avoid freezing.

PACKAGING
1 syringe, 10 syringes for NESP 20 μg, 30 μg, 40 μg, 60 μg, 120 μg, respectively.

MANUFACTURED BY:
Takeda Pharmaceutical Co., Ltd.
1040-22 Matsubara, Takatsuki-shi, Osaka, Japan
Kyowa Hakko Kirin Co., Ltd.
105-1 Higashimurayama-cho, Takaoka-shi, Gifu, Japan

IMPORTED BY:
Kyowa Kirin K.K.
176 Aca Tower, 490, Northpoint, Gangnam-gu, Seoul, 06223, Rep. of Korea
TEL: 02-3471-4613 FAX: 02-3471-4632
http://www.kyowa-kirin-korea.com
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 Yeoui-daero,
Yeongdeungpo-gu, Seoul, 07320, Rep. of Korea
Telephone: +822 2146 8800
Fax: +822 3453 9213
www.freseniusmedicalcare.asia
You can trust, Atacand

Easy to administration by small size of 7 mm
(based on ATACAND* 16 mg)

Proven data on Heart Failure**

Strong and Sustained BP Control†-‡

** Heart failure and impaired left ventricular systolic function (NYHA class II–IV, LVEF ≤35%) as add-on therapy to Angiotensin Converting Enzyme (ACE) inhibitors or (2) when ACE inhibitors are not tolerated

† Reference
3. FDA drug safety alert. Available at: https://www.fda.gov, as of 10-10-2021.

AstraZeneca
제품명
솔리리스®
조성
1바이알(30mL)중 에 kull리주맙 300mg
효능·효과
1) 발작성 야간 혈색소뇨증(PNH : Paroxysmal Nocturnal Hemoglobinuria)용혈을 감소시키기 위한 발작성 야간 혈색소뇨증(PNH : Paroxysmal Nocturnal Hemoglobinuria)환자의 치료. 수혈 이력과 관계없이, 높은 질병 활성을 의미하는 임상 증상이 있는 환자의 용혈에 임상적 이익이 확립되었다.
2) 비정형 용혈성 요독 증후군(aHUS : atypical Hemolytic Uremic Syndrome)보체 매개성 혈전성 미세혈관병증을 억제하기 위한 비정형 용혈성 요독 증후군(aHUS : atypical Hemolytic Uremic Syndrome)환자의 치료
사용제한 : 시가(Shiga) 톡신 생성 대장균에 의한 용혈성 요독 증후군(STEC-HUS)환자 대상의 적용을 권장하지 않는다.
3) 전신 중증 근무력증(Generalized Myasthenia Gravis)항아세틸콜린 수용체 항체 양성인 환자의 불응성 전신 중증 근무력증(Refractory gMG: Refractory Generalized Myasthenia Gravis)의 치료
4) 시신경 척수염 범주 질환(KR.ECU.21.03.16)(Neuromyelitis optica spectrum disorder)항아쿠아포린-4(AQP-4) 항체 양성인 환자의 시신경 척수염 범주질환(NMOSD: Neuromyelitis optica spectrum disorder)의 치료
용법·용량
심각한 감염에 대한 위험을 줄이기 위해서 환자들은 최신의 백신 접종 지침(Advisory Committee on Immunization Practices(ACIP)recommendations)에 따라 백신 접종을 해야 한다.(사용상의 주의사항 1. 경고 항 참고)
이 약은 정맥투여되어야 하며 급속정맥투여(IV push) 또는 일시정맥투여(IV bolus)로 투여해서는 안된다. 

성인
1) 발작성 야간 혈색소뇨증(PNH) : 첫 4주간은 매 7일마다 600 mg, 네 번째 용량 투여 7일 후에 다섯 번째 용량으로 900 mg을 투여하고, 그 후에는 매 14일마다 900 mg을 투여한다. 이 약은 권장 투여량과 일정에 맞게 투여, 혹은 예정된 일정의 2일 전/후로 투여 되어야 한다.
2) 비정형 용혈성 요독 증후군(aHUS) 및 불응성 전신 중증 근무력증(Refractory gMG) 및 시신경 척수염 범주질환(NMOSD) : 첫 4주간은 매 7일마다 900 mg, 네 번째 용량 투여 7일 후에 다섯 번째 용량으로 1200 mg을 투여하고, 그 후에는 매 14일마다 1200 mg을 투여한다. 

소아
1) 비정형 용혈성 요독증후군(aHUS) 만 18세 미만의 aHUS 환자일 경우, 체중에 따라 권장 일정으로 투여한다. (제품정보 원문 용법·용량 [표 1] 만 18세 미만 환자에서의 권장투여법 참고) 이 약은 권장 투여량과 일정에 맞게 투여, 혹은 예정된 일정의 2일 전/후로 투여되어야 한다.

혈장교환요법 및 신선 동결혈장투여시 성인 및 소아 비정형 요독증후군, 성인 불응성 전신 중증 근무력증 및 시신경 척수염 범주질환 환자에 대해 PE/PI(혈장 교환요법 [plasma exchange 또는 plasmapheresis], 또는 신선 동결혈장투여)가 필요하다. (제품정보 원문 용법·용량 [표 2] PE/PI 이후 이 약의 추가적 투여법 참고)
사용상의 주의사항
1. 경고
중대한 수막구균 감염 작용기전으로 인하여 이 약의 사용은 중대한 수막구균 감염(패혈증 그리고/또는 뇌수막염)에 대한 환자의 감수성을 증가시킨다. 이 약의 투여 환자에서 치명적이고 생명을 위협하는 수막구균 감염이 발생하였다. 수막구균 감염은 어느 혈청군에 의해서도 발생할 수 있지만, 이 약의 투여 환자들은 흔하지 않은 혈청군(X 등)에 의한 질환이 발생할 수 있다. 감염의 위험성을 낮추기 위하여, 이 약의 치료가 지연됨으로 인한 위험이 수막구균 감염 발생의 위험성보다 큰 경우를 제외하고는 모든 환자들은 반드시 이 약의 투여 시작 최소한 2주 전에 수막구균 백신을 투여 받아야 한다. 만약 접종 받지 않은 환자가 긴급히 이 약의 치료를 받아야 하면, 최대한 빨리 수막구균 백신을 투여 받도록 한다. 수막구균 백신 접종 이후 2주 이내 이 약을 투여할 경우, 4가 수막구균 백신 접종 이후 2주 동안 적절한 예방적 항생요법으로 치료 받아야 한다. 흔한 병원성 수막구균 혈청군을 예방하기 위하여 가능하다면 혈청군 A, C, Y, W135, B에 대한 백신이 권장된다. 환자들은 백신 사용을 위한 최신의 백신 접종 지침(Advisory Committee on Immunization Practices(ACIP)recommendations)에 따라 백신을 접종 혹은 재접종 받아야 한다. 백신 접종은 보체를 더욱 활성화시킬 수 있다. 결과적으로, PNH, aHUS, 불응성 gMG 및 NMOSD를 포함한 보체 매개 질환을 가진 환자들은 용혈(PNH의 경우)이나 혈전성 미세혈관병증(TMA; aHUS의 경우) 또는 중증 근무력증의 악화(불응성 gMG의 경우) 또는 재발(NMOSD의 경우)과 같은 그들의 기저 질환의 징후 및 증상이 증가하는 경험을 할 수 있다. 따라서, 지침에 따른 백신 접종 이후 질환의 증상에 대해 면밀히 관찰되어야 한다. 백신 접종은 수막구균 감염 위험을 줄일 수 있지만, 완전히 없애지는 않는다. 적절한 항생제 사용에 대한 공식 지침(예: 국내 성인 세균성 수막염의 임상진료지침 권고안 등)을 고려하여야 한다. 수막구균 감염의 초기 징후나 증상이 나타나는지 면밀히 관찰하고, 감염이 의심되면 즉시 검사받아야 한다. 환자는 이러한 징후와 증상 및 즉시 치료를 받는 절차에 대해 안내 받아야 하며, 담당 의사는 반드시 환자와 이 약의 치료의 위험과 이익을 상의해야 한다. 수막구균 감염은 초기에 발견하고 치료하지 않으면 급격히 치명적이고 생명을 위협하게 될 수 있다. 중대한 수막구균 감염을 치료받는 환자는 이 약의 투여를 중지하도록 한다.
2. 다음 환자에는 투여하지 말 것
1) 이 약의 주성분, 뮤린 단백질 또는 기타 구성성분에 과민반응이 있는 환자
2) 치료되지 않은 중대한 수막구균(Neisseria meningitidis) 감염 환자
3) 수막구균(Neisseria meningitidis) 백신을 현재 접종하지 않은 환자 또는 백신 접종 이후 2주 동안 적절한 예방적 항생요법으로 치료를 받지 않은 환자(이 약의 치료를 늦추는 것이 수막구균 감염을 일으키는 것보다 중대하지 않은 경우)
3. 다음 환자에는 신중히 투여할 것
1) 기타 전신 감염: 작용기전으로 인하여 이 약의 치료는 활성 전신 감염이 있는 환자들에게 주의하여 투여하여야 한다. 이 약은 말단 보체 활성을 차단하므로 환자들은 감염, 특히 Neisseria균 및 피낭성 세균(encapsulated bacteria) 감염에 대한 감수성이 증가할 수 있다. 파종성 임균 감염을 포함하는 N. meningitidis 외의 Neisseria 종에 의한 중대한 감염이 보고되었다. 잠재적인 중대한 감염과 그 증상 및 징후에 대한 인식을 높이기 위하여 환자용 정보 안내서의 정보를 환자에게 제공해야 한다. 임질 예방에 관해 환자에게 조언해야 하고 위험성이 있는 환자는 정기적인 검사를 권고한다. 더욱이, 면역력이 약화된 환자와 호중구 감소 환자에서 아스페르길루스 감염이 발생하였다. 이 약을 투여 받는 소아는 폐렴연쇄상구균(Streptococcus pneumonia)과 인플루엔자 간균 B형(Haemophilus influenza type b(Hib))에 의해 중대한 감염을 일으킬 위험이 증가할 수 있다. 폐렴연쇄상구균(Streptococcus pneumonia)과 인플루엔자 간균 B형(Haemophilus influenza type b(Hib))에 의한 감염을 예방하기 위해 최신의 백신 접종 지침에 따라 백신 접종을 받도록 한다.
4. 약물이상반응
시판 후 보고 및 완료된 임상시험에서 보고된 약물이상반응(발생률 1% 이상 발췌): 매우 흔하게(≥1/10) – 두통, 흔하게(≥1/100 ~ <1/10) - 폐렴, 상기도감염, 비인두염, 기관지염, 요로 감염, 구강 헤르페스, 백혈구감소증, 빈혈, 불면, 현기증, 미각이상, 고혈압, 기침, 입인두통, 설사, 구토, 구역, 복부통증, 발진, 탈모, 소양증, 관절통, 근육통, 열, 피로감, 인플루엔자 유사질환모든 임상시험에서, 가장 중대한 이상반응은 수막구균 패혈증이었고, 이는 이 약으로 치료받은 환자에서 수막구균 감염증의 흔한 증상이었다. 수막구균 패혈증의 징후와 증상에 대해 환자에게 알리고 즉시 의료 조치 받아야 한다. Neisseria gonorrhoeae, Neisseria sicca / subflava, Neisseria spp unspecified로 인한 패혈증을 포함하여 Neisseria 종의 다른 사례들이 보고되었다.
MDS-101
Asahi Dialysis System MDS-101
Dialysis Equipment

Slim & Smart
High visibility and Simplified procedures
Secured ultrafiltration system
Easy maintenance
Boryung Renal Business Unit provides **TOTAL RENAL CARE**

- **One-Chart Care**: We provide one-stop service by building an integrated pipeline.
- **Lifetime Care**: We always put the patient's health first and care for the whole life.
- **Sustainable Care**: We devote for continuous product development and service improvement.
- **Care Companion**: We work with therapists to find the optimal solution.
At B. Braun, we don't just develop products. We provide solution for life.

Diacap Pro
THE TRUSTED PERFORMER

Dialog+
THE POWER OF FLEXIBILITY
그래 이제! 크레 메진!
크레메진은 당뇨병성 콤플병 환자의 신장보호효과를 통한 만성신부전 진행을 억제시킵니다.

복용이 더욱 편리해진 크레메진 정 출시 예정
(21년 8월 신규허가획득)

inno.N
Making adherence part of their daily lives

Effective phosphate management, simplified

- Increased Patient Satisfaction: Effective control with 3000mg/day
- Reduce Pill Burden: One tablet or powder each meal
- Well Established Safety Profile: Over 10 years of safety data


Prescribing Information: Before prescribing please consult the Full Summary of Product Characteristics (SmPC). Presentation: Chewable tablets containing 500 mg, 750 mg of lanthanum (as lanthanum carbonate) (hydroxide). Oral powder containing 1000 mg of lanthanum (as lanthanum carbonate hydrate). Both the chewable tablets and oral powder contain citric acid, containing active (SmPC). Fosrenol is indicated in adult patients as a phosphate binding agent for use in the control of hyperphosphatemia in chronic kidney failure patients on haemodialysis or continuous ambulatory peritoneal dialysis (CAPD). Fosrenol is also indicated in adult patients with chronic kidney disease not on dialysis with serum phosphate levels >5.5 mg/dl. In whom a decrease of phosphate diet alone is insufficient to control serum phosphate level. Dosage and Administration: For oral use. Adults, including older people (>65 years): Fosrenol should be taken with or immediately after food, with the daily dose divided between meals. The tablets must be chewed completely and not swallowed whole. To aid with chewing the tablets may be crushed. Fosrenol oral powder is intended to be mixed with a small quantity of soft food (e.g., applesauce or other similar food products) and consumed immediately (within 15 minutes). The dose of Fosrenol should be titrated every 2.5 weeks until an acceptable serum phosphate level is reached. Controlled studies have demonstrated an adequate serum phosphate level for 750mg per day. The maximum daily dose studied, in a limited number of patients, is 3750mg. Patients who require a lanthanum therapy usually have an acceptable serum phosphate level at doses of 1500–3000mg lanthanum per day. Pediatrist population (<18 years): The safety and efficacy of Fosrenol in children and adolescents has not been established. Use in children and adolescents is not recommended. Hepatic impairment: The effect of hepatic impairment on Fosrenol pharmacokinetics has not been assessed. Due to its mechanism of action and the lack of hepatic metabolism, doses in hepatic impairment should not be modified, but patients should be monitored for adverse effects. Adverse Effects: Very common: (≥1/10): headache, abdominal pain, diarrhea, nausea, vomiting, allergic skin reactions. Common: <1/100 to <1/10: patients: constipation, dyspepsia, flatulence, hypocalcemia. Consult SmPC for information on less common side effects. Date of Revision: March 2018.

For further information, please refer to the latest prescribing information at www.fosrenol.co.kr or http://drugs.medicines.org.uk.

JW Pharmaceutical
2477, Namdaseowon-ro, Seocho gu, Seoul, 06725, Korea
Tel: +82-2-840-6777  Customer Call: +82-3588-2675
www.jw-pharma.co.kr

Takeda
The 1st launched medicine of Calcium polypropylene sulfonate in Korea

Various formulations for medication convenience (Powder/Granule/Suspension)

Treatment agent of Hyperkalemia

KALIMATE

Powder / Granule / Suspension

REFERENCES

1. 신흥의약품인증, 원활한약품도시어: 히알론산-카리타트
2. 2019 SO IQVIA DATA 기준(국내 고갈혈증 치료제 판매량)

KALIMATE

The most prescribed treatment agent of Hyperkalemia in Korea

Various formulations for medication convenience (Powder/Granule/Suspension)

Treatment agent of Hyperkalemia

KALIMATE

Powder / Granule / Suspension

REFERENCES

1. 신흥의약품인증, 원활한약품도시어: 히알론산-카리타트
2. 2019 SO IQVIA DATA 기준(국내 고갈혈증 치료제 판매량)

KALIMATE

The most prescribed treatment agent of Hyperkalemia in Korea

Various formulations for medication convenience (Powder/Granule/Suspension)

Treatment agent of Hyperkalemia

KALIMATE

Powder / Granule / Suspension

REFERENCES

1. 신흥의약품인증, 원활한약품도시어: 히알론산-카리타트
2. 2019 SO IQVIA DATA 기준(국내 고갈혈증 치료제 판매량)

KALIMATE

The most prescribed treatment agent of Hyperkalemia in Korea

Various formulations for medication convenience (Powder/Granule/Suspension)

Treatment agent of Hyperkalemia

KALIMATE

Powder / Granule / Suspension

REFERENCES

1. 신흥의약품인증, 원활한약품도시어: 히알론산-카리타트
2. 2019 SO IQVIA DATA 기준(국내 고갈혈증 치료제 판매량)
Homechoice Claria enabled by Sharesource
from pediatric to elderly population

Homechoice Claria | SIMPLE & SMART APD for your patient to maintain daily life

- Intuitive Triage Dashboard
- Patient Snapshot
- Treatment Summary
고혈압 치료의 시작은 세르비에 고혈압 Family로!

COUNT ON FABRAZYME

Treat your Fabry disease patients with Fabrazyme

1 mg/kg
once every 2 weeks\(^1\)