Autophagy and regulation of aquaporins in the kidneys

Acute kidney disease: an overview of the epidemiology, pathophysiology, and management

Comparison of cardiovascular event predictability between the 2009 and 2021 Chronic Kidney Disease Epidemiology Collaboration equations in a Korean chronic kidney disease cohort: the KoreaN Cohort Study for Outcome in Patients With Chronic Kidney Disease study

Comparison of the medium cutoff dialyzer and postdilution hemodiafiltration on the removal of small and middle molecule uremic toxins

Shared Decision Making for Choosing renAl Replacement Therapy in Chronic Kidney Disease Patients (SDM-ART trial): study protocol for randomized clinical trial
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.

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Sun Ki Kim, Hye-Ja Park, Dong-Ho Yang
As the number of end-stage kidney disease (ESKD) patients with complex comorbid conditions increases rapidly, the medical burden to treat them is increasing, and efforts to improve the quality of life and prognosis of ESKD patients are important issues in the medical field [1].

Patients with ESKD have worse overall survival compared with the general population [2]. Survival rates may vary depending on age, comorbidities, and type of treatment, and the quality of dialysis facilities, and medical staff can affect the overall outcome of patients with ESKD, including patient safety and treatment effectiveness.

In particular, the role of the dialysis specialist can be an important factor in determining patient prognosis [3]. Dialysis specialists consider various factors, including the patient’s overall health, lifestyle, preferences, vascular access, and medical history, to determine the most suitable dialysis regimen for each individual. They continuously monitor the patient’s clinical condition and make necessary adjustments to the treatment plan based on responses to dialysis, blood test results, fluid balance assessments, medication, and potential complications. Additionally, dialysis specialists evaluate and manage vascular access, ensuring proper functioning and resolving any issues that may arise. To enhance patients’ psychosocial well-being and adherence to treatment, it is important for medical staff to provide emotional support and address patients’ concerns.

The role of dialysis specialists, such as ongoing monitoring, prompt intervention, and collaboration with the medical team, can significantly enhance the quality of life and overall well-being of patients with ESKD, ultimately leading to improved patient outcomes.

Therefore, it is important to define the qualifications of medical staff and develop appropriate quality control programs to manage them. Policies regarding the care of patients undergoing dialysis vary across countries. However, many countries have established specific guidelines, regulations, and qualifications for healthcare providers or medical staff involved in dialysis care, recognizing the importance of including physicians trained in dialysis management in patient care [4,5].

In the United States, prescription and administration of dialysis are regulated by guidelines and policies. The Centers for Medicare and Medicaid Services oversees the reimbursement and quality standards for dialysis services through the End-Stage Renal Disease program [6].

In the United States, physicians typically require specialized training in nephrology and board certification to
provide dialysis care. They are responsible for overseeing the overall treatment of dialysis patients, including prescription and monitoring of dialysis, and managing complications. Collaboration with nephrologists is important to ensure proper patient care and dialysis management.

In Japan, physicians with nephrology training are qualified to prescribe and provide dialysis to patients [3]. Other countries also have systems in place to strengthen collaboration between physicians, nephrologists, and other specialists, with financial incentives for specialist care for patients with ESKD [4,7].

In Korea, the designation of dialysis specialists is a voluntary system provided by the Korean Society of Nephrology to identify specialists who meet certain requirements and demonstrate competence in the field of nephrology. To be certified as a dialysis specialist, physicians must complete at least 1 year of training at a dialysis specialist training hospital. Certification also requires ongoing professional development and continuing medical education.

However, it is important to note that the dialysis specialist system operated by the Korean Society of Nephrology is not mandatory in Korea. Efforts are being made to institutionalize the system; however, there are currently no supportive legal regulations. Consequently, physicians in Korea who have not received systematic training in dialysis patient management can prescribe and administer dialysis, although the government evaluates the proper operation of outpatient dialysis centers and assesses the quality of care provided.

Park et al.’s study [8] in *Kidney Research and Clinical Practice* provides strong support for the institutionalization of dialysis specialists. This study utilized large-scale national insurance data to enhance their reliability and value as evidence for improving dialysis-related systems and national policies. The study employed propensity score matching to enhance the data analysis. Although the socioeconomic level, insurance type, cause of death, and other factors were not analyzed, this study effectively demonstrated variations in the long-term prognosis of patients based on the quality of medical staff. The analysis incorporated diverse data such as hemoglobin, albumin, calcium, phosphorus, and dialysis adequacy, offering valuable insights into the impact of physician quality on patient mortality, dialysis efficiency, and important complications such as hypertension, anemia, and mineral metabolism.

Thus, this study significantly contributes to our understanding of the broad effects of physician quality in these areas. These results emphasize the need to improve the safety and survival of dialysis patients while highlighting the importance of institutional support.

Recognizing that regulations concerning medical staff are crucial for the quality management of dialysis centers, it is imperative to make efforts to establish a foundation for system improvements, as demonstrated in this paper. With these considerations, it is hoped that the national system will be enhanced through the continuous efforts of the medical community and government participation, ultimately creating a safe treatment environment for patients undergoing dialysis.

**Conflicts of interest**

The author has no conflicts of interest to declare.

**Data sharing statement**

The data presented in this study are available on request from the corresponding author.

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**References**


In 2021, researchers of the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) published new CKD-EPI equations without race coefficients [1]. These equations showed acceptable estimation of the measured glomerular filtration rate (GFR), and the equation incorporating both creatinine and cystatin C showed better performance than the equations incorporating either creatinine or cystatin C alone. Therefore, the National Kidney Foundation and the American Society of Nephrology Task Force recommend the immediate adoption of the new equations and the use of cystatin C in all laboratories in the United States [2]. However, the publication of these new estimated GFR (eGFR) equations was largely driven by efforts to address healthcare disparities associated with racial diversity in the United States [3]. Because this change was based on social rather than biological issues in the United States, further scientific background should be collated to decide whether these new equations should be adopted in other countries.

Two aspects must be evaluated for the adoption of the new equations: predictability and accuracy. Kim et al. [4] evaluated the predictive performance of the 2021 CKD-EPI equations for cardiovascular disease and mortality using data from the KoreaN Cohort Study for Outcome in Patients With Chronic Kidney Disease (KNOW-CKD). This study showed that the 2021 CKD-EPI equations based on creatinine alone and both creatinine and cystatin C did not show superior predictability compared to the original 2009 creatinine-based CKD-EPI equation. The results of this study should be interpreted with caution because of the relatively lower incidence of cardiovascular disease and mortality in the KNOW-CKD cohort than in other CKD cohorts. However, I and other KNOW-CKD investigators have also previously evaluated the predictive performance of the new equations for the risk of kidney failure [5] and found a similar performance of the new equations compared to the original 2009 equation. In both studies, the difference in eGFR between the 2009 and 2021 creatinine-based equations was approximately 3 mL/min/1.73 m². Therefore, the small eGFR difference between the 2009 and 2021 equations is not expected to have a significant impact on the predictive performance. However, in terms of accuracy, a recent Korean study showed that the 2021 creatinine-based equation overestimated the measured GFR such that the median bias was 4.8 mL/min/1.73 m², which was significantly larger than that of the 2009 equation (1.8 mL/min/1.73 m²) [6].

The difference in bias between the equations was almost
The accuracy of the 2021 CKD-EPI equations should be further validated in various Asian cohorts, especially those with cystatin C. However, based on current evidence, there is no benefit in using the new CKD-EPI equations in Asians (Table 1). The new equations reclassify a significant proportion of CKD grade 3 patients close to the threshold of 60 mL/min/1.73 m² to grade 2, which may delay diagnosis and intervention of CKD for many Asian patients. Moreover, the application of the new equations is unlikely to improve the prediction of outcomes in Asian patients. Furthermore, changes in the prevalence of CKD can influence CKD-related research and healthcare policies in Asian countries. Therefore, the adoption of the new CKD-EPI equations requires further discussion among healthcare professionals and other stakeholders in Asian countries. In particular, it requires careful discussion which eGFR equation should be recommended in the next CKD guidelines of the Kidney Disease: Improving Global Outcomes.

Table 1. Application of new race-free creatinine-based CKD-EPI equation for Asians

<table>
<thead>
<tr>
<th>Effects</th>
<th>2021 equation vs. 2009 equation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Predictability</td>
<td></td>
</tr>
<tr>
<td>Cardiovascular disease and mortality [4]</td>
<td>Not significant</td>
</tr>
<tr>
<td>Kidney failure [5]</td>
<td>Not significant</td>
</tr>
<tr>
<td>Accuracy, median bias (mL/min/1.73 m²)</td>
<td></td>
</tr>
<tr>
<td>Korea [6]</td>
<td>4.8 vs. 1.8</td>
</tr>
<tr>
<td>China [7]</td>
<td>6.4 vs. 3.3</td>
</tr>
<tr>
<td>CKD prevalence (%)</td>
<td></td>
</tr>
<tr>
<td>Korea [6]</td>
<td>11.0 vs. 10.3</td>
</tr>
<tr>
<td>Korea [8]</td>
<td>3.1 vs. 2.2</td>
</tr>
<tr>
<td>Singapore [8]</td>
<td>23.3 vs. 18.2</td>
</tr>
<tr>
<td>China [8]</td>
<td>2.0 vs. 1.6</td>
</tr>
<tr>
<td>India [8]</td>
<td>14.8 vs. 10.8</td>
</tr>
<tr>
<td>Russia (Central Asia) [8]</td>
<td>29.1 vs. 22.2</td>
</tr>
</tbody>
</table>

CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration.

Conflicts of interest

The author has no conflicts of interest to declare.

Data sharing statement

The data presented in this study are available on request from the corresponding author.

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References

As renal function deteriorates, uremic toxins accumulate in the body and are traditionally classified as small water-soluble compounds, protein-binding compounds, and middle molecules. These accumulated uremic toxins not only cause various uremic symptoms, such as nausea, vomiting, anorexia, fatigue, pruritus, mental status changes, and restless leg syndrome, but are also associated with mortality and morbidity [1]. Therefore, efficient removal of these uremic toxins through dialysis is a carefully considered therapeutic strategy by nephrologists. Removal of these uremic toxins is thought to improve uremic symptoms and clinical outcomes. Among the uremic toxins, small water-soluble compounds are effectively removed by conventional hemodialysis (HD), whereas protein-bound compounds and middle molecules are not. However, technological advances, including high-efficiency hemodiafiltration (HDF) and the development of new HD membranes, such as medium cutoff (MCO) dialyzers, have made it possible to remove molecules of up to approximately 50 kDa [2].

Recent studies have reported that high-volume HDF improves clinical outcomes, such as all-cause mortality [3]. The survival benefit of high-volume HDF is thought to be partly related to the removal of protein-bound compounds and middle molecules. Because MCO-HD is as effective as high-volume HDF in the removal of protein-binding compounds and middle molecules, MCO-HD is expected to show survival benefits similar to those of high-volume HDF [4]. However, unlike high-volume HDF, no study has reported that MCO-HD shows a survival benefit. Moreover, the results of previous studies on the effects of MCO-HD on the removal of middle molecules have been inconsistent [4,5].

In this respect, the paper titled “Comparison of the medium cutoff dialyzer and postdilution hemodiafiltration on the removal of small and middle molecule uremic toxins” published in *Kidney Research and Clinical Practice* by Kim et al. [6] is interesting. In this prospective non-randomized crossover study involving nine patients, Kim et al. [6] compared the small and middle molecule clearance of MCO-HD with that of postdilution HDF. There was no difference in the removal of uremic toxins under 12,000 Da between high-flux HD, MCO-HD, and postdilution HDF, which is consistent with the results of previous studies [5]. However, Kim et al. [6] reported that MCO-HD was more effective than postdilution HDF for the middle molecules. Among the middle molecules, there was no significant difference in the reduction ratio (RR) of β2-microglobulin (B2MG) (HDF vs. MCO-HD, 67.9% ± 11.7% vs. 71.6% ± 5.7%; p = 0.26), but myoglobin, kappa free light chain (FLC), and lambda FLC (HDF vs. MCO-HD, 15.8% ± 8.5% vs. 49.8% ± 6.5%; p = 0.008) were significantly higher in MCO-HD.
than in postdilution HDF. However, these results are inconsistent with those of previous studies [4,5]. In 2022, Hadad-Arrascue et al. [4] compared the clearance of middle molecules in postdilution HDF (n = 21) and MCO-HD (n = 22) in an open randomized clinical study. In this study, the RRs of B2MG, kappa FLC, and lambda FLC were not significantly different between the two groups. In 2022, Kim et al. [5] conducted a study with a design very similar to that of Kim et al. [6] and compared the clearance of HF-HD, postdilution HDF, and MCO-HD for urea, B2MG, indoxyl sulfate (IS), p-cresyl sulfate (pCS), kappa FLC, and lambda FLC [5]. There was no significant difference in urea clearance between dialysis modalities, as reported by Kim et al. [6]. However, the RR of B2MG was significantly higher in postdilution HDF than in MCO-HD (HDF vs. MCO-HD, 79.54% ± 4.72% vs. 75.32% ± 4.64%; p < 0.001). On the other hand, the RR of lambda FLC was significantly higher in MCO-HD than in postdilution HDF, similar to the study by Kim et al. [6] (HDF vs. MCO-HD, 43.48% ± 7.41% vs. 51.52% ± 6.08%; p < 0.001). This discrepancy in the results is likely due to differences in the study design. The study by Kim et al. [5] differed from that by Kim et al. [6] in that it was a randomized study with more patients (22 patients), used a hemodiafilter with a larger inner diameter for postdilution HDF treatment, and had a higher convection volume. In particular, the possibility that the use of a hemodiafilter for

**Figure 1.** The modeled effect of increasing dialytic clearance on time required to reach solute concentration equilibrium. Modeling was performed for four hypothetical solutes with varying dialytic RRs (0% for CMPF, 25% for β2-microglobulin, 50% for hippurate, and 75% for urea, respectively) when receiving hemodialysis as a 4-hour thrice-weekly treatment. It was assumed that the intercompartment clearance was higher than the dialytic clearance so that the accessible compartments would rapidly refill from the inaccessible compartments during dialysis; therefore, RR can represent blood, plasma or serum concentration. It was also assumed that each solute was generated constantly and has no nondialytic clearance. The colored lines represent the average concentration of each solute per week. The arrow indicates the time at which dialytic clearance of each solute increases. The asterisks (*) indicate the time at which the concentration for each solute was within 1% of equilibrium during the following week’s dialysis. The solute concentration is plotted as a relative percentage of prehemodialysis concentration on the y-axis, with the weeks following increase in dialytic clearance on the x-axis. Modified from Husain-Syed et al. [8] with permission of Karger.

B2MG, β2-microglobulin; CMPF, 3-carboxy-4-methyl-5-propyl-2-furanpropionic acid; RR, reduction ratio.

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HDF (FX 800) instead of a high-flux dialyzer (FX 80) during HDF treatment affected the clearance of B2MG cannot be ruled out. Therefore, these limitations must be considered when interpreting the results of Kim et al’s study [6].

As in this study, there are several points to consider when conducting research on the removal of uremic toxins by dialysis or interpreting the results. First, when HD is performed intermittently thrice a week, the unpredictable effect of kinetics on the removal of various uremic toxins must be taken into account [7]. Therefore, when evaluating the ability to remove uremic toxins, the predialysis concentration after a sufficiently long equilibration (>4 weeks) might be a better measure than the RR calculated by measuring the blood concentration before and immediately after the end of dialysis [1,8], as in the study by Kim et al. [6] (Fig. 1). An equilibration time of 4 weeks allows most of the solutes to reach equilibrium while minimizing the occurrence of confounding factors caused by residual kidney function, use of antibiotics, dialytic prescription, and changes in dietary intake [1]. Second, it is necessary to determine the association of removal of uremic toxins with clinical outcomes and quality of life measures [1,9]. Uremic toxins are traditionally classified as small water-soluble compounds with low molecular mass (<500 Da), protein-bound solutes, and middle molecules (≥500 Da). This classification was developed by the European Uremic Toxin (EUTox) work group in 2003 based on their physicochemical properties that affect removal during HD, such as molecular weight, water solubility, and protein affinity. The problem with the physicochemical classification of uremic toxins is that it does not adequately address or reflect the methods of toxin removal from current or contemporary HD techniques (adsorption, convection, and diffusion mechanisms).

To overcome these limitations of EUTox classification, Rosner et al. [1] proposed a new classification system for uremic toxins in 2021. Unlike the EUTox classification, which focuses on the physicochemical properties of uremic toxins, this new classification is characterized by linking uremic toxins with clinical outcomes and quality of life in patients with severe renal failure [1,9]. In this classification, Rosner et al. [1] categorized uremic toxins into two major

<table>
<thead>
<tr>
<th>Uremic toxin source</th>
<th>Water solubility or protein affinity</th>
<th>Molecular characteristics</th>
<th>Marker molecules with known toxicity</th>
<th>Removal by dialysis modalities</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Low-flux HD</td>
<td>High-flux HD</td>
</tr>
<tr>
<td>Exogenous (gut-derived)</td>
<td>Water soluble (protein-bound &lt;80%)</td>
<td>&lt;0.5 kDa, small molecules</td>
<td>Hcy, IS, pCS, CML, and kynurenines</td>
<td>✓</td>
</tr>
<tr>
<td></td>
<td>Protein-bound ≥80%</td>
<td>&lt;0.5 kDa, small protein-bound molecules</td>
<td>Hcy, IS, pCS, CML, kynurenines</td>
<td>✓</td>
</tr>
<tr>
<td>Endogenous (generation by endogenous metabolism)</td>
<td>Water soluble (protein-bound &lt;80%)</td>
<td>&lt;0.5 kDa, small molecules</td>
<td>ADMA, SDMA, uric acid, carbamylated compounds, urea, TMAO</td>
<td>✓</td>
</tr>
<tr>
<td></td>
<td>Water soluble (protein-bound &lt;80%)</td>
<td>0.5–15 kDa, small-middle molecules</td>
<td>β2-microglobulin, IL-8</td>
<td>✓</td>
</tr>
<tr>
<td></td>
<td>Water soluble (protein-bound &lt;80%)</td>
<td>&gt;15–25 kDa, medium-middle molecules</td>
<td>TNF, IL-18, IL-10, IL-6, kappa FLC, myoglobin, sTNFR2, FGF-2, prolactin, complement factor D</td>
<td>✓</td>
</tr>
<tr>
<td></td>
<td>Water soluble (protein-bound &lt;80%)</td>
<td>&gt;25–58 kDa, large-middle molecules</td>
<td>Pentraxin-3, sTNFR1, AGES, FGF23, lambda FLC, CXCL12, IL-2, YKL-400</td>
<td>✓</td>
</tr>
<tr>
<td></td>
<td>Water soluble (protein-bound &lt;80%)</td>
<td>&gt;58–170 kDa, large molecules</td>
<td>Modified albumin</td>
<td>✓</td>
</tr>
</tbody>
</table>

ADMA, asymmetric dimethylarginine; AGES, advanced glycosylation end products; CML, carboxymethyl lysine; CXCL12, C-X-C motif chemokine 12; CX-3CL1, chemokine (C-X3-C motif) ligand 1; FGF, fibroblast growth factor; FLC, free light chain; Hcy, homocysteine; HD, hemodialysis; HDF, hemodiafiltration; IL, interleukin; IS, indoxyl sulfate; pCS, paracresyl sulfate; SDMA, symmetric dimethylarginines; sTNFR, soluble tumor necrosis factor receptor; TMAO, trimethylamine N-oxide; TNF, tumor necrosis factor; YKL-400, chitinase-3-like protein 1.

Modified from Rosner et al. [1] and Kashani et al. [10] with permission of Karger.
groups, exogenous and endogenous uremic toxins, and subdivided each according to their molecular characteristics. The clearance of these uremic toxins was also classified according to dialyzer characteristics (Table 1) [1,10]. In addition, Rosner et al. [1] proposed a panel of biomarkers representative of each uremic toxin in this classification: urea for small (<500 Da) water-soluble molecular mass clearance, parathyroid hormone (9.5 kDa) and B2MG (11.8 kDa) for small-middle (0.5–15 kDa) molecular mass clearance, kappa FLC (22.5 kDa) for medium-middle (>15–25 kDa) molecular mass clearance, and lambda FLC (45 kDa) for large-middle (>25–58 kDa) molecular mass clearance. Additionally, IS and pCS have been proposed for the clearance of protein-bound solutes.

In conclusion, several studies, including this, have revealed that uremic toxins, which are not well removed by conventional high-flux HD, are more effectively removed by new dialysis modalities, such as high-volume HDF or MCO-HD. However, it will be necessary to clarify whether the removal of uremic toxins is related to clinical outcomes in future studies.

Conflicts of interest

The author has no conflicts of interest to declare.

Data sharing statement

The data presented in this study are available on request from the corresponding author.

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References

Introduction

Under physiological conditions, the proteins in the cells or body undergo constant turnover and changes in intracellular protein synthesis and degradation. The fine balance of the protein pool is maintained by several adaptive mechanisms, e.g., the activation of autophagy, endoplasmic reticulum-associated degradation, and an unfolded protein response [1,2]. Protein localization at the membrane is maintained by the interaction between the cytosolic domains of membrane proteins and cytosolic proteins. Membrane protein expression (e.g., transporters and channels) is usually highly dynamic due to protein trafficking between the membrane and cytoplasm and posttranslational modification. Autophagy, a highly conserved lysosomal-dependent degradation pathway of proteins, plays an important role in preserving cellular homeostasis. The importance of autophagy in kidney disease and homeostasis has been previously reviewed [3]. Emerging evidence suggests that autophagy may influence tubular transport in the kidney.

In this article, we aimed to provide an overview of the physiological and pathophysiological roles of autophagy in kidney diseases and, in particular, the current evidence on the pathophysiological roles of autophagy in tubular transport. The therapeutic potentials and challenges are also
discussed when autophagy is targeted for the prevention and treatment of tubular dysfunction in kidney diseases.

**Overview of the autophagic process**

Autophagy is a highly conserved pathway of degrading organelles and proteins in eukaryotes. Autophagy is strictly regulated by autophagy-related genes (ATGs) and many other genes. In autophagy, cellular components, e.g., organelles or proteins, are wrapped in autophagosomes with a double-layer membrane structure, which later fuse with lysosomes for degradation [4]. Thereafter, the degraded products, such as carbohydrates and amino acids, are re-released into the cytoplasm to synthesize new amino acids, nucleotides, and organelles, and they can also provide cells with energy to maintain their basic survival [5,6]. Under basic conditions, only a low level of autophagy is involved in the degradation of damaged or aging organelles, misfolded proteins, and protein aggregates to preserve the normal survival and function of cells [7]. In contrast, when cells are damaged or stimulated by several factors, such as oxidative stress, hypoxia, DNA damage, chemicals, nutrient deprivation, and intracellular microorganisms, autophagy is activated. Autophagy in the body is, therefore, crucial for cell proliferation, differentiation, metabolism, and other physiological processes.

Autophagy was first demonstrated as a protective pathway against starvation conditions, while later evidence indicates that autophagy also contributes to the dysfunction of the cells and the damage to the organs. Three types of autophagy have been categorized, which are dependent on the delivery routes of substrates to the lysosomes, including macroautophagy (or autophagy), microautophagy, and chaperone-mediated autophagy (CMA) [3].

Macroautophagy or autophagy involves multiple steps including initiation, nucleation, expansion, fusion, and degradation [3]. The canonical activation route is induced by formation of a protein complex composed of serine/threonine protein kinases ULK1, ULK2, and other protein partners [3,8]. Activation of the ULK1 induces phosphorylation of the phosphoinositide 3-kinase complex and recruitment of intracellular membranous domains (e.g., endoplasmic reticulum [ER], plasma membrane) to form the omegasome [9]. Two ubiquitin (Ub)-like conjugation systems, the ATG12–ATG5–ATG16L system and the microtubule-associated protein 1 light chain 3 (LC3) system, control the expansion and completion of the autophagosome [10], supporting the maturation of the omegasome into the phagophore. The phagophore segregates the cytoplasmic cargoes and closes upon itself to form the autophagosome [9]. The sequestration of cytoplasmic components could be either selective or nonselective. Selectivity in autophagy could be induced by exploiting autophagy receptors, such as SQSTM1 (p62) and optineurin, to carry specific proteins/organelles to the phagophores [9]. Autophagosomes then merge with early and/or late endosomes and finally fuse with lysosomes, forming the autolysosome [11]. Autolysosomes are not perpetual. When cargo inside the autolysosome gets degraded, autolysosomes disintegrate, allowing the recycling of lysosomal membrane proteins and the regeneration of lysosomes from autolysosomes [3] (Fig. 1).

Microautophagy indicates the process in which cytoplasmic contents are submerged with lysosomes for degradation after lysosome invagination [12]. To date, however, the process of microautophagy and its mechanism have not been thoroughly studied.

CMA is a highly specific form of autophagy that mediates the degradation of soluble cytoplasmic proteins in lysosomes [13]. CMA has only been studied in mammalian cells so far. Unlike macroautophagy and microautophagy, proteins degraded through CMA are recognized by the cytoplasmatic chaperone Hsc70 [14]. Hsc70 and accessory partners bring substrates to the lysosome surface. Subsequently, lysosomal membrane protein 2A recognizes and binds to substrate proteins containing the KFERQ pentapeptide sequence and finally completes the degradation of the protein [15].

Autophagy is not always a simple and non-selective cytosolic degradation pathway, and it can be selective to eliminate specific cargoes [16]. For example, mitophagy is the best-studied form of selective autophagy of mitochondria and is chiefly mediated by LC3-associated autophagy receptors by either Ub-independent or Ub-dependent pathways [3].

Besides the autophagy-lysosome pathway, the Ub–proteasome system also contributes to cellular homeostasis. Through this pathway, Ub-tags are added to damaged or unfolded proteins by E3 Ub–ligases and thereby degraded by the proteasome. A fine balance between the Ub–proteas-
Figure 1. Schematic overview of the regulation of autophagy on AQP2 in the kidney. The classical autophagy process is initiated by the formation of the ULK1/2 complex, which promotes the phosphorylation of PI3K complex, contributing to the formation of the autophagosome membrane. The expansion and maturation of the autophagosome are completed under the regulation of ATG12-ATG5-ATG16L and LC3 systems. In NDI models like hypokalemia, lithium treatment, hypercalcemia, and BUO models, autophagy is induced in the renal principal cells, causing lysosomal-dependent degradation of AQP2 (left). Protein expression and intracellular trafficking of AQP2 are modulated by arginine vasopressin (AVP) through short- and long-term regulation (right). AVP induces the rapid translocation of vesicles containing AQP2 to the apical membrane in the collecting duct principal cells. When AVP is retrieved, a large fraction of AQP2 returns to the cytoplasm to be recycled or to respond to a new AVP challenge, while other AQP2 is ubiquitinated and then degraded via the lysosomal pathway. AQP2 is subjected to post-translational modifications, including phosphorylation and ubiquitylation, which potentially play key roles in its function. Long-term regulation is based on changes in AQP2 abundance via AVP-induced prolongation of the AQP2 protein half-life and Aqp2 gene transcription (right).

AC, adenylate cyclase; AQP, aquaporin; ATG, autophagy-related gene; BUO, bilateral ureteral obstruction; cAMP, cyclic adenosine monophosphate; ER, endoplasmic reticulum; LC3, light chain 3; NDI, nephrogenic diabetes insipidus; PI3K, phosphoinositide 3-kinase; PKA, protein kinase A.

The use of ubiquitination as a recognition signal indicates a close connection between both pathways [9]. Autophagy seems to degrade larger protein aggregates, while the Ub-proteasome system clears small protein oligomers and misfolded proteins in the cell [9,17].

Dysregulated autophagy has been found to contribute to the pathogenesis of acute kidney injury (AKI), incomplete kidney repair, and chronic kidney diseases, indicating the key roles of autophagy in maintaining kidney homeostasis. However, questions remain as to whether autophagy plays a protective or a pathogenetic role in kidney diseases. The signaling pathways and precise mechanisms underlying autophagy in different types of renal cells and several kil-
ney diseases remain unknown.

Aquaporins in the kidney

Water permeability in the nephron and high medullary interstitial osmolality are important factors for urine concentration [18,19]. Aquaporins (AQPs) are water channel proteins that mediate the osmotic water transport across the cell membrane [20].

Water reabsorption in the kidney is mainly facilitated by AQPs located in the tubular epithelial cells. At least seven AQPs have been found to be expressed in the renal tubule. For example, AQP1 is expressed in the apical and basolateral plasma membranes of the proximal tubule and thin descending limb, while AQP2 is expressed in the principal cells of collecting ducts from the cortex to the inner medulla and undergoes arginine vasopressin (AVP)-regulated water reabsorption. Separately, AQP3 and AQP4, which are expressed at the basolateral membrane of collecting duct principal cells, represent exit pathways for water reabsorbed via AQP2 expression at the apical plasma membrane.

AQP2 is regulated by the anti-diuretic hormone vasopressin on both a short- and long-term basis for water reabsorption in the collecting ducts [21]. Short-term regulation is dependent on the translocation of AQP2-expressing vesicles. AVP induces the rapid translocation of vesicles containing AQP2 to the apical membrane and increases the water permeability in the collecting duct principal cells. When AVP stimulation is retrieved, a large fraction of AQP2 on the plasma membrane can be recycled and participate in a new round of translocation to the apical membrane in response to another AVP challenge, while another fraction of AQP2 is ubiquitinated and degraded via the proteasomal and lysosomal pathways [22]. Long-term regulation is based on the changes in AQP2 abundance via AVP-induced prolongation of the AQP2 protein half-life and Aqp2 gene transcription [23] (Fig. 1).

AQP2 is subjected to posttranslational modifications, including phosphorylation and ubiquitylation, which may play key roles in its function. Intracellular shuttle signaling and protein–protein interaction are associated with AQP2 phosphorylation at several sites in the C-terminus. The vasopressin-dependent activation of cyclic adenosine monophosphate-dependent kinase A (protein kinase A) leads to the phosphorylation of AQP2 at serine 256 (S256), which is considered a priming event for downstream phosphorylation at S269 and S264. Vasopressin stimulation also results in the significant dephosphorylation of AQP2 at S261 [24–26]. There are a trio of putative potential ubiquitination sites (cytosolic lysine residues) within the C-terminal domain of AQP2 (K228, K238, and K270). Among them, K270 is the only substrate for ubiquitination, with 1–3 Ubs added in a K63-linked chain [22,27–30]. The ubiquitination of AQP2 at the plasma membrane promotes AQP2 internalization and subsequent proteasomal degradation [22]. Phosphorylation at S261 follows ubiquitination and may stabilize AQP2 intracellularly [31].

Dysregulation of AQP2 has been demonstrated to play a role in water balance disorders, e.g., nephrogenic diabetes insipidus (NDI) and systemic water retention [32]. NDI is triggered by the kidney’s incapability to respond to vasopressin stimulation, leading to polyuria and polydipsia [33]. Compared to the inherited type of NDI, acquired forms of NDI are much more common, among which electrolyte disorders (hypokalemia and hypercalcemia), ureteral obstruction, and lithium use are associated with reduced messenger RNA and protein expression of AQP2 in the kidney [19,34]. The precise underlying molecular mechanisms of these types of NDI remain to be resolved. However, emerging data imply the role of autophagy in the degradation of AQP2 protein during NDI (Table 1).

Autophagy-induced degradation of aquaporin 2 in nephrogenic diabetes insipidus

Electrolyte imbalances, like hypokalemia and hypercalcemia, are a relatively common kind of electrolyte disorder clinically. Both hypokalemia and hypercalcemia can cause mild NDI characterized by reduced AQP2 protein expression in the collecting duct principal cells [35,36]. Recent studies have demonstrated that AQP2 downregulation seen in hypokalemia and hypercalcemia may be mediated by autophagic degradation [37–39] (Fig. 1).

By mass spectrometry (MS)-based proteomics and liquid chromatography-MS/MS, Khositseth et al. [38] demonstrated a reduction in the abundance of AQP2 in the inner medullary collecting ducts (IMCD) and proteins associated with energy metabolism in mitochondria, the organization of the actin cytoskeleton, and cellular adhesion in

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hypokalemic rats. AQP2 phosphorylation at both S256 and S261 was also downregulated. Under electron microscopy, single-membrane autophagolysosomes containing electron-dense membrane structures and double-membrane autophagosome vesicles or phagophores were identified in IMCD cells of the potassium-deprived rats. Immunofluorescence and double-label immunogold electron microscopy revealed the co-localization of AQP2 with both autophagosomes (LC3) and lysosomes (Lamp1) in the IMCD cells of the potassium-deprived rats, supporting the role of autophagic protein degradation as the mechanism involved in the downregulation of AQP2 in IMCD cells after hypokalemia. Interestingly, after potassium replenishment, the normal phenotype of IMCD cells was restored, which coincided with the normalization of AQP2 levels, and its colocalization with autophagy markers was abolished. This indicates that autophagic degradation at least partially contributes to AQP2 downregulation during hypokalemia [38].

Ideally, setting up hypokalemia models in animals with knockdown of various ATGs may be an excellent way to better understand the role of autophagy in AQP2 regulation [38]. Kim et al. [39] generated conditional knockout mice in whom ATG7, a catalyst in autophagy conjugation systems and autophagosome formation, was genetically ablated specifically in AQP2-positive principal cells (Atg7Δpc) of the collecting duct. Thereafter, the group investigated AQP2 regulation in hypokalemia in these mice, and their findings support the role of autophagy in the degradation of AQP2 and further indicate the importance of the canonical autophagy pathway for AQP2 regulation in hypokalemia.

Consumption of a low-K⁺ diet for 2 weeks caused a significant polyuria and urine concentration defect in both Atg7Δ/Δ and Atg7Δpc mice, with these changes being much more pronounced in the Atg7Δpc mice compared to the Atg7Δ/Δ mice. Consistent with this, the protein abundance and apical expression of both AQP2 and pS261-AQP2 in IMCD cells were markedly reduced in both strains, albeit again more so in Atg7Δpc mice compared to Atg7Δ/Δ mice. Notably, after K⁺-depletion, in Atg7Δ/Δ mice, pS261-AQP2 was located restrictively in the intracellular vesicles, while, in Atg7Δpc mice, pS261-AQP2 was found diffusely throughout the cytoplasm, indicating a block of pS261-AQP2 internalization in IMCD cells. In Atg7Δpc mice, in contrast to the reduction of AQP2 protein expression, urinary AQP2 excretion was significantly increased after hypokalemia compared to in Atg7Δ/Δ mice [39].

As expected, hypokalemia induced LC3-positive canonical autophagy in the IMCD cells of K⁺-depleted Atg7Δ/Δ mice, while, in K⁺-depleted Atg7Δpc mice, LC3-negative noncanonical autophagy seemed to have occurred, as more LC3-negative vacuoles were seen in IMCD cells. Interestingly, in K⁺-depleted Atg7Δ/Δ mice, pS261-AQP2 and LC3 were colocalized with LC3-positive puncta, which

Table 1. The roles of autophagy in the degradation of AQP2 during hypokalemic situations

<table>
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<th>Downregulated AQP2</th>
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<td>Hyperkalemia</td>
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<td>AQP2</td>
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<td>SNX27 directly interacts with AQP2 and prevents lysosomal degradation of AQP2 [48]</td>
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<td>BUO</td>
<td>Lyosomal marker cathepsin D</td>
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<td>I/R and H/R</td>
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<td>Activation of autophagy by TDZD-8 ameliorates AQP1 downregulation by inhibiting the NLRP3 inflammasome signaling pathway [58]</td>
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AQP, aquaporin; BUO, bilateral ureteral obstruction; GSK, glycogen synthase kinase; H/R, hypoxia/reoxygenation; I/R, ischemia/reperfusion; LiCl, lithium chloride; NDI, nephrogenic diabetes insipidus; NLRP3, NLR family pyrin domain containing 3; TDZD-8, 4-Benzyl-2-methyl-1,2,4-thiadiazolidine-3,5-dione.
were confirmed by immunoelectron microscopy to be large irregular-shaped autophagic vacuoles. Surprisingly, in K\(^-\)-depleted Atg\(^{+/+}\) mice, pS261-AQP2 immunolabeling was not detected in the small, round autophagic vacuoles (non-canonical autophagic vacuoles), indicating that pS261-AQP2 is subject to the same degradation pathway as total AQP2 in hypokalemia. A large intracellular accumulation of pS261-AQP2 in concert with ATG7 deletion may be attributed to the impairment of other compensatory lysosomal-degradation mechanisms by inactivated lysosomes [39].

Khositseth et al. [37] further investigated the role of autophagy in NDI induced by hypercalcemia. Similar to hypokalemia, autophagy was responsible for AQP2 downregulation in IMCDs and, thereby, the urine concentration defects in hypercalcemia induced by either vitamin D or parathyroid hormone.

Unilateral ureteral obstruction and bilateral ureteral obstruction (BUO) or release are associated with decreased levels of water channel proteins, including AQP2 in the collecting ducts, which leads to impaired urinary concentrations [40]. In early BUO, AQP2 and pS261-AQP2 are redistributed more intracellularly and in a more clustered fashion. They are also colocalized with early endosomes and lysosomes, suggesting an early downregulation of AQP2 likely through a lysosomal-degradation pathway [41]. Supporting the increased degradation of AQP2 after ureteral obstruction, a recent study showed that, in early BUO, AQP2 was degraded by the autophagy pathway together with some other critical proteins and damaged organelles [42]. However, whether pharmacological or genetic inhibition of autophagy prevents the downregulation of AQP2 and improves NDI was not examined in these studies.

Lithium treatment results in a downregulation of AQP2 with consequent polyuria in vivo [43,44]. However, the molecular mechanisms underlying this remain unclear. Proteomics [45] and RNA sequencing [46] demonstrated that several signaling pathways are activated by lithium treatment, such as gene expression, cytoskeletal organization, apoptosis, cell proliferation [45], and an inflammatory-like response [46]. Lithium-induced lysosomal degradation through glycogen synthase kinase-3β (GSK3β) [47] or autophagy-lysosomal degradation through SNX27 might play a role in the downregulation of AQP2 [48]. Lithium was actually considered a potent autophagy inducer, and its autophagy-enhancing property likely contributes to the therapeutic benefit of patients with neuropsychiatric disorders [49]. Interestingly, chloroquine, an autophagy inhibitor that acts by impairing autophagosome fusion with lysosomes, mitigates the lithium-induced downregulation of AQP2 and polyuria. A study from our laboratory showed that lithium treatment induced ER stress in IMCD cells, and the attenuation of ER stress by chaperon improved lithium-induced NDI [50]. Interestingly, a remarkable characteristic in BUO is the presence of ER stress together with autophagy in IMCD cells [42]. It is known that sustained and unsolved ER stress can cause autophagy [51]. Whether the inhibition of ER stress prevents autophagy and improves NDI has not yet been examined.

The role of autophagy in NDI is important, yet a few questions remain. First, is the degradation of AQP2 in the NDI specific? In hypercalcemia, in addition to AQP2, proteins involved in regulating actin filament polymerization, cytoskeletal protein binding, and cell–cell junctions are also downregulated, which are associated with the disruption of cell–cell junctions between IMCD cells and disorganized actin filaments at tight junctions [37]. These histopathological changes are unfavorable for AQP2 intracellular trafficking and expression. In contrast, in hypokalemia, the presence of damaged mitochondria and mitophagy in IMCD was clearly observed in addition to decreased cytoskeletal protein levels, indicating that intracellular K\(^-\) depletion may alter mitochondrial function, decrease adenosine triphosphate production, and promote the generation of reactive oxygen species (ROS), which are supposed to cause damage to IMCD cells. Secondly, why does autophagy occur in NDI? Is autophagy a friend or a foe? Autophagy can be protective or can cause damage, depending on the specific disease stage and cell types. The initiation of autophagy in the early period of NDI may be beneficial for maintaining cell homeostasis when tubular cells face stress coming from electrolyte imbalance, ROS, etc. Autophagy may be required for tubular cells to discontinue tubular transport and to decrease energy consumption for survival, as reviewed recently [52]. However, if autophagy in NDI is not specific to target AQPs (and/or channels, transporters), extensive apoptosis and cell death will be unavoidable. The next question will be whether suppression of autophagy improves NDI. Theoretically, autophagy inhibition increases AQP2 protein expression and improves urine concentra-
tion, as seen in a prior lithium study [53]. Anti-autophagy is not simple, and targeting autophagy as a therapeutic intervention may be challenging. Non-specific inhibitors could have effects other than autophagy inhibition. Interfering with autophagy may ameliorate clinical symptoms for a short time, but the outcome will need to be carefully evaluated in the long term.

**Regulation of aquaporin 1 by autophagy in the kidney**

Renal ischemia/reperfusion (I/R) is the main cause of AKI and contributes to high morbidity and mortality rates. Early studies have demonstrated that I/R-induced AKI is associated with reduced AQPs protein expression [54,55]. The role of autophagy in kidney I/R injury—in particular, in proximal tubules—has been extensively investigated. The induction of autophagy in kidney tubular cells, particularly in proximal tubular epithelial cells, has been documented in rodent models of I/R-induced AKI [3], although suppressed autophagy has also been observed [56,57]. Our recent study revealed that the induction of autophagy by TDZD-8 (a GSK-3β inhibitor) after I/R can rescue reduced AQP1 protein expression, likely by way of clearing deleterious factors (e.g., interleukin-1β) [58]. GSK-3β is known to modulate autophagy. GSK-3β overexpression activates the mammalian target of rapamycin complex 1 and suppresses autophagy, while its inhibition with inhibitors increases autophagic flux [59]. *In vitro* hypoxia/reoxygenation (H/R) induced suppression of autophagy and downregulation of AQP1 in murine IMCD 3 cells expressing endogenous AQP1, which was fully prevented by TDZD-8 [58]. Interestingly, the inhibition of autophagy by 3-methyladenine or Atg5 gene knockdown attenuated the recovery of AQP1 protein expression induced by TDZD-8 in mIMCD3 cells with H/R. The activation of autophagy by TDZD-8 can also inhibit the activation of the NLR family pyrin domain containing 3 inflammasome. Therefore, it is believed that autophagy mediates the removal of protein aggregates, damaged organelles, and deleterious molecules to maintain cellular homeostasis, which might protect cells and tissues against injury.

In mammals, the renal medulla is constantly under hypertonic conditions. This extreme hyperosmotic condition is generally harmful to other cells, and renal medullary cells must make themselves adapt to this harsh environment and survive and function normally. In one study, mIMCD3 cell line was derived from the terminal IMCDs of mice transgenic for the early region of simian virus SV40 [60]. It is highly useful for the study of cellular adaptation to osmotic stress and the transport physiology of this nephron segment. Our unpublished data showed that hypooxosmotic stress (300 mOsm) activates autophagy and downregulates AQP1 expression, which can be prevented by the inhibition of autophagy with 3-methyladenine, chloroquine, or Atg gene knockdown (unpublished data). Taken together, the activation of autophagy regulates AQP1 expression in both renal injury and physiological conditions.

In the kidney, AQP3 and AQP4 are expressed at the basolateral membrane of collecting duct principal cells [61–63], AQP6 is found in intercalated cells in the collecting ducts [64], AQP7 is located in the proximal tubules [65], and AQP11 is expressed intracellularly in the proximal tubules and identified in the ER [66]. So far, whether the degradation of these AQPs is associated with autophagy is still unknown, and more studies are required.

**Perspectives**

Emerging evidence has demonstrated that autophagy plays a key role in AQPs regulation in the kidney. Autophagy contributes to the downregulation of AQPs in several animal models of NDI, although its significance is unclear. The modulation of autophagy might provide an option to improve types of water balance disorders. One would suppose that adequate induction of autophagy might reduce water reabsorption in the kidney, which may prevent water retention. To accomplish this, it is crucial to clarify the mechanisms of autophagy induction in tubular cells and define the underlying signaling pathways and the resulting roles played by autophagy. The other noteworthy question is whether autophagy is regulated by the altered expression of AQPs in the kidney. AQP11 null mice exhibit the phenotype of rapid polycyst development in association with stimulated autophagy with enhanced apoptosis and ER stress before and after cyst formation [67,68]. Autophagy is likely induced by ER stress in this condition; however, autophagy could also cause ER stress and apoptosis [69]. This finding indicates, at least partly, that the conditions provoked by AQP11 deficiency regulate autophagy. In
addition, our unpublished data suggest that either knockdown or inhibition of AQP1 suppresses autophagy induced by rapamycin in mIMCD3 cells (unpublished data). More studies are required to define the physiological role of AQPs in autophagy, which would provide insights and an understanding of the regulatory mechanism of autophagy.

Conflicts of interest

Tae-Hwan Kwon is the Associate Editors of *Kidney Research and Clinical Practice* and were not involved in the review process of this article. All authors have no other conflicts of interest to declare.

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Data sharing statement

The data presented in this study are available on request from the corresponding author.

Authors’ contributions

Conceptualization: YK, THK, CL, WW
Funding acquisition, Supervision: WW
Writing–original draft: XG
Writing–review & editing: YK, THK, CL, WW
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Acute kidney disease: an overview of the epidemiology, pathophysiology, and management

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Acute kidney injury (AKI) increases the risk of chronic kidney disease (CKD), and AKI and CKD are seen as interconnected syndromes. Acute kidney disease (AKD) is defined as subacute damage and/or loss of kidney function occurring 7 to 90 days after AKI, during which period key interventions may be initiated to hinder the development of CKD. While AKD is usually under-recognized, it is associated with high morbidity and mortality globally. This review article aims to summarize the current knowledge concerning the epidemiology, pathophysiology, and management of AKD with the aim to develop monitoring strategies and therapeutic agents of AKD. Generally, AKD tends to occur more frequently in the elderly and those with chronic diseases, such as hypertension, diabetes mellitus, and metabolic syndrome. In addition, the severity, duration, and frequency of AKI are independent risk factors for AKD. Investigations of several mechanisms of AKD, such as renal tubular epithelium cell-cycle arrest, epigenetic change, chronic inflammation, mitochondrial dysfunction, failed regeneration of tubular cells, metabolic reprogramming, and renin-angiotensin system (RAS) activation, have identified additional potential pharmacotherapy targets. Management of AKD includes prevention of repeated AKI, early and regular follow-up by a nephrologist, resumption and adjustment of essential medication, optimization of blood pressure control and nutrition management, and development of new pharmaceutical agents including RAS inhibitors. Finally, we outline a care bundle for AKD patients based on important lessons learned from studies and registries and identify the need for clinical trials of RAS inhibitors or other novel agents to impede ensuing CKD development.

Keywords: Acute kidney disease, Acute kidney injury, AKI-CKD continuum, Chronic kidney diseases, End-stage kidney disease
and incidence of ESKD [5,6].

There is a critical phase in the process of the AKI-CKD transition, which is referred to as acute kidney disease (AKD). The concept of AKD was first proposed in the 2012 Kidney Disease Improving Global Outcomes (KDIGO) guideline for AKI. In 2017, the report from the 16th Acute Dialysis Quality Initiative (ADQI) consensus conference defined AKD as subacute damage and/or loss of kidney function, as indicated by changes in serum creatinine or biomarkers occurring 7 to 90 days after AKI and classified as stages 0 to 3 according to the highest serum creatinine level during the AKD period (Fig. 1) [4,7]. This 7- to 90-day period represents the window during which key interventions may be initiated to hinder CKD.

Given that AKD increases the risk of CKD, it is important to enhance awareness of preventive, diagnostic, and therapeutic strategies. We provide a comprehensive review of the literature addressing the epidemiology, pathophysiology, and frameworks for monitoring and treating AKD.

**Diagnosis and epidemiology**

While AKD is a common sequela of acute illness during hospitalization, it is generally under-recognized; this is problematic because AKD is associated with high morbidity, long-term adverse outcomes, and mortality globally [8]. However, AKD has not been extensively investigated nor have its long-term clinical outcomes. In a large study of 62,977 hospitalized adults with preserved baseline kidney function, See et al. [8] found that AKD occurred in 22.2% and AKI in 7.7% of the patients; 906 (1.4%) had AKD with AKI, and 485 (0.8%) had AKD without AKI. Those who had AKD without AKI had a greater risk of major adverse kidney events (36.21 per 100 person-years; hazard ratio [HR] 2.26, 95% confidence interval [CI] 1.89–2.70), CKD (22.94 per 100 person-years; sub-HR 2.69, 95% CI 2.11–3.43), kidney failure (0.28 per 100 person-years; sub-HR 12.63, 95% CI 1.48–107.64), and death (14.86 per 100 person-years; HR 1.57, 95% CI 1.19–2.07). Patients who were elderly and had more comorbidities were more vulnerable to AKD [8,9].

Additional tools, such as clinical scoring systems, imaging techniques, functional testing, and biomarkers, are needed to diagnose AKD early [3]. Kidney injury molecule-1 (KIM-1) and neutrophil gelatinase-associated lipocalin (NGAL) have possible roles as biomarkers for AKD [10–12]. In Cheng et al.’s animal study [13], sustained upregulation of KIM-1 and NGAL was evident 4 weeks after ischemia-reperfusion AKI (IRI-AKI), which was associated
with persistent tubular injury and interstitial inflammation. In a clinical study, tissue inhibitor metalloproteinase-2 and insulin-like growth factor-binding protein 7 were found to predict long-term outcomes of AKI patients [14]. In a recent single-center study of 430 patients with community-acquired and hospital-acquired AKI, concurrent clinical evaluation with “risk scoring” and urine sediment analysis was reported to be a promising method to predict the AKI-CKD transition [15]. Elevated urinary angiotensinogen is also considered a strong predictor of AKI progression [16]. To improve diagnosis and risk stratification after a hospitalized episode of AKI, an ongoing multicenter study (ASSESS-AKI study) is investigating differences in the occurrence of renal and cardiovascular outcomes and death within a cohort of patients with or without AKI. This study will also evaluate the efficacy of urine biomarkers (NGAL, KIM-1, cystatin C, interleukin [IL]-18, L-type fatty-acid-binding protein, and N-acetyl-β-D-glucosaminidase) and blood biomarkers (serum NGAL, serum cystatin C, and plasma IL-6) [17]. Several studies have been performed using the database of the ASSESS-AKI study. First, Wen et al. [18] found that adjusting urine IL-18, urine KIM-1, and monocyte chemoattractant protein-1 (MCP-1) concentrations for urine creatinine or urine osmolarity in patients with AKI could strengthen predictions of subsequent CKD. In addition, when the biomarkers assessed in the ASSESS-AKI study were applied in a mouse model of IRI-AKI, greater MCP-1 and YKL-40 concentrations were associated with greater reduction of eGFR and increased incidence of the composite renal outcome, whereas greater uromodulin concentration was associated with lower incidence of the composite kidney outcome [19]. Second, Coca et al. [20] reported that plasma soluble tumor necrosis factor receptor 1 (sTNFR1) and sTNFR2 measured 3 months after hospital discharge were independently associated with kidney disease progression, heart failure, and mortality regardless of AKI status. Another study conducted by Mansour et al. [21] found that greater angiopoietin-1 to angiopoietin-2 ratio was strongly associated with less frequent CKD progression, heart failure, and mortality. We look forward to using these novel biomarkers to predict and diagnose AKD in the future and propose that a multimarker score be used to improve risk stratification of patients and to increase prognostic accuracy.

Moreover, a meta-analysis of nine studies suggested that an elevated Doppler-based renal resistive index was an accurate predictor of persistent AKI in critically ill patients [22]. Chawla and Ronco [23] proposed that invasive kidney stress testing, an approach using appropriate stimuliants to assess reserve capacity in the kidney, could be used to monitor renal function and improve prognostic predictions. The abovementioned biomarkers and detection methods may allow more timely diagnosis and earlier intervention than conventional renal function tests, such as serum creatinine concentration [24].

Risk factors

Several complications may occur in AKD patients, including cardiovascular events, diminished quality of life, development of disability, and increased mortality [25]. Many patient characteristics are risk factors for AKD, such as age, race, genetic factors, hypertension, diabetes mellitus, and metabolic syndrome [3]. In addition, the severity, duration, and frequency of AKI are independent risk factors for CKD. Kellum et al. [26] found that the severity of AKI, as classified by the KDIGO criteria, was a powerful predictor of progression to CKD. Thakar et al. [27] assessed 3,679 diabetic patients and found that AKI episodes were associated with a cumulative risk of progressive CKD.

Advanced age, as well as history of surgery, coronary angiography, coronavirus disease 2019 (COVID-19) infection, fluid overload, and some pharmacological agents, such as chemotherapeutic agents and the frequently used nonsteroidal anti-inflammatory drugs (NSAIDs), are modifiable factors that contribute to AKD [28–32]. Chou et al. [33] conducted a single-center cohort study of 6,101 patients with stage 3B–5 CKD from 2005 to 2018 and concluded that older patients were more vulnerable to AKI and progression to ESKD compared with younger patients. Ishani et al. [34] assessed 29,388 patients undergoing cardiac surgery and found that increased risk of subsequent CKD could be predicted by an increase in serum creatinine after cardiac surgery, even in those with mild severity. Among 11,249 Canadian residents aged 18 years or older undergoing coronary angiography, James et al. [30] discovered a relationship of AKI after coronary angiography with an elevated risk of sustained renal function loss. Notably, in a recent cohort study of 1,017 COVID-19 patients who were ever admitted to a hospital but survived until the day of discharge,
Hadadi et al. [32] reported a possible long-term influence of COVID-19-associated AKI on the persistence of renal dysfunction. In a large observational study performed over five centers across the United States that included patients from different demographic groups, Bouchard et al. [28] analyzed 610 critically ill patients who had ever consulted a specialist for AKI occurring in the intensive care unit. They found that fluid overload at the time of diagnosis of AKI, defined as a greater than 10% increase in body weight relative to baseline, was not related to kidney function recovery. However, fewer patients in whom peak serum creatinine concentration occurred concurrently with fluid overload recovered kidney function compared with those who did not have these factors (35% vs. 52%, p = 0.007) [28]. On the other hand, AKI and CKD can both give rise to and result from malignancy. Some traditional chemotherapeutic agents are nephrotoxic and can aggravate kidney dysfunction, and impairment of renal function also appears following the use of some newly developed chemotherapeutic agents. Proper diagnosis and management are required to reduce chemotherapy-related renal toxicity [31].

**Mechanisms**

Several plausible mechanisms leading to AKD have been proposed, including renal tubular epithelium cell-cycle arrest, epigenetic changes, failure to recover from inflammation after AKI, mitochondrial dysfunction, failed regeneration of proximal tubules, endothelial dysfunction, metabolic reprogramming, and activation of the renin-angiotensin system (RAS) (Fig. 2). Novel monitoring strategies and therapeutic agents could be developed from investigations of these mechanisms.

**Renal tubular epithelium cell-cycle arrest**

A recent study demonstrated G2/M cell-cycle arrest of renal tubular epithelial cells (TECs) as a key factor contributing to maladaptive repair and progression to CKD after AKI [35]. Notably, in these G2/M-arrested tubular epithelium cells, activated c-jun NH2-terminal kinase signaling can boost the production of profibrogenic growth factors such as transforming growth factor-β1 (TGF-β1) and connective tissue growth factor. While TGF-β1 can lead to cell apoptosis, it also reinforces tubular cell arrest in the G2/M phase. Elevated production of profibrogenic cytokines activated the generation and transformation of pericytes to myofibroblasts and enhanced advanced fibrosis in a murine obstructive AKI model [36].

**Epigenetic change**

Epigenetic change, an inheritable gene expression change not caused by alterations in the primary nucleotide sequence, was first proposed by Waddington in 1942 [37]. Epigenetic regulation of gene expression is the result of DNA methylation, histone acetylation/deacetylation, and microRNA (miRNA) expression. Bechtel et al. [38] demonstrated that RASAL1 is a gene encoding the RAS oncoprotein inhibitor. Hypermethylation of RASAL1 induces fibroblast activation, proliferation of fibroblasts, and renal fibrogenesis following folic acid-induced AKI, leading to the CKD transition. Kidney fibrosis is ameliorated by the demethylating agent 5-azacytidine which acts upon the methyltransferase Dnmt1 [38]. Recently, Chou et al. [39] reported that demethylation by 5-azacytidine could restore the microvascular stabilization of activated pericytes and reverse the profibrotic features of inactivated pericytes, preventing the transition to CKD and attenuating fibrogenesis. In conclusion, blockage of hypermethylation in pericytes after AKI could block the transition to CKD.

Alternation of histone expression is also involved in the mechanism of AKD. Two major gene-activating histone modifications (histone 3 lysine 4 trimethylation and histone variant H2A.Z) have been demonstrated in a murine model of IRI-AKI. These changes increase the production of renal cortical TGF-1/MCP-1 cytokines and collagen deposition [40].

Multiple miRNAs are involved in epigenetic changes after AKI, especially miRNA-24, miRNA-494, miRNA-21, miRNA-127, and miRNA-687 [41]. Specifically, miRNA-24 stimulates endothelial and TEC apoptosis, leading to renal ischemic injury. After AKI, upregulated miRNA-494 leads to inflammation or adhesion-molecule-induced kidney injury by inhibiting the expression of activating transcription factor 3. Upregulation of miRNA-21 protects against AKI through interacting with miRNA-21 and hypoxia-inducible factor (HIF); miRNA-127 likewise protects against IRI-AKI through HIF-1. The PTEN gene is inhibited by miRNA-687,
facilitating renal tubular epithelium cell-cycle activation for proliferation.

**Chronic inflammation**

Inflammation can develop during an episode of AKI and persist thereafter. Initially, resident dendritic cells and macrophages increase in response to cell injury to release chemotactic signals that recruit leukocytes to the kidney [42]. A recent study in an aged mouse model showed that impaired M2 macrophage polarization with cell-cycle arrest might accelerate progression from AKI to CKD. During the recovery phase in aged mice, the expression of cell-cycle arrest markers was increased in renal TECs in the G1 phase. Mononuclear cells and M1 macrophages have impaired M2 polarization *in vitro*. This finding indicates that persistent M1 inflammation may result from prolonged G1 arrest in aged mice. Finally, fibrosis is developed in aged mice due to M1-dominant inflammation [42]. These findings may underlie the phenomenon of higher risk of CKD after AKI among elderly patients.

With regard to the evolution of renal injury, Cheng et al. [13] showed that B and T cells infiltrate and persist despite functional recovery even 28 days after IRI-AKI in mice.

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**Figure 2. Molecular mechanisms of acute kidney disease.** (1) Renal tubular epithelium cell-cycle arrest, (2) epigenetic change, (3) chronic inflammation, (4) dysfunction of mitochondria, (5) failed regeneration of tubular cells, (6) endothelial dysfunction, (7) metabolic reprogramming, and (8) RAS activation.

AGT, angiotensinogen; AKI, acute kidney disease; ANG I, angiotensin I; ANG II, angiotensin II; AT1R, angiotensin type-1 receptor; FAO, fatty acid β-oxidation; IL, interleukin; RAS, renin-angiotensin system; ROS, reactive oxygen species; TNF-α, tumor necrosis factor α.
Moreover, tertiary lymphoid tissues (TLTs), which are the site of origin of local immune responses and play an essential role in chronic inflammation, have been found in aged mice after AKI and in elderly patients with several diseases [43]. However, the associations of TLTs with renal function progression are unclear. Therefore, Sato et al. [44] analyzed kidney samples from elderly patients and patients with pyelonephritis and found that the stage of TLT could reflect local injury and inflammation. Furthermore, in a murine model of IRI-AKI, deletion of CD4+ cells and late administration of dexamethasone were accompanied by a reduction in TLT stage and further improvement of renal function, fibrosis, and inflammation.

Other emerging studies have shown that salt-inducible kinase 1 (SIK1) plays an essential role in the AKI-CKD transition. Hu et al. [45] reported that SIK1 was down-regulated in AKI and could induce the AKI-CKD transition through activation of the WNT/β-catenin signaling pathway. Over-expression of SIK1 alleviated the AKI-CKD transition in vivo and renal tubular cellular injury in vitro.

**Mitochondrial dysfunction**

Recent findings have revealed that fragmented mitochondria induce persistent renal injury by releasing harmful molecules that can activate nucleotide-binding oligomerization domain-like receptors and increase the release of proinflammatory cytokines. Mitochondrial damage persists long enough after ischemic renal injury to activate sustained chronic inflammation, which can cause continued endothelial and podocyte damage and microvascular rarefaction, ultimately leading to glomerular and interstitial fibrosis. In addition, under oxidative stress, a damaged mitochondrial membrane leads to the release of reactive oxygen species and proapoptotic factors, such as cytochrome complex and apoptosis-inducing factor; apoptosis is therefore enhanced, and renal recovery from AKI is impaired [46].

**Failed regeneration of tubular cells**

Some surviving dedifferentiated tubules fail to undergo regeneration after AKI. Endo et al. [47] demonstrated that acute tubular injury caused significant shortening of proximal tubules and was associated with limited repair and subsequent interstitial fibrosis. Failure of tubular regeneration leads to reduced renal mass, which results in increased intraglomerular pressure and glomerular hyperfiltration [13,25]. Loss of parenchyma following renal mass reduction elicits hemodynamically mediated processes that give rise to glomerulosclerosis and tubulointerstitial fibrosis [48].

**Endothelial dysfunction**

Microvascular rarefaction is thought to play a crucial role in nephron damage and has been associated with progression to chronic nephropathy. Basile et al. [49] found loss of capillaries even tubular morphology was essentially normal at 4 and 8 weeks after IRI-AKI in a murine model, indicating deficient regenerative potential of the renal vascular system. Microvascular rarefaction-induced renal hypoxia leads to mitochondrial dysfunction, proinflammatory induction, and profibrogenic processes [50]. Epithelial cells produce an endogenous cytokine named vascular endothelial growth factor, which affects endothelial cells directly and is reduced after AKI. Therefore, microvascular dysfunction and morphologic changes are induced in the nephron upon AKI [51,52]. In addition, renal pericytes are widely recognized to play a key role in microvascular stability. Following AKI, pericytes detach from capillaries and then differentiate into myofibroblasts. The loss of pericytes leads to transient injury of the renal tubules and long-term rarefaction of peritubular capillaries, which increases the risk of progression to CKD after AKI [53]. Loss of capillaries induces hypoxia, which stimulates production of fibrogenic factors including TGF-β1 and extracellular matrix [54,55]. A vicious cycle ensues, such that the larger is the number of interstitial scars, the longer is the distance for diffusion to the renal parenchyma, which aggravates hypoxia and renal fibrosis [56,57]. Yamaguchi et al. [58] also demonstrated that hypoxia may induce inflammation by causing overexpression of CCAAT/enhancer-binding protein δ through nuclear factor-κB-dependent pathways.

**Metabolic reprogramming**

During AKI, reprogramming of energy metabolism occurs in TECs due to hypoxia, mitochondrial dysfunction, and disordered nutrient-sensing pathways. Fatty acid transporters including CD36 and fatty-acid-binding proteins
as well as fatty acid β-oxidation (FAO)-related metabolic enzymes such as carnitine palmitoyltransferase I and medium chain-specific acyl-CoA dehydrogenase are reduced in TECs [59]. Therefore, the metabolic process switches from FAO to glycolysis. Enhanced glycolysis provides the energy supply; however, in the long-term, glycolysis leads to inflammation, lipid accumulation, and fibrosis, which promote the AKI-CKD transition [60].

**Renin-angiotensin system activation**

An increasing number of studies have demonstrated activation of the RAS after AKI. In cardiac surgery-associated AKI (CSA-AKI), low blood flow, low pressure, hypothermia, and neurohormonal factors related to surgery are risks for AKI because of increased renal vasoconstriction due to RAS activation [61]. In addition, RAS activation in AKI patients is proportional to the severity of AKI and the level of urinary angiotensinogen [62].

Hsu et al. [63] conducted a retrospective cohort study that demonstrated an independent association between AKI and subsequent development of elevated blood pressure. In *vivo*, Cheng et al. [13] demonstrated a link between blood pressure elevation/innarenal RAS activation and CKD. Losartan treatment initiated 1 month after functional recovery from AKI significantly reduced the rate of subsequent CKD and mortality. Clinically, Chou et al. [64] analyzed a cohort study retrospectively and confirmed a greater decrease in the rate of subsequent CKD (users vs. nonusers, 26.6% vs. 42.2%) and a longer median CKD-free survival time (users vs. nonusers, 1,079 days vs. 520 days) in patients who initiated and maintained compliance with RAS blockade after full renal recovery from CSA-AKI.

However, RAS blockade is not usually initiated during the acute stage of AKI and should be used cautiously. It also has been reported that AKI admission rates are associated with increased prescriptions of RAS inhibitors [65].

**Treatment and prevention**

**Prevention of repeated acute kidney injury**

The best way to prevent AKD is to decrease the occurrence of AKI [66]. A number of studies have focused on this topic [67,68]. However, once an episode of AKI occurs, it becomes crucial to prevent the transition to CKD and improve AKI recovery. This can be achieved through the use of promising new pharmacological agents or the development of innovative therapies, such as stem cell therapy. [69,70] to attenuate the risk of CKD. A meta-analysis of four randomized controlled trials and nine non-randomized studies that included 25,776 patients and 30,276 AKI episodes found that AKI care bundles reduced the rate of moderate to severe AKI [71]; however, it is unclear whether this improvement translates into better long-term outcomes.

**Early and regular follow-ups by a nephrologist**

Studies reporting observations of AKI survivors are rare, and the lack of prospective observational studies that have followed discharged AKI survivors to obtain long-term outcomes may lead to over- or underestimation of CKD evolution. This lack of data may reflect hospitalization-related fatigue, unwillingness to add more doctors to outpatient care, and long travel distances to medical centers [71]. This data gap suggests a missed opportunity to block the AKI-CKD transition and improve outcomes [72]. Siew et al. [73] reported that 3,929 survivors of AKI were hospitalized between January 2003 and December 2008, as recorded in the United States Department of Veterans Affairs database, which demonstrated that AKI severity did not affect referral rates, but only a few high-risk survivors were transferred to nephrologists. However, it has been shown that early nephrology follow-up has many benefits, such as timely interventions, improved outcomes, better access to medical resources, and more consistent follow-up. A cohort study showed that early nephrologist follow-up, meaning a visit with a nephrologist within 90 days of discharge, reduced all-cause mortality [74]. However, there is disparity between what nephrologists consider ideal care after discharge and the transitional care currently provided in practice. Some Canadian nephrologists demonstrated in 2015 that 16% of AKI patients without preexisting CKD visited a nephrologist at 6 months after AKI, whereas this frequency increased to 24% among AKI survivors who had preexisting CKD and had been visited by a nephrologist before or during their AKI hospitalization period (78% and 41%, respectively) [75].
Resume and adjust essential medications

Certain medications are withdrawn or adjusted during an episode of AKI, such as NSAIDs, diuretics, RAS inhibitors, statins, and oral hypoglycemic agents. In addition, the combination of spironolactone, NSAIDs, and RAS inhibitors should be avoided. Although ‘sick day medication guidance’ has been applied in clinical practice for patients with diabetes mellitus and CKD, it has not yet been affirmed that withdrawal of medications such as angiotensin-converting enzyme inhibitors (ACEi) and/or angiotensin receptor blockers (ARBs) could prevent adverse events, including AKI. The timing of drug reinitiation needs to consider the degree of post-AKI recovery, the interval to AKI insult, the drug’s metabolic and excretion pathways, indications for the drug, and whether there is any suitable substitute [3]. After the introduction of ACEi/ARB, spironolactone, trimethoprim, and loop diuretics (especially for patients with preexisting CKD), renal function should be monitored closely for a brief period. Finally, drug choice, dosing, and surveillance during the AKI-CKD transition must be emphasized, and nephrotoxic medicines should be avoided [7].

Optimize blood pressure control and nutrition management

A large retrospective cohort study of adult patients who were hospitalized between 2008 and 2011 (after exclusion of those who had at least two blood pressure readings greater than 140/90 mmHg or those with evidence of CKD) found that AKI was independently associated with subsequent development of elevated blood pressure [63]. Accordingly, it is worth investigating how to optimize blood pressure control after AKI.

Baek et al. [76] conducted a retrospective cohort study including 1,612 noncritically ill hospitalized patients with AKI and found a U-shaped curve between the average systolic blood pressure (SBP) within 48 hours after AKI and AKI severity or 90-day mortality. The lowest event rate occurred when SBP was controlled to within approximately 110 and 129 mmHg. In contrast, another prospective study found the inverse relationship. McCoy et al. [77] found that SBP 3 months after discharge was not associated with the risk of AKI, loss of kidney function, mortality, or heart failure events among hospitalized AKI patients. In addition, a Japanese study that enrolled 746 patients admitted to intensive care units after cardiac surgery demonstrated no association between hypotension and subsequent progression of AKI [78]. In view of the aforementioned studies, the optimal strategy for post-AKI blood pressure control to prevent ensuing CKD requires additional randomized controlled trials for validation.

After an episode of AKI and during recovery, patients are at risk of protein-energy malnutrition, and this is not ideal for a good prognosis. Renal function loss affects the metabolism of all macronutrients, and hypertriglyceridermia and hyperglycemia are common in this situation. It is necessary to individualize AKI survivor nutrition support based on etiology, severity, comorbidities, and dialysis demands [79]. Fiaccadori et al. [80] suggested in 2010 that AKI patients requiring dialysis should take in at least 1.5 g/kg/day of protein with an extra 0.2 g/kg/day due to dialysis-related losses. No more than 30 kcal/kg/day of nonprotein calories or 1.3 × basal energy expenditure calculated by the Harris-Benedict equation, with 30% to 35% from lipids, should be considered in the energy intake. The use of the gut (oral or enteral support) is favored [80]. A recent original article using evidence-based medicine methods to review the medical literature for Taiwanese AKI patients from 2014 to 2018 also supported that suggestion [81].

For fluid requirements, it is not wise to apply standard fluid equations. Close medical assessment based on the patient’s fluid balance is crucial [77]. Electrolytes should be carefully monitored and adjusted, especially food containing a high level of potassium. Requirements for micronutrients are not well documented. Whether micronutrient supplementation improves outcomes remains unknown [82]. However, Fiaccadori et al. [83] pointed out that the recent guideline was aimed at providing evidence-based nutritional recommendations for different clinical settings of hospitalized patients.

Potential pharmaceutical agents to prevent the acute kidney injury-chronic kidney disease continuum

To promote AKI recovery, Silver et al. [84] suggested clinicians in the care of AKI survivors consider lifestyle modifications, medication adjustment, blood pressure control, medical record documentation, and patient education in
**Figure 3.** A suggested flowchart of follow-up actions to be undertaken by the nephrologist after patients experience an AKI episode. This flowchart demonstrates individualized and dynamic strategies for patient monitoring after an AKI episode. The intensity of follow-up depends on the patient’s risk of adverse events.

AKI, acute kidney injury; CKD, chronic kidney disease; CVD, cardiovascular disease.

**Figure 4.** Monitoring strategies and potential therapeutical agents of AKD. (A) Monitoring strategies considering time points after acute kidney injury. (B) Potential therapeutic agents of AKD. AKD, acute kidney disease; DPP-4, dipeptidyl peptidase-4; RAS, renin-angiotensin system.

their management plan. Moreover, individualized care should be provided. In addition, glycemic control for diabetic patients, RAS blockade, and statins could reduce the risks of adverse long-term cardiovascular and renal outcomes after AKI [9]. Interestingly, some bioactive compounds, such as growth factors and cytokines, have shown
effectiveness in facilitating kidney function recovery [85].

Because RAS activation is one of the mechanisms of AKD, RAS inhibitors could become robust and safe pharmacological agents for blocking the AKI-CKD transition [13,69,86]. One animal study and another clinical study showed that RAS inhibitors could reduce post-AKI mortality and progression to CKD [13,64]. Moreover, an animal study also demonstrated that treatment with spironolactone, an antagonist of the downstream RAS effector aldosterone, either before or after ischemia, prevented subsequent CKD [87].

Chou et al. [39] reported a breakthrough experimental result that, in 5-azacytidine-treated mice, the number of myofibroblasts and severity of fibrosis decreased along with decreased blood urea nitrogen and creatinine concentrations on day 180 after AKI compared with the control group. These findings suggest that demethylation by 5-azacytidine attenuates the AKI-CKD continuum; however, more clinical trials are needed to investigate the effects of demethylating agents in clinical applications.

Current guidelines suggest statin therapy for CKD patients aged over 50 years or with known coronary disease, diabetes mellitus, or prior ischemic stroke or at high cardiovascular risk. A nationwide cohort study found that statins used in patients who were first hospitalized because of AKI requiring dialysis (AKI-D) led to a lower risk (21%) of 1-year all-cause mortality [88]. The survival benefit was dose-dependent, compliance-dependent, sustainable, and similar across patient subgroups. Interestingly, Brar et al. [89] also reported that statin use reduced mortality and rehospitalization rates in AKI survivors who subsequently developed CKD. Based on the current findings and given the not yet established guidelines for statin use in AKI individuals, it is accepted that patients with AKI-D should not discontinue using statins. In the future, more studies must confirm these results and verify the role of statin therapy in the optimal care of AKI patients.

Dipeptidyl peptidase-4 inhibitor (DPP-4 inhibitor), a widely used antihyperglycemic medication for type 2 diabetic control, has also shown some efficacy in reducing ESKD and mortality in type 2 diabetic patients recovering from AKI with dialysis [90]. The potential renal effect of DPP-4 inhibitor may offer resources to enhance success rates in blocking the AKI to CKD transition.

**Summary and perspective**

To date, no reliable trials have assessed which are the most powerful pharmacotherapies for treating AKD. Additional investigation of the etiology and underlying mechanisms of AKI progression to AKD are needed to guide the development of effective treatments. The current gold standard for AKD prevention includes identifying at-risk patients, reviewing medical records, and minimizing nephrotoxic exposure. In addition, it is worth emphasizing the value of the clinical utilization of newly identified biomarkers and close follow-up by nephrologists. Therefore, we are proposing a care bundle for AKD based on important lessons from available studies and registries, as shown in Fig. 3, and list monitoring strategies and potential therapeutical agents of AKD in Fig. 4. Considering the significant prognostic impact of AKD, it is crucial to initiate randomized, controlled clinical trials of strategies for AKD prevention and therapy.

**Conflicts of interest**

All authors have no conflicts of interest to declare.

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**Data sharing statement**

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Comparison of cardiovascular event predictability between the 2009 and 2021 Chronic Kidney Disease Epidemiology Collaboration equations in a Korean chronic kidney disease cohort: the KoreaN Cohort Study for Outcome in Patients With Chronic Kidney Disease study

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Background: The 2009 Chronic Kidney Disease Epidemiology Collaboration creatinine-based estimated glomerular filtration rate (eGFRcr) equation contains a race component that is not based on biology and may cause a bias in results. Therefore, the 2021 eGFRcr and creatinine-cystatin C–based eGFR (eGFRcr-cysC) equations were developed with no consideration of race. This study compared the cardiovascular event (CVE) and all-cause mortality and CVE combined predictability among the three eGFR equations in Korean chronic kidney disease (CKD) patients.

Methods: This study included 2,207 patients from the KoreaN Cohort Study for Outcome in Patients With Chronic Kidney Disease. Receiver operating characteristic (ROC) and net reclassification improvement (NRI) index were used to compare the predictability of the study outcomes according to the 2009 eGFRcr, 2021 eGFRcr, and 2021 eGFRcr-cysC equations.

Results: The overall prevalence of CVE and all-cause mortality were 9% and 7%, respectively. There was no difference in area under the curve of ROC for CVE and mortality and CVE combined among all three equations. Compared to the 2009 eGFRcr, both the 2021 eGFRcr (NRI, 0.013; 95% confidence interval [CI], –0.002 to 0.028) and the eGFRcr-cysC (NRI, –0.001; 95% CI, –0.031 to 0.029) equations did not show improved CVE predictability. Similar findings were observed for mortality and CVE combined predictability with both the 2021 eGFRcr (NRI, –0.019; 95% CI, –0.039–0.000) and the eGFRcr-cysC (NRI, –0.002; 95% CI, –0.023 to 0.018).

Conclusion: The 2009 eGFRcr equation was not inferior to either the 2021 eGFRcr or eGFRcr-cysC equation in predicting CVE and the composite of mortality and CVE in Korean CKD patients.

Keywords: Cardiovascular diseases, Chronic renal insufficiency, Creatinine, Cystatin C, Racial groups
**Introduction**

Estimated glomerular filtration rate (eGFR) is a surrogate marker of kidney function calculated using endogenous filtration byproducts of creatinine and cystatin C (cysC). In 1999, the Modification of Diet in Renal Disease (MDRD) eGFR equation was developed from a cohort of Caucasian and African-American chronic kidney disease (CKD) patients with glomerular filtration rate (GFR) less than 60 mL/min/1.73 m² [1]. However, eGFR calculated from this equation was often underestimated in patients with GFR greater than 60 mL/min/1.73 m². To overcome this limitation, the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) developed a new eGFR equation using creatinine in 2009. The new equation was more accurate than that of the MDRD, especially in patients with GFR less than 60 mL/min/1.73 m² [2]. Since the introduction of the 2009 CKD-EPI eGFR creatinine (eGFRcr) equation, it has been employed widely in global medical practice.

Factors including ethnicity, age, and sex, which are associated with amount of muscle mass and muscle metabolism, affect the creatinine level and, consequently, eGFR calculations [3]. Young to middle-aged African-Americans, especially males, often have higher creatinine levels compared to Caucasians [4]. Therefore, both MDRD and CKD-EPI eGFRcr equations had correction factors for age, sex, and African-American race [1,2]. However, this led to disproportionate diagnosis of CKD in different ethnicities due to varying levels of creatinine and cysC and use of a ‘race’ coefficient developed to correct eGFR difference between African-American and white individuals [5]. Also, lack of consideration of individual diversity in African-Americans often led to inappropriate early or delayed referral to nephrologists [6,7]. Therefore, in 2021, the CKD-EPI group developed two new eGFR equations using creatinine (eGFRcr) and creatinine-cysC (eGFRcr-cysC) and omitting the race factor [8].

In 2022, the National Kidney Foundation and American Society of Nephrology published a joint statement that recommends use of the 2021 eGFRcr or eGFRcr-cysC equation over the current 2009 eGFRcr equation [9]. Other studies have also reported that the 2021 eGFR equations were more accurate than the 2009 eGFRcr equation, especially in African-Americans with lower kidney function [10,11]. Therefore, the new 2021 equations have the greatest benefits in CKD screening, detection, and risk prediction in African-Americans adults [9]. However, its benefits in an Asian population are unclear as the percentage of Asian CKD patients included in previous landmark studies was low, and those included were classified as ‘non-black,’ which mostly included Caucasians [8,10,11]. Also, previous studies that proposed an Asian coefficient for MDRD and 2009 CKD-EPI eGFR equations reported variable values depending on Asian ethnicity and study methods [12].

It is widely known that cardiovascular morbidity and mortality risk are elevated in both early and advanced stages of CKD [13,14]. Therefore, it is important to accurately predict cardiovascular event (CVE) risk in CKD patients. As Korea is a monoethnic Asian country, this study was conducted to evaluate the efficiency of the new 2021 eGFRcr and eGFRcr-cysC equations, which do not include a race factor, compared to the 2009 eGFRcr equation. The predictability of CVE and composite of all-cause mortality and CVE among eGFR equations was compared in a Korean nondialysis CKD cohort.

**Methods**

**Study design**

The KoreaN Cohort Study for Outcome in Patients With Chronic Kidney Disease (KNOW-CKD) is a national, prospective, multicenter study of Korean nondialysis CKD patients from nine major nephrology centers of university hospitals in Korea. Study exclusion criteria are 1) inability or unwillingness to provide written consent; 2) previous maintenance dialysis or organ transplantation; 3) heart failure (New York Heart Association functional class 3 or 4) or cirrhosis (Child-Pugh class 2 or 3); 4) history of or current malignancy; 5) pregnancy; or 6) single kidney due to trauma or donation.

From September 2011 to January 2016, a total of 2,238 adult nondialysis CKD patients between the ages of 20 and 75 years were enrolled. Patients with missing information on CVE and all-cause mortality due to follow-up loss within 6 months of study entry were excluded.

The KNOW-CKD study was conducted in accordance with the principles of the Declaration of Helsinki and was supervised by the Korea Centers for Disease Control and Prevention. The study was approved by the Institutional...
Review Boards of all nine university hospitals including Seoul National University Hospital in 2011 (No. 1104-089-359). A detailed study protocol of the KNOW-CKD has been previously published [15].

Laboratory and clinical variables

All laboratory and clinical variables were collected from patients on their initial visit to the enrolled hospital.

Blood samples were collected after at least 8 hours of fasting. Baseline laboratory measurements were hemoglobin (Hb), blood urea nitrogen (BUN), creatinine, cysC, sodium, potassium, calcium, phosphorus, uric acid, parathyroid hormone (PTH), high-sensitivity C-reactive protein (hs-CRP), troponin T, fasting glucose, HbA1C, total cholesterol, high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C).

Serum creatinine, cysC, PTH, and urine protein and creatinine values were measured at one central laboratory (LabGenomics). Serum creatinine was measured using the isotope dilution mass spectrometry-traceable method, and serum cysC was measured using the immunonephelometry method for consistency [16]. Other laboratory measurements were conducted in the appropriate hospital laboratory.

Baseline clinical information on age, sex, underlying comorbidity, medication, and lifestyle patterns including cigarette smoking status (never, former, current) were collected using self-reported questionnaires with the assistance of trained staff. Information regarding CVE was collected through medical interview and review of the patient’s electronic medical records during the hospital visits initially and at 6 months after enrollment and annually after that. Review of the CVE by the nephrologist in charge of the KNOW-CKD study in each hospital was repeated, and CVE was classified into 10 categories: acute myocardial infarction, hospitalization for unstable angina or heart failure, percutaneous coronary artery intervention or coronary bypass graft surgery, ischemic stroke, hemorrhagic stroke, carotid artery disease, peripheral artery disease, symptomatic arrhythmia, and any other CVE that required hospitalization or intervention. Finally, CVE was cross-checked by another nephrologist among the participating hospitals of the KNOW-CKD study to ensure accuracy and objectivity of the outcome data. For fatal CVE, information regarding the time and causes of mortality was obtained from the patient’s electronic medical records or the Korean Statistical Information Service.

Blood pressure was measured by a trained nurse using an electronic sphygmomanometer after 5 minutes of rest in a sitting position. Hypertension was defined as (a) systolic blood pressure (SBP) of >140 mmHg or diastolic blood pressure (DBP) of >90 mmHg or (b) previous diagnosis of hypertension. Mean arterial pressure (MAP) was calculated using the following equation: MAP = DBP + 1/3 (SBP – DBP).

Diabetes mellitus (DM) was defined as (a) fasting serum glucose of >126 mg/dL or (b) previous diagnosis of DM.

Estimated glomerular filtration rate calculation

Each eGFR was calculated using three CKD-EPI equations: 2009 CKD-EPI eGFRcr, 2021 CKD-EPI eGFRcr, and 2021 eGFRcr-cysC equations [2,8]. These equations are listed below.

2009 CKD-EPI eGFRcr equation

Female
- Serum creatinine (Scr) ≤ 0.7 mg/dL: 144 × (Scr/0.7)−0.329 × (0.993)AGE
- Scr > 0.7 mg/dL: 144 × (Scr/0.7)−1.209 × (0.993)AGE

Male
- Scr ≤ 0.9 mg/dL: 141 × (Scr/0.9)−0.411 × (0.993)AGE
- Scr > 0.9 mg/dL: 141 × (Scr/0.9)−1.209 × (0.993)AGE

2021 CKD-EPI eGFRcr equation

Female
- Scr ≤ 0.7 mg/dL: 142 × (Scr/0.7)−0.241 × 0.9938AGE × 1.012
- Scr > 0.7 mg/dL: 142 × (Scr/0.7)−1.200 × 0.9938AGE × 1.012

Male
- Scr ≤ 0.9 mg/dL: 142 × (Scr/0.9)−0.302 × 0.9938AGE
- Scr > 0.9 mg/dL: 142 × (Scr/0.9)−1.200 × 0.9938AGE

2021 CKD-EPI eGFRcr-cysC equation

Female
- Scr ≤ 0.7 mg/dL
  1) Serum cysC (ScysC) ≤ 0.8 mg/dL: 135 × (Scr/0.7)−0.219 × (ScysC/0.8)−0.323 × 0.9961AGE × 0.963
2) ScysC > 0.8 mg/dL:
   $135 \times (\text{Scr}/0.7)^{-0.219} \times (\text{ScysC}/0.8)^{-0.778} \times 0.9961^{\text{Age}} \times 0.963$
   - Scr > 0.7 mg/dL
1) ScysC ≤ 0.8 mg/dL:
   $135 \times (\text{Scr}/0.7)^{-0.544} \times (\text{ScysC}/0.8)^{-0.323} \times 0.9961^{\text{Age}} \times 0.963$
2) ScysC > 0.8 mg/dL:
   $135 \times (\text{Scr}/0.7)^{-0.544} \times (\text{ScysC}/0.8)^{-0.778} \times 0.9961^{\text{Age}} \times 0.963$

Male
- Scr ≤ 0.9 mg/dL
  1) ScysC ≤ 0.8 mg/dL:
     $135 \times (\text{Scr}/0.9)^{-0.144} \times (\text{ScysC}/0.8)^{-0.323} \times 0.9961^{\text{Age}}$
  2) ScysC > 0.8 mg/dL:
     $135 \times (\text{Scr}/0.9)^{-0.144} \times (\text{ScysC}/0.8)^{-0.778} \times 0.9961^{\text{Age}}$
- Scr > 0.9 mg/dL
  1) ScysC ≤ 0.8 mg/dL:
     $135 \times (\text{Scr}/0.9)^{-0.544} \times (\text{ScysC}/0.8)^{-0.323} \times 0.9961^{\text{Age}}$
  2) ScysC > 0.8 mg/dL:
     $135 \times (\text{Scr}/0.9)^{-0.544} \times (\text{ScysC}/0.8)^{-0.778} \times 0.9961^{\text{Age}}$

Study outcomes

As cardiovascular disease is one of the most critical complications of CKD, primary outcome was defined as the first occurrence of either non-fatal or fatal CVE. CVE included acute myocardial infarction, hospitalization for unstable angina or heart failure, percutaneous coronary artery intervention or coronary bypass graft surgery, ischemic stroke, hemorrhagic stroke, carotid artery disease, peripheral artery disease, symptomatic arrhythmia, or any other CVE that required hospitalization or intervention. The secondary outcome was the composite event of all-cause mortality and CVE.

Statistical analysis

Baseline characteristics were analyzed according to CVE. Continuous variables were expressed as mean ± standard deviation or median and interquartile range and analyzed using the Kruskal-Wallis test or one-way analysis of variance. Categorical variables were expressed as percentages. Comparison of categorical variables was conducted using chi-square test. Cox proportional hazard analysis was used to evaluate the predictive risk of CVE and all-cause mortality and CVE combined according to eGFR equation. Evaluated risks were expressed as hazard ratio (HR) and 95% confidence interval (CI). For Cox proportional hazard analysis, the multivariable model was adjusted for age, sex, DM, smoking, body mass index (BMI), MAP, LDL-C, ejection fraction (EF), and proteinuria (urine protein/creatinine ratio, >0.2 g/day). Receiver operating characteristic (ROC) curve analysis was conducted to compare the predictability of the three equations on study outcome. Also, the net reclassification improvement (NRI) index was calculated to compare improvement in predictability of one equation over another. The multivariable model for ROC and NRI analysis was adjusted for age, sex, DM, smoking, BMI, MAP, LDL-C, and EF. Two-sided p-values of <0.05 were considered statistically significant. All statistical analyses were performed using R version 4.0.4 (R Foundation for Statistical Computing).

Results

Baseline characteristics of the study population

From September 2011 to January 2016, a total of 2,238 adult nondialysis CKD patients between the ages of 20 and 75 years were enrolled. Among them, 31 patients were excluded due to missing information on CVE and all-cause mortality or to follow-up loss within 6 months of study entry. Finally, 2,207 patients were enrolled in this study. The median follow-up duration of the above patients was 8.6 years (Fig. 1).

Among the total of 2,207 patients, the overall prevalence of CVE was 9.1% (n = 200). The types of CVE experienced

![Figure 1. Flow diagram of patient enrollment.](http://www.krcp-ksn.org)
by the 200 patients included acute myocardial infarction (n = 24), hospitalization for unstable angina (n = 23), hospitalization for heart failure (n = 14), percutaneous coronary artery intervention or coronary bypass graft surgery (n = 25), ischemic stroke (n = 34), hemorrhagic stroke (n = 17), carotid artery disease (n = 2), peripheral artery disease (n = 7), symptomatic arrhythmia (n = 13), and any other CVE that required hospitalization or intervention (n = 41).

Baseline characteristics of the study population were compared according to the presence of CVE. CVE patients were older with a larger percentage of males. In CVE patients, serum BUN, creatinine, and cysC levels were slightly higher and the eGFR level calculated using the 2009 eGFR-cr equation was slightly lower than in non-CVE patients. Also, fasting glucose and HbA1C levels were higher with a higher percentage of underlying DM. Regarding the cardiovascular aspect, the percentage of patients with underlying coronary artery disease was approximately six-fold higher (23.5% vs. 4.3%, p < 0.001) in patients with CVE. In addition, CVE patients had slightly higher levels of hs-CRP and troponin T and lower left ventricular EF percentage as measured with echocardiogram. In comparison of lipid profiles, CVE patients had lower HDL-C, LDL-C, and total cholesterol levels. Regarding lifestyle, the percentages of current and former smokers were higher among CVE patients (Table 1).

**Comparison of estimated glomerular filtration rate level according to estimated glomerular filtration rate equation**

In comparison of the three eGFR equations, eGFR level was approximately 3 mL/min/1.73 m² higher when calculated using the 2021 eGFRcr equation and 1.5 mL/min/1.73 m² higher when calculated using the 2021 eGFRcr-cysC equation compared to that calculated using the 2009 eGFRcr equation. The distribution of difference in calculated eGFR level between eGFR equations is shown using the Bland-Altman plot (Fig. 2).

In comparison of 2009 and 2021 eGFRcr equations, CKD stage classification according to the 2021 eGFRcr equation allocated a higher number of patients to CKD stages 1 and 2 (38.9% vs. 35.1%) and a lower number of patients to CKD stages 3 to 5 (61.1% vs. 64.9%). A similar trend was observed when CKD stages were classified according to the 2021 eGFRcr-cysC equation. Prevalence of CVE and composite of all-cause mortality and CVE were highest in patients with CKD stages 3 and 4 for all three equations (Table 2).

**Predictive value of estimated glomerular filtration rate for cardiovascular event and composite of all-cause mortality and cardiovascular event**

The predictive value of eGFR for CVE, calculated using each of the three eGFR equations, was statistically significant only in the unadjusted model. In that model, every 10 mL/min/1.73 m² increase in eGFR was associated with lower predicted risk of CVE in all three equations (2009 eGFRcr equation: HR, 0.90; 95% CI, 0.86–0.95; 2021 eGFRcr equation: HR, 0.91; 95% CI, 0.87–0.96; and 2021 eGFRcr-cysC equation: HR, 0.90; 95% CI, 0.85–0.95). However, in prediction of the composite of all-cause mortality and CVE, significantly lower predictive risks were observed in all univariate and multivariate models across all three equations (2009 eGFRcr equation: HR, 0.94; 95% CI, 0.89–0.99; 2021 eGFRcr equation: HR, 0.94, 95% CI, 0.90–0.99; and 2021 eGFRcr-cysC equation: HR, 0.92, 95% CI, 0.87–0.97) (Table 3).

**Comparison of cardiovascular event and the composite of all-cause mortality and cardiovascular event predictability**

The area under the ROC curve (AUC) for CVE predictability was similar among the three equations (2009 eGFRcr equation: 0.715; 95% CI, 0.679–0.752; 2021 eGFRcr equation: 0.715; 95% CI, 0.679–0.752; and 2021 eGFRcr-cysC equation: 0.716; 95% CI, 0.679–0.753) (Fig. 3A). Similar findings were observed in comparison of predictability for the composite of all-cause mortality and CVE with slightly increased AUC value for the 2021 eGFRcr-cysC equation compared to that of 2009 and 2021 eGFRcr equations (2009 eGFRcr equation: 0.747; 95% CI, 0.719–0.776; 2021 eGFRcr equation: 0.747; 95% CI, 0.719–0.776; and 2021 eGFRcr-cysC equation: 0.751; 95% CI, 0.723–0.779) (Fig. 3B).

Additionally, NRI was used to compare the predictability of CVE and the composite of all-cause mortality and CVE among eGFR equations. Neither the 2021 eGFRcr nor 2021 eGFRcr-cysC equation had improved predictive power for CVE and all-cause mortality outcomes compared to the 2009 eGFRcr equation, and none of the NRI values were
significant. Also, in comparison of the 2021 eGFRcr and eGFRcr-cysC equations, there was no difference in predictability of the study outcomes (Table 4).

**Table 1: Baseline characteristics of study population according to CVE**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total</th>
<th>CVE (+) group</th>
<th>CVE (-) group</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>2,207</td>
<td>200</td>
<td>2,007</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>55.0 (45.0–63.0)</td>
<td>61.0 (55.0–67.5)</td>
<td>54.0 (44.0–63.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male sex</td>
<td>1,353 (61.3)</td>
<td>145 (72.5)</td>
<td>1,208 (60.2)</td>
<td>0.001</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24.4 (22.3–26.5)</td>
<td>24.4 (22.6–26.0)</td>
<td>24.4 (22.3–26.5)</td>
<td>0.65</td>
</tr>
<tr>
<td>Hb (g/dL)</td>
<td>12.8 (11.3–14.3)</td>
<td>12.5 (10.8–14.1)</td>
<td>12.8 (11.3–14.4)</td>
<td>0.09</td>
</tr>
<tr>
<td>BUN (mg/dL)</td>
<td>24.0 (17.0–35.0)</td>
<td>27.6 (19.9–35.5)</td>
<td>23.6 (17.0–35.0)</td>
<td>0.01</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>1.5 (1.1–2.2)</td>
<td>1.7 (1.2–2.3)</td>
<td>1.5 (1.0–2.2)</td>
<td>0.02</td>
</tr>
<tr>
<td>Cystatin C (mg/dL)</td>
<td>1.5 (1.1–2.2)</td>
<td>1.7 (1.3–2.2)</td>
<td>1.5 (1.0–2.2)</td>
<td>0.003</td>
</tr>
<tr>
<td>eGFR &lt;sup&gt;a&lt;/sup&gt; (mL/min/1.73 m²)</td>
<td>46.2 (28.3–73.0)</td>
<td>41.8 (28.2–60.3)</td>
<td>47.4 (28.4–75.0)</td>
<td>0.006</td>
</tr>
<tr>
<td>Sodium (mEq/L)</td>
<td>143.0 (140.0–148.0)</td>
<td>142.0 (139.0–148.0)</td>
<td>143.0 (140.0–148.0)</td>
<td>0.046</td>
</tr>
<tr>
<td>Potassium (mEq/L)</td>
<td>6.1 (5.1–9.0)</td>
<td>6.2 (5.3–8.6)</td>
<td>6.1 (5.1–9.0)</td>
<td>0.95</td>
</tr>
<tr>
<td>Calcium (mg/dL)</td>
<td>9.4 (9.1–9.8)</td>
<td>9.3 (9.0–9.6)</td>
<td>9.5 (9.1–9.8)</td>
<td>0.004</td>
</tr>
<tr>
<td>Phosphorus (mg/dL)</td>
<td>5.0 (4.2–6.3)</td>
<td>4.9 (4.1–6.2)</td>
<td>5.1 (4.2–6.3)</td>
<td>0.29</td>
</tr>
<tr>
<td>Uric acid (mg/dL)</td>
<td>7.0 (5.8–8.3)</td>
<td>7.2 (5.9–8.5)</td>
<td>7.0 (5.8–8.3)</td>
<td>0.73</td>
</tr>
<tr>
<td>PTH (pg/dL)</td>
<td>51.0 (34.8–79.8)</td>
<td>49.4 (33.2–76.4)</td>
<td>51.1 (35.0–79.9)</td>
<td>0.64</td>
</tr>
<tr>
<td>hs-CRP (mL/min/1.73 m²)</td>
<td>0.6 (0.2–1.7)</td>
<td>0.8 (0.3–1.8)</td>
<td>0.6 (0.2–1.7)</td>
<td>0.03</td>
</tr>
<tr>
<td>Troponin T (ng/mL)</td>
<td>0.01 (0.01–0.02)</td>
<td>0.02 (0.01–0.03)</td>
<td>0.01 (0.01–0.02)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fasting glucose (mg/dL)</td>
<td>100.0 (92.0–114.5)</td>
<td>107.0 (93.0–129.5)</td>
<td>99.0 (92.0–113.0)</td>
<td>0.001</td>
</tr>
<tr>
<td>HbA1C (%)</td>
<td>6.4 (5.7–7.5)</td>
<td>6.9 (6.1–7.8)</td>
<td>6.4 (5.7–7.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total cholesterol (mg/dL)</td>
<td>171.0 (146.0–198.0)</td>
<td>161.0 (135.0–191.0)</td>
<td>171.0 (147.0–199.0)</td>
<td>0.002</td>
</tr>
<tr>
<td>HDL-C (mg/dL)</td>
<td>47.0 (38.0–58.0)</td>
<td>44.0 (36.0–52.5)</td>
<td>47.0 (38.0–58.0)</td>
<td>0.003</td>
</tr>
<tr>
<td>LDL-C (mg/dL)</td>
<td>93.0 (73.0–116.0)</td>
<td>88.0 (70.0–112.0)</td>
<td>94.0 (74.0–116.0)</td>
<td>0.02</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>127.0 (118.0–137.0)</td>
<td>128.0 (116.0–139.0)</td>
<td>127.0 (118.0–136.0)</td>
<td>0.34</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>77.0 (70.0–84.0)</td>
<td>76.0 (69.0–82.0)</td>
<td>77.0 (70.0–84.0)</td>
<td>0.03</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>93.0 (86.0–101.0)</td>
<td>93.0 (85.0–100.0)</td>
<td>93.0 (87.0–101.0)</td>
<td>0.32</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>64.0 (60.0–68.0)</td>
<td>63.0 (58.9–67.0)</td>
<td>64.0 (60.1–68.0)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

**Comorbidity**

- Hypertension: 2,114 (95.8), 197 (98.5), 1,917 (95.5), 0.07
- Diabetes mellitus: 741 (33.6), 105 (52.5), 636 (31.7), <0.001
- Coronary artery disease: 133 (6.0), 47 (23.5), 86 (43.0), <0.001

**Smoking status**<sup>b</sup>

- Current: 347 (15.8), 38 (19.1), 309 (15.4), 0.02
- Former: 676 (30.7), 73 (36.7), 603 (30.1)
- Never: 1,179 (53.5), 88 (44.2), 1,091 (54.5)

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

BMI, body mass index; BP, blood pressure; BUN, blood urea nitrogen; CVE, cardiovascular event; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; Hb, hemoglobin; LDL-C, low-density lipoprotein cholesterol; MAP, mean arterial pressure; PTH, parathyroid hormone.

<sup>a</sup>2009 creatinine-based eGFR equation. <sup>b</sup>Patients with missing information on smoking status were excluded.

Subgroup analysis of comparison of cardiovascular event and the composite of all-cause mortality and cardiovascular event predictability

As the prevalence of CVE and all-cause mortality was higher in CKD stages 3 to 5, subgroup analysis of outcome pre-
Figure 2. Bland-Altman plot of differences in eGFR among the three equations. (A) Difference between 2009 eGFRcr and 2021 eGFRcr equation. (B) Difference between 2009 eGFRcr and 2021 eGFRcr-cysC equation. (C) Difference in eGFR between 2021 eGFRcr and 2021 eGFRcr-cysC equation.

eGFR, estimated glomerular filtration rate; eGFRcr, creatinine-based eGFR; eGFRcr-cysC, creatinine-cystatin C–based eGFR; SD, standard deviation.
Table 2. Comparison of average eGFR, CVE and composite of all-cause mortality and CVE prevalence according to CKD stages in each eGFR equation

<table>
<thead>
<tr>
<th>Variable</th>
<th>2009 eGFRcr equation</th>
<th>2021 eGFRcr equation</th>
<th>2021 eGFRcr-cysC equation</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>355</td>
<td>420</td>
<td>827</td>
</tr>
<tr>
<td>eGFR (mL/min/1.73 m²)</td>
<td>107.0 ±11.0</td>
<td>108.7 ±10.5</td>
<td>108.7 ±10.5</td>
</tr>
<tr>
<td>CVE</td>
<td>12 (3.4)</td>
<td>12 (3.0)</td>
<td>12 (3.0)</td>
</tr>
<tr>
<td>All-cause mortality and CVE</td>
<td>14 (3.9)</td>
<td>15 (3.8)</td>
<td>15 (3.8)</td>
</tr>
</tbody>
</table>

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

CKD, chronic kidney disease; CVE, cardiovascular event; eGFR, estimated glomerular filtration rate; eGFRcr, creatinine-based eGFR; eGFRcr-cysC, creatinine-cystatin C–based eGFR.

Discussion

The results of this study show that the average eGFR level calculated using the 2021 eGFRcr equation was approximately 3 mL/min/1.73 m² higher and 1.5 mL/min/1.73 m² higher than the results using the 2021 eGFRcr-cysC equation and the 2009 eGFRcr equation, respectively. There was an overall reduction in prevalence of CKD stages 3 to 5 when the 2021 eGFR equations were used for CKD stage classification (2009 eGFRcr, 64.9% vs. 2021 eGFRcr, 61.1% vs. 2021 eGFRcr-cysC, 63.4%). The AUC values for predictability of CVE and the composite of all-cause mortality and CVE were similar across equations, and the NRI values were not statistically significant. This suggests that the 2009 eGFRcr equation is not inferior in predicting CVE and the composite of all-cause mortality and CVE compared to the 2021 eGFRcr and eGFRcr-cysC equations.

The overall prevalence of CVE in this study was 9.1% (n
Table 3. Predictive value of each eGFR to CVE and composite of all-cause mortality and CVE

<table>
<thead>
<tr>
<th>Variable</th>
<th>2009 eGFRcr (+10)</th>
<th>p-value</th>
<th>2021 eGFRcr (+10)</th>
<th>p-value</th>
<th>2021 eGFRcr-cysC (+10)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CVE</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted</td>
<td>0.90 (0.86–0.95)</td>
<td>&lt;0.01</td>
<td>0.91 (0.87–0.96)</td>
<td>&lt;0.01</td>
<td>0.90 (0.85–0.95)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Sex-age</td>
<td>0.98 (0.92–1.04)</td>
<td>0.46</td>
<td>0.98 (0.93–1.04)</td>
<td>0.48</td>
<td>0.96 (0.91–1.02)</td>
<td>0.15</td>
</tr>
<tr>
<td>Multivariable&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.99 (0.91–1.07)</td>
<td>0.75</td>
<td>0.99 (0.91–1.07)</td>
<td>0.73</td>
<td>0.97 (0.90–1.04)</td>
<td>0.41</td>
</tr>
<tr>
<td>All-cause mortality and CVE</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted</td>
<td>0.84 (0.80–0.88)</td>
<td>&lt;0.01</td>
<td>0.85 (0.81–0.89)</td>
<td>&lt;0.01</td>
<td>0.84 (0.80–0.87)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Sex-age</td>
<td>0.90 (0.86–0.95)</td>
<td>&lt;0.01</td>
<td>0.91 (0.87–0.95)</td>
<td>&lt;0.01</td>
<td>0.89 (0.85–0.94)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Multivariable&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.94 (0.89–0.99)</td>
<td>0.02</td>
<td>0.94 (0.90–0.99)</td>
<td>0.02</td>
<td>0.92 (0.87–0.97)</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

Data are expressed as hazard ratio (95% confidence interval).

CVE, cardiovascular event; eGFR, estimated glomerular filtration rate; eGFRcr, creatinine-based eGFR; eGFRcr-cysC, creatinine-cystatin C–based eGFR.

<sup>a</sup>Multivariable model was adjusted for age, sex, diabetes mellitus, smoking, body mass index, mean arterial pressure, low-density lipoprotein cholesterol, ejection fraction, and proteinuria.

Figure 3. Receiver operating characteristic curve analysis for CVE (A) and the composite of all-cause mortality and CVE predictability (B).

AUC, area under the curve; CVE, cardiovascular event.

Table 4. NRI for comparison of predictability according to eGFR equations

<table>
<thead>
<tr>
<th>Variable</th>
<th>NRI (%)</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CVE</td>
<td></td>
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<tr>
<td>2009 eGFRcr vs. 2021 eGFRcr</td>
<td>0.013</td>
<td>−0.002 to 0.028</td>
<td>0.09</td>
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<tr>
<td>2009 eGFRcr vs. 2021 eGFRcr-cysC</td>
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<td>−0.031 to 0.029</td>
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</tr>
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<td>2021 eGFRcr vs. 2021 eGFRcr-cysC</td>
<td>−0.015</td>
<td>−0.048 to 0.018</td>
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<tr>
<td>All-cause mortality and CVE</td>
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<tr>
<td>2009 eGFRcr vs. 2021 eGFRcr</td>
<td>−0.019</td>
<td>−0.039 to 0.000</td>
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<td>2009 eGFRcr vs. 2021 eGFRcr-cysC</td>
<td>−0.002</td>
<td>−0.023 to 0.018</td>
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<td>2021 eGFRcr vs. 2021 eGFRcr-cysC</td>
<td>0.017</td>
<td>−0.004 to 0.039</td>
<td>0.11</td>
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</tbody>
</table>

CI, confidence interval; CVE, cardiovascular event; eGFR, estimated glomerular filtration rate; eGFRcr, creatinine-based eGFR; eGFRcr-cysC, creatinine-cystatin C–based eGFR; NRI, net reclassification improvement.
CVE risk is increased in CKD patients and is the cause of death in approximately 40% to 50% of cases, which is approximately two-fold higher than in the general population with normal kidney function [17]. The CVE and mortality risks are increased in CKD patients through both traditional and non-traditional risk factors [13]. Traditional risk factors including DM, hypertension, dyslipidemia, and smoking aggravate atherosclerosis, which is associated not only with cardiovascular disease but also CKD progression [18]. Nontraditional risk factors include accelerated vascular calcification in vessels and cardiac valves and chronic systemic inflammation [19,20]. The overall CVE prevalence of this study was relatively low compared to other western CKD cohort studies, where the CVE prevalences were 33.4% (CRIC, United States), 47.2% (CRISIS, United Kingdom), and 39.1% (MERENA, Spain) [21–24]. Also, another study that compared longitudinal outcomes across multiple international CKD cohorts, including the current KNOW-CKD cohort, showed that the CVE risk was lower in Korean and Japanese CKD cohorts compared to western CKD cohorts [25]. This finding may be due to differences in genetics, lifestyle patterns including diet, and lower incidence of traditional cardiovascular risk factors in Asian CKD patients compared to western patients [25,26]. Due to the relatively small number of CVEs in this study, the predictive value of eGFR for CVE did not show a statistically significant association across the three eGFR equations. However, the association between eGFR and the composite of all-cause mortality and CVE was significant in both univariate and multivariate analyses, where the analysis was conducted with a larger number of clinical outcome events. This finding shows that the power of event prediction was valid and significant in all three eGFR equations. Even though the overall CVE prevalence of this study was relatively low, the CVE group had distinctive traditional and nontraditional characteristics associated with CVE. The group was older with a higher percentage of metabolic comorbidities including hypertension, DM, and coronary artery disease. Also, inflammatory markers including hs-CRP were elevated, and the percentage of former and current smokers was higher in the CVE group.

As CVE and all-cause mortality events were concentrated in CKD stage 3 to 5 patients, subgroup analysis was conducted to compare the outcome predictability in early (stages 1 and 2) and advanced (stages 3 to 5) CKD stages. For CVE, the 2009 eGFRcr equation had slightly improved predictability compared to the 2021 eGFRcr equation in CKD stages 1 and 2. For the composite of all-cause mortality and CVE, the 2009 eGFRcr equation had slightly improved predictability compared to the 2021 eGFRcr equation. Also, the 2021 eGFRcr-cysC equation had slightly improved predictability compared to the 2021 eGFRcr equation in CKD stages 3 to 5. These findings are in line with the core results of our study that the current 2009 eGFRcr equation was not inferior to the 2021 eGFRcr and eGFRcr-cysC equations in CVE prediction. The 2021 eGFRcr-cysC equation had slightly improved predictability compared to the 2021 eGFRcr equation in advanced CKD patients, in accordance with the findings of Inker et al. [8], which showed that the 2021 eGFRcr-cysC equation was more accurate than the 2021 eGFRcr equation, with smaller differences in eGFR between the race groups. However, direct comparison of outcome predictability power and eGFR accuracy may not be appropriate.

The average eGFR level calculated using the 2021 eGFRcr equation was approximately 3 mL/min/1.73 m² higher and 1.5 mL/min/1.73 m² higher than that calculated using the 2021 eGFRcr-cysC equation and the 2009 eGFRcr equation. Therefore, approximately 10% of patients (224 of 2,207) were reclassified to a lower CKD category when using the 2021 eGFRcr equation compared to the 2009 eGFRcr equation. For the 2021 eGFRcr-cysC equation, approximately 8% of patients (181 of 2,145) were reclassified into a lower CKD category when using the 2021 eGFRcr-cysC equation and the 2009 eGFRcr equation. Therefore, approximately 10% of patients (224 of 2,207) were reclassified to a lower CKD category when using the 2021 eGFRcr equation compared to the 2009 eGFRcr equation. These findings are in agreement with the study by Inker et al. [8] that the calculated eGFR of the ‘non-black’ subpopulation was overestimated when using both 2021 eGFRcr and eGFRcr-cysC equations, resulting in a higher CKD category (Supplementary Table 2, available online). These findings are in agreement with the study by Inker et al. [8] that the calculated eGFR of the ‘non-black’ subpopulation was overestimated when using both 2021 eGFRcr and eGFRcr-cysC equations compared to the 2009 eGFRcr equation [8]. These findings are attributed to the changes in the variable constants of the new 2021 eGFR equations.

The prevalence of CKD 3 to 5 was reduced by 3.8% when using the 2021 eGFRcr equation and by 1.5% when using the 2021 eGFRcr-cysC equation. The Kidney Disease Improving Global Outcomes guidelines recommend thorough work-up, treatment, and regular follow-up for management of CKD and its complications, especially when the eGFR is less than 60 mL/min/1.73 m². CVE risk is increased dramatically in CKD stages 3 to 5, and careful examinations and
risk stratification are needed [13]. Inappropriate diagnosis of advanced CKD can be problematic in medication dose adjustment and unnecessary limitations of medication prescriptions including renin-angiotensin-system blockade agents. Even though the prevalence of CKD stages 3 to 5 was reduced using the 2021 eGFR equations, neither CVE nor the composite of all-cause mortality and CVE predictability differed with CKD 3 to 5 prevalence. This is in line with a previous study showing that the clinical significance of the new 2021 eGFR equations is minimal, especially in non-black patients [11].

The main limitation of this study is that the overall CVE prevalence was relatively low. Therefore, subtle differences in calculated eGFR among the three equations may not have sufficient statistical power to result in changes in CVE predictability. Also, there was no information on measured GFR using exogenous filtration markers. Therefore, no definite validation of accuracy of one equation over another was achieved as a direct comparison of calculated to measured eGFR values. However, to our knowledge, this is the first study to evaluate the efficacy of the 2021 eGFRcr and eGFRcr-cysC equations in a large-scale, all-Asian CKD cohort. As the KNOW-CKD study is an ongoing prospective cohort, CVE and all-cause mortality events were clearly defined and accurately documented. Also, serum creatinine and cysC were measured in a central laboratory, ensuring the accuracy of eGFR calculations.

In conclusion, the 2009 eGFRcr equation was not inferior to either the 2021 eGFRcr or eGFRcr-cysC equation in predicting risks of CVE and the composite of all-cause mortality and CVE in Korean CKD patients. Further longitudinal studies with higher CVE prevalence and availability of measured GFR are needed to validate the efficacy of the new 2021 eGFRcr and eGFRcr-cysC equations in Asian populations.

Conflicts of interest
Tae-Hyun Yoo is the Editor-in-Chief of *Kidney Research and Clinical Practice* and was not involved in the review process of this article. All authors have no other conflicts of interest to declare.

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Data sharing statement
The data presented in this study are available on request from the corresponding author.

Authors’ contributions
Conceptualization: JHK, MK, EK, KHO
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Formal analysis: JHK, YJ, JK
Investigation, Methodology: JK, SKP
Supervision: JCJ, THY, HL
Validation: JHK, THY, YK, YCK, SSH, HL
Writing–original draft: JHK
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References


Background: The medium cutoff (MCO) dialyzer increases the removal of several middle molecules more effectively than high-flux hemodialysis (HD). However, comparative data addressing the efficacy and safety of MCO dialyzers vs. postdilution hemodiafiltration (HDF) in Korean patients are lacking.

Methods: Nine patients with chronic HD were included in this pre-post study. Patients underwent HD with an MCO dialyzer for 4 weeks, followed by a 2-week washout period using a high-flux dialyzer to minimize carryover effects, and then turned over to postdilution HDF for 4 weeks. Reduction ratios and differences in the uremic toxins before and after dialysis were calculated from the MCO dialysis, postdilution HDF, and high-flux HD. In the in vitro study, EA.hy926 cells were incubated with dialyzed serum.

Results: Compared to postdilution HDF, the MCO dialyzer achieved significantly higher reduction ratios for larger middle molecules (myoglobin, kappa free light chain [κFLC], and lambda FLC [λFLC]). Similarly, the differences in myoglobin, κFLC, and λFLC concentrations before and after the last dialysis session were significantly greater in MCO dialysis than in postdilution HDF. The expression of Bax and nuclear factor κB was decreased in the serum after dialysis with the MCO dialyzer than with HDF.

Conclusion: Compared with high-volume postdilution HDF, MCO dialysis did not provide greater removal of molecules below 12,000 Da, whereas it was superior in the removal of larger uremic middle molecule toxins in patients with kidney failure. Moreover, these results may be expected to have an anti-apoptotic effect on the human endothelium.

Keywords: Artificial membranes, Apoptosis, Endothelium, Hemodiafiltration, Uremic toxins

Introduction

Kidney failure is characterized by a progressive loss of elimination capacity, followed by the accumulation of various compounds referred to as uremic toxins [1]. With growing concern about the association of middle molecules or larger low-molecular-weight proteins with increased mortality and morbidity of chronic hemodialysis (HD) patients, new dialysis modalities, including convective therapy, have been developed to remove these uremic toxins [2]. Hemodiafiltration (HDF) provides both effective diffusive clearance of small molecules and superior remov-
al of middle molecules. Previous studies have shown that HDF can reduce intradialytic hypotension, amyloidosis, and accelerated atherosclerosis [3–6]. Moreover, a previous randomized controlled trial supported the superiority of high-convective-volume HDF in reducing all-cause mortality when compared with high-flux HD [7], possibly due to more effective removal of larger uremic retention solutes. However, several meta-analyses did not find a significant difference in the overall mortality between patients treated with HDF and those treated with HD, because some trials were of suboptimal quality and underpowered [8–10].

In this regard, medium cutoff (MCO) dialyzers utilize a novel class of membranes that are designed to increase the removal of larger middle molecules, yet have low permeability for albumin [11]. Specifically, MCO membranes have slightly larger pores and a tighter pore distribution than high-flux membranes [12]. Although a few studies have compared the removal of uremic toxins by MCO dialyzers or high-flux HD [13–16], comparisons between MCO dialyzers and high-convective volume postdilution HDF in terms of the removal of large uremic molecules, particularly free light chains (FLC), and endothelial toxicity in dialysis patients are scarce. In this study, we compared the efficacy of the reduction of middle molecules between MCO dialyzers and high-volume postdilution HDF. Additionally, we performed an in vitro study to determine whether filtered serum obtained after dialysis with an MCO dialyzer was less toxic to EA.hy926 human vascular endothelial cells than serum obtained after high-volume HDF.

**Methods**

**Patients and study design**

Maintenance HD patients participated in this prospective, controlled, open-label, nonrandomized, single-center pre-post study. Among HD patients aged ≥20 years, 12 were enrolled in the study. However, three patients dropped out due to withdrawal of consent during the eligibility period. Patients received HD with an MCO dialyzer for 4 weeks, followed by a 2-week washout period using a high-flux dialyzer to minimize carryover effects. Subsequently, the patients turned over to postdilution HDF for 4 weeks. The present study used serum samples collected from patients at the Chonnam National University Hwasun Hospital.

The study protocol was approved by the Institutional Review Board of the Chonnam National University Hwasun Hospital (No. CNUHH-2017-186). All patients provided written informed consent before inclusion in the study.

**Dialysis materials and treatment procedures**

Patients underwent HD performed with either a Theranova 400 dialyzer (Baxter International Inc.) or an FX 60 or 80 dialyzer (Fresenius Medical Care) according to body surface area. All patients underwent 4 hours of dialysis three times a week using Artis Physio machines (Baxter International Inc.). Online HDF was conducted in a postdilution pressure-controlled mode with a target convective ultrafiltration volume of ≥20 L. The dialysis regimens of each patient, including blood flow, dialysate flow, and treatment duration per session, were not altered.

**Determination of small and middle molecules**

We measured differences in the clearance of uremic toxins provided by the two treatment options. The uremic toxins were classified into the following types as specified by the European Union Toxin Working Group: small molecules, including blood urea nitrogen (BUN) (60 Da), creatinine (113 Da), and uric acid (168 Da); middle molecules, including β2-microglobulin (β2MG) (11,800 Da), myoglobin (17,800 Da), kappa FLC (κFLC, 25,000 Da), and lambda FLC (λFLC, 50,000 Da); and albumin (66,000 Da).

**Clinical outcomes**

Baseline clinical information was collected, including age, sex, body weight, height, dialysis vintage, and type of vascular access, and Kt/V was calculated using the second-generation formula for single-pool values to determine the appropriate level of HD for each patient [17]. The efficacy of each dialysis treatment was assessed by calculating the reduction ratios (RRs) and differences in the uremic toxins before and after each MCO dialysis, postdilution HDF, and high-flux HD at the end of the 2- or 4-week treatment period. The RRs were calculated using the following formula:

\[
\text{Reduction ratio} \% = \left( 1 - \frac{C_{\text{post}}}{C_{\text{pre}}} \right) \times 100
\]
where $C_{\text{pre}}$ and $C_{\text{post}}$ are the measured concentrations of the solute before and at the end of the treatments, respectively. The corrected plasma concentrations of the middle molecules were determined using the following formula [18]:

$$\text{Corrected concentration} = \frac{\text{Concentration}_{\text{post}}}{1 + \frac{BW_{\text{pre}} - BW_{\text{post}}}{0.2 \times BW_{\text{post}}}}$$

where $BW_{\text{pre}}$ and $BW_{\text{post}}$ are the body weights before and after dialysis, respectively.

**In vitro study**

Blood samples were obtained from patients at the last dialysis session of the MCO dialysis and postdilution HDF treatment periods, and the serum was separated by centrifugation and transferred to contamination-free bottles. All samples were stored at –80 °C until analysis. The EA.hy926 human vascular endothelial cell line (American Type Culture Collection [ATCC]) was cultured in Dulbecco’s modified Eagle’s medium (30-2002, ATCC) at 37 °C in 5% CO$_2$. Heparin (0.6 IU/mL) was added to the incubation medium for all experiments. The cells were incubated with 2.5% serum from patients or 2.5% fetal bovine serum for 16 hours. The final concentration and duration of serum incubation were determined to be based on the appropriate viscosity of the incubation media and the activation of apoptotic proteins (Supplementary Fig. 1; available online).

**Western blot analyses and primary antibodies**

Western blot analyses were performed as described previously [19]. The cells were harvested, resuspended in lysis buffer, and briefly sonicated. After centrifugation, the supernatant was prepared as a protein extract. Equal concentrations of protein were separated on 8% or 12% sodium dodecyl sulfate-polyacrylamide gels, and the proteins were transferred onto nitrocellulose membranes. Densitometry was performed using Scion Image software (Scion Corporation). The experiments were repeated at least twice. The primary and secondary antibodies used for western blotting are listed in Supplementary Table 1 (available online).

**Cell viability test**

Cell viability was determined using the CyQUANT MTT cell viability assay kit (V13154; Invitrogen). Absorbance at 570 nm was detected using a 96-well microplate reader (BioTek Instruments). Cell viability was expressed as the fraction of the surviving cells relative to the fetal-bovine-serum-treated cells.

**Statistical analyses**

The sample size was determined on the basis of the $\beta2$MG concentrations. When the effect size was assumed by the mean and standard deviation of differences of $\beta2$MG at the level of the in the pre- and postdialysis of both HDF and the MCO dialyzer, eight patients were calculated to provide 80% power at a two-sided alpha level of 0.05 using the Wilcoxon signed-rank test. The expected dropout rate was assumed to be 20%; accordingly, at least 10 patients were required initially. The results were expressed as the median and interquartile range. The statistical significance of differences between the treatments was determined using the Friedman or Wilcoxon signed-rank test. Carryover effects were assessed by comparing the predialysis concentrations of uremic toxins in the first sessions of MCO and HDF. For a more conservative interpretation, p-values of <0.017 (Bonferroni method) were considered statistically significant for multiple comparisons. For the in vitro studies, the statistical significance of differences was determined using an unpaired Student t test or one-way analysis of variance followed by a post hoc Tukey test. All statistical analyses were performed using IBM SPSS version 25.0 (IBM Corp.) and GraphPad Prism version 9.1.2 (GraphPad Software, Inc.).

**Results**

**Baseline characteristics of patients**

Baseline characteristics are shown in Table 1. The median age of all patients was 58.0 years (interquartile range [IQR], 50.0–69.5 years), and 55.6% were male. The median Kt/V value was 1.58 (IQR, 1.46–1.78). Only one patient underwent dialysis using an arteriovenous graft. The median values of blood flow rate and dialysis vintage were 270 mL/
Table 1. Clinical characteristics of the study patients

<table>
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<tr>
<th>Characteristic</th>
<th>Median (interquartile range)</th>
<th>Patient</th>
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<tr>
<td>Dialyzer</td>
<td>FX80</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>FX80</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>FX80</td>
<td>3</td>
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<td></td>
<td>FX80</td>
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<td>FX80</td>
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<td>FX80</td>
<td>6</td>
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<td></td>
<td>FX80</td>
<td>7</td>
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<tr>
<td></td>
<td>FX80</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>FX80</td>
<td>9</td>
</tr>
</tbody>
</table>

Table 2. Comparison of blood flow rates, filtration fractions, and convection volumes among patients who underwent high-flux HD for 4 weeks, then postdilution HDF washout for 2 weeks, and then turned to MCO dialysis for 4 weeks

<table>
<thead>
<tr>
<th>Variable</th>
<th>High-flux HD, 1 wk</th>
<th>Postdilution HDF</th>
<th>MCO dialysis, 4 wk</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood flow rate (mL/min)</td>
<td>270 (250–285)</td>
<td>270 (250–290)</td>
<td>270 (250–290)</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>Filtration fraction (%)</td>
<td>NA</td>
<td>34.0 (32.8–36.5)</td>
<td>35.0 (33.5–37.0)</td>
<td>0.39</td>
</tr>
<tr>
<td>Convection volume (L)</td>
<td>NA</td>
<td>21.0 (18.8–22.9)</td>
<td>23.3 (20.9–24.3)</td>
<td>0.13</td>
</tr>
<tr>
<td>Convection volume/BSA (L)</td>
<td>NA</td>
<td>12.9 (11.7–13.5)</td>
<td>13.5 (13.2–14.4)</td>
<td>0.16</td>
</tr>
</tbody>
</table>

Data are expressed as median (interquartile range).
BSA, body surface area; HD, hemodialysis; HDF, hemodiafiltration; MCO, medium cutoff membrane; NA, not applicable.
*Friedman test.

We compared the pre- and postdialysis serum concentrations of small and middle uremic toxins during the last session of each dialysis modality (Table 3). Of note, BUN, creatinine, uric acid, β2MG, myoglobin, κFLC, and λFLC concentrations were significantly lower after dialysis compared with predialysis measurements regardless of dialysis modality. Differences in pre- and postdialysis concentrations of BUN, creatinine, and uric acid did not differ between high-flux HD, postdilution HDF, and the MCO dialyzer (Table 4); however, differences in the values for β2MG, myoglobin, κFLC, and λFLC were significantly greater after MCO dialysis. In particular, compared with postdilution HDF, differences in myoglobin and λFLC were significantly greater after MCO dialysis.

Next, we investigated the RRs of small and middle uremic toxins in patients receiving postdilution HDF and MCO dialysis at the last session of each dialysis modality (Fig. 1; Supplementary Table 3, available online).

In the post hoc analyses, the RRs of β2MG were not different between the postdilution HDF and MCO dialysis (67.9% ± 11.7% vs. 71.6% ± 5.7%, p = 0.26). However, MCO dialysis resulted in a significantly greater RR for myoglobin, κFLC, and λFLC compared with postdilution HDF. Interestingly,
Table 3. Comparison of pre- and postdialysis concentrations of uremic toxins in patients who underwent high-flux HD for 4 weeks, then postdilution HDF washout for 2 weeks, and then turned to MCO dialysis for 4 weeks

<table>
<thead>
<tr>
<th>Variable</th>
<th>High-flux HD</th>
<th>Predialysis</th>
<th>Postdialysis</th>
<th>p-value</th>
<th>Predialysis</th>
<th>Postdialysis</th>
<th>p-value</th>
<th>Predialysis</th>
<th>Postdialysis</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albumin (mg/dL)</td>
<td>3.5 (3.5–3.85)</td>
<td>3.2 (3.05–3.60)</td>
<td>3.7 (3.7–3.9)</td>
<td>0.008</td>
<td>3.5 (3.2–3.7)</td>
<td>3.5 (3.2–3.7)</td>
<td>0.02</td>
<td>3.8 (3.6–3.9)</td>
<td>3.4 (3.2–3.6)</td>
<td>0.008</td>
</tr>
<tr>
<td>Total protein (mg/dL)</td>
<td>6.6 (6.4–6.9)</td>
<td>6.0 (5.7–6.4)</td>
<td>6.7 (6.5–7.0)</td>
<td>0.008</td>
<td>6.2 (5.8–6.6)</td>
<td>6.2 (5.8–6.6)</td>
<td>0.03</td>
<td>6.7 (6.4–7.0)</td>
<td>6.1 (5.6–6.4)</td>
<td>0.008</td>
</tr>
<tr>
<td>BUN (mg/dL)</td>
<td>53.5 (32.2–62.0)</td>
<td>10.4 (9.4–13.0)</td>
<td>50.4 (33.9–62.2)</td>
<td>0.008</td>
<td>10.9 (9.0–12.1)</td>
<td>10.9 (9.0–12.1)</td>
<td>0.008</td>
<td>50.8 (35.5–67.3)</td>
<td>11.4 (6.9–12.5)</td>
<td>0.008</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>9.15 (7.33–10.17)</td>
<td>2.51 (2.01–3.11)</td>
<td>7.97 (6.51–9.80)</td>
<td>0.008</td>
<td>2.36 (2.04–2.69)</td>
<td>2.36 (2.04–2.69)</td>
<td>0.008</td>
<td>8.24 (6.93–9.47)</td>
<td>2.21 (1.76–2.65)</td>
<td>0.008</td>
</tr>
<tr>
<td>Uric acid (mg/dL)</td>
<td>3.8 (3.6–4.9)</td>
<td>0.8 (0.5–1.0)</td>
<td>4.0 (2.6–5.1)</td>
<td>0.008</td>
<td>0.7 (0.4–1.1)</td>
<td>0.7 (0.4–1.1)</td>
<td>0.008</td>
<td>4.7 (3.2–5.7)</td>
<td>0.8 (0.5–1.1)</td>
<td>0.008</td>
</tr>
<tr>
<td>β2MG (μg/L)</td>
<td>273,753 (22,546.5–26,008.5)</td>
<td>12,121.2 (9,586.4–13,951.1)</td>
<td>21,659.0 (15,043.5–23,918.0)</td>
<td>0.008</td>
<td>6,002.3 (4,614.9–6,875.6)</td>
<td>6,002.3 (4,614.9–6,875.6)</td>
<td>0.008</td>
<td>23,141.0 (21,705.5–26,281.0)</td>
<td>6,277.5 (5,217.5–7,518.3)</td>
<td>0.008</td>
</tr>
<tr>
<td>Myoglobin (ng/mL)</td>
<td>349.0 (215.5–545.5)</td>
<td>321.5 (197.1–512.9)</td>
<td>274.0 (238.0–357.5)</td>
<td>0.01</td>
<td>196.0 (144.8–274.2)</td>
<td>196.0 (144.8–274.2)</td>
<td>0.02</td>
<td>293.0 (211.0–357.5)</td>
<td>99.1 (50.5–143.1)</td>
<td>0.008</td>
</tr>
<tr>
<td>Kappa FLC (mg/L)</td>
<td>241.7 (203.0–291.9)</td>
<td>180.8 (139.6–199.5)</td>
<td>231.4 (189.8–288.6)</td>
<td>0.008</td>
<td>118.5 (101.1–131.3)</td>
<td>118.5 (101.1–131.3)</td>
<td>0.008</td>
<td>249.2 (203.0–291.5)</td>
<td>74.9 (60.3–87.2)</td>
<td>0.008</td>
</tr>
<tr>
<td>Lambda FLC (mg/L)</td>
<td>188.8 (151.9–243.9)</td>
<td>158.3 (115.7–214.4)</td>
<td>186.4 (147.3–255.8)</td>
<td>0.008</td>
<td>99.1 (50.5–143.1)</td>
<td>99.1 (50.5–143.1)</td>
<td>0.008</td>
<td>192.5 (149.2–262.0)</td>
<td>100.1 (83.0–117.9)</td>
<td>0.008</td>
</tr>
</tbody>
</table>

Data are expressed as the median (interquartile range).
BUN, blood urea nitrogen; β2MG, β2-microglobulin; FLC, free light chain; HD, hemodialysis; HDF, hemodiafiltration; MCO, medium cutoff membrane.
a Wilcoxon signed-rank test.

Table 4. Differences between pre- and postdialysis concentrations of uremic toxins in patients who underwent high-flux HD for 4 weeks, postdilution HDF washout for 2 weeks, and then turned to MCO dialysis for 4 weeks

<table>
<thead>
<tr>
<th>Variable</th>
<th>Variable</th>
<th>High-flux HD</th>
<th>Postdilution HDF</th>
<th>MCO dialysis</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Δ of albumin (mg/dL)</td>
<td>0.31</td>
<td>0.29–0.37</td>
<td>0.42 (0.10–0.54)</td>
<td>0.32 (0.22–0.56)</td>
<td>0.97</td>
</tr>
<tr>
<td>Δ of total protein (mg/dL)</td>
<td>0.60</td>
<td>0.43–0.70</td>
<td>0.70 (0.16–1.02)</td>
<td>0.53 (0.37–0.98)</td>
<td>0.91</td>
</tr>
<tr>
<td>Δ of BUN (mg/dL)</td>
<td>41.0</td>
<td>25.3–50.1</td>
<td>40.0 (25.0–50.3)</td>
<td>40.9 (26.0–53.9)</td>
<td>0.46</td>
</tr>
<tr>
<td>Δ of creatinine (mg/dL)</td>
<td>6.67</td>
<td>4.89–7.65</td>
<td>6.06 (3.88–7.40)</td>
<td>5.93 (4.92–6.97)</td>
<td>0.24</td>
</tr>
<tr>
<td>Δ of uric acid (mg/dL)</td>
<td>3.05</td>
<td>2.77–3.68</td>
<td>3.48 (1.86–4.10)</td>
<td>3.56 (2.70–4.53)</td>
<td>0.37</td>
</tr>
<tr>
<td>Δ of β2MG (μg/L)</td>
<td>12,052</td>
<td>8,711–13,512</td>
<td>16,318 (8,557–17,474)</td>
<td>17,173 (14,237–19,771)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Δ of myoglobin (ng/mL)</td>
<td>20.90</td>
<td>7.90–38.40</td>
<td>72.5 (27.5–96.0)</td>
<td>190.8 (148.7–324.5)</td>
<td>0.001</td>
</tr>
<tr>
<td>Δ of kappa FLC (mg/L)</td>
<td>64.7</td>
<td>50.6–97.9</td>
<td>107.8 (70.8–148.0)</td>
<td>174.2 (136.0–208.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Δ of lambda FLC (mg/L)</td>
<td>33.0</td>
<td>18.7–44.4</td>
<td>31.5 (15.4–52.3)</td>
<td>84.3 (71.5–148.2)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Data are expressed as median (interquartile range).
BUN, blood urea nitrogen; β2MG, β2-microglobulin; FLC, free light chain; HD, hemodialysis; HDF, hemodiafiltration; MCO, medium cutoff membrane.
a Difference values between predialysis and postdialysis.
b Friedman test.
c Wilcoxon signed-rank test, p-value for high-flux HD vs. postdilution HDF.
d Wilcoxon signed-rank test, p-value for high-flux HD vs. MCO dialysis.
e Wilcoxon signed-rank test, p-value for postdilution HDF vs. MCO dialysis.
MCO dialysis produced a three-fold greater RR for λFLC compared with postdilution HDF (49.8% ± 6.5% vs. 15.8% ± 8.5%, p = 0.008), while the RRs high-flux HD and postdilution HDF did not differ (15.3% ± 8.0% vs. 15.8% ± 8.5%, p = 0.95). A comparison of albumin loss showed no significant differences between postdilution HDF and MCO dialysis (Table 4; Supplementary Table 3, available online).

**Figure 1.** Reduction ratios for small and middle uremic toxins in patients who underwent MCO dialysis for 4 weeks, high-flux HD washout for 2 weeks, and then turned to postdilution HDF for 4 weeks.

BUN, blood urea nitrogen; β2MG, β2-microglobulin; FLC, free light chain; HD, hemodialysis; HDF, hemodiafiltration; MCO, medium cut-off membrane; NS, not statistically significant.

***p < 0.001.

To examine whether the remaining uremic toxins in serum after each dialysis modality exacerbated vascular injury, we performed *in vitro* studies to explore the effects of purified sera on vascular apoptosis and the nuclear factor κB (NF-κB) signaling pathway (Fig. 2A, B). After incubation of human endothelial cells with serum obtained after MCO dialysis, the ratio of Bax/Bcl-2 expression was lower than after postdilution HDF, as was NF-κB p65 expression. In...
addition, we found that recovered cell viability in endothelial cells treated with MCO serum compared with serum after postdilution HDF. We added this in the results section (Fig. 2C).

**Discussion**

Among the uremic retention compounds, middle molecules or low-molecular-weight proteins with molecular weights ranging from approximately 5,000 to 50,000 Da, including β2MG, myoglobin, FLC, parathyroid hormone, fi-

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**Figure 2.** Serum obtained from patients after completing 4 weeks of MCO dialysis and again after 4 weeks of postdilution HDF was added to human vascular endothelial cells (2.5%) for 16 hours, and the expression of Bax, Bcl-2, and NF-κB p65 was assessed. (A) Western blot analyses of Bax, Bcl-2, and NF-κB p65 protein expression in human endothelial cells incubated with serum after each dialysis modality. (B) Relative protein intensities are presented. The values for control cells incubated with fetal bovine serum were set to 1. (C) Cell viability assay. All values are presented as the mean ± standard error of the mean.

HDF, hemodiafiltration; MCO, medium cutoff membrane; NF-κB, nuclear factor κB; NS, not statistically significant. **p < 0.01; ***p < 0.001.
broblast growth factor-23, and retinol-binding protein, are considered to have detrimental clinical effects in patients with uremia [20]. Plasma myoglobin concentrations are typically greater in patients with both pre- and postdialysis than in healthy controls [21]. Furthermore, β2MG and FLC have been recognized as surrogate markers for predicting mortality in patients undergoing HD [22,23].

This pre-post study revealed that the MCO dialyzer had a high efficacy for the removal of β2MG, myoglobin, κFLC, and λFLC. Additionally, compared with high convection volume postdilution HDF, the MCO dialyzer treatment showed a greater RR for myoglobin, κFLC, and λFLC.

Previous studies have shown the superiority of the MCO dialyzer over high-flux HD in the reduction of β2MG, κFLC, λFLC, myoglobin, interleukin (IL)-1β, and IL-6 [13–15]. In addition, a previous randomized crossover trial also showed that mRNA expression of the inflammation markers tumor necrosis factor-a and IL-6 were reduced to a greater extent with the MCO dialyzer than with high-flux HD [16]. Similar to our results, a recent multicenter, randomized controlled study in which 86 patients received 24 weeks of treatment with the MCO dialyzer demonstrated a 33% RR of λFLC, while the RR was only 17% when using a similarly sized high-flux dialyzer [24]. However, these results are not surprising when considering the characteristics of an MCO membrane, which has a high-retention onset, and a cutoff value that limits the loss of albumin compared to conventional high-flux membranes [25,26]. Consequently, the MCO dialyzer can provide remarkable convective clearance of medium- to high-molecular-weight solutes while avoiding significant albumin loss.

In terms of the efficacy of middle molecule removal, online HDF can provide combined diffusive and convective transport, resulting in markedly enhanced clearance of middle to large molecules [27]. There are two major dilution techniques in HDF: pre- and postdilution. A recent observational prospective study demonstrated that the MCO dialyzer produced a greater reduction in λFLC compared with predilution online HDF (43.2% vs. 33.0%, respectively) even with a high mean convection volume of 49.9 L/session of HDF [28]. Conversely, there have been conflicting reports of the efficacy of β2MG removal by the MCO dialyzer compared with postdilution HDF, regardless of convection volume [29–32]. Recently, a controlled crossover study showed that there was no significant difference in the RR for β2MG between the MCO dialyzer and a high convection volume of a mean 24.5 L/session postdilution HDF [33]. Consistent with previous studies [21,29,30,33], our results showed no significant differences in the RRs for β2MG after MCO dialysis or postdilution HDF.

There have been few previous comparisons of the efficacy of FLC removal following MCO dialysis or postdilution HDF. Kirsch et al. [32] showed that the RRs of κFLC and λFLC were 72.9% and 48.1%, respectively, when using the MCO AA prototype dialyzer. These results were superior to the removal of λFLC, but not of κFLC, compared to postdilution HDF. Although the RRs of 69.2% and 49.8% for κFLC and λFLC, respectively, for MCO dialysis in our study were similar to previously reported results [29], the MCO dialyzer treatment resulted in a significantly greater RR for both κFLC and λFLC than postdilution HDF (κFLC, 47.8% and λFLC, 15.8%). Based on these results, MCO dialyzers may be a good therapeutic option for dialysis patients with elevated FLC concentrations, such as those with multiple myeloma or amyloidosis.

Myoglobin-induced endothelial dysfunction is linked to oxidative stress, inflammation, and apoptosis [34,35]. In addition, excessive FLC can lead to apoptosis of proximal tubular epithelial cells and induce the activation of NF-κB [36,37]. Herein, we postulated that a low concentration of middle uremic toxins after MCO dialysis, including myoglobin and FLC, could attenuate the apoptosis of endothelial cells in vitro. To support our hypothesis, we assessed the expression of Bax, an apoptotic marker, and NF-κB proteins in human endothelial cells incubated with serum obtained after each dialysis modality. We found that the expression of these proteins was lower when the patient was treated with MCO dialyzed serum, which suggests that dialysis using MCO membranes could prevent uremic toxin-induced endothelial injury. This result is consistent with the findings of a previous study using ingenuity pathway analysis, which suggested that the serum metabolites and proteins after MCO dialysis have properties of increased proliferation and decreased apoptosis in endothelial cells compared to those after high-flux HD [38].

To the best of our knowledge, this is the first pre-post study assessing the RRs of middle molecules, including FLC, after treatment with a commercial MCO dialyzer, and comparing the results with those produced after treatment using high convection volume postdilution HDF. However,
this study had several limitations. First, the study duration was relatively short. Second, the sample size was small; however, this study was conducted with an adequate number of patients to meet the desired statistical power. Lastly, the enrolled patients were not randomly assigned to the MCO dialyzer or the HDF.

In conclusion, this study showed that, compared with high-volume postdilution HDF, dialysis using the MCO dialyzer was superior in terms of the reduction of myoglobin, κFLC, and λFLC in Korean patients, whereas there were no differences in the removal of molecules below 12,000 Da and serum albumin. Moreover, these results may be expected to have an anti-apoptotic effect on the human endothelium. Further long-term prospective studies with large sample sizes are needed to clarify the clinical implications of the substantial reduction of middle molecules using the MCO dialyzer.

Conflicts of interest

Eun Hui Bae and Soo Wan Kim are the Associate Editors of *Kidney Research and Clinical Practice* and were not involved in the review process of this article. All authors have no other conflicts of interest to declare.

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Data sharing statement

The data presented in this study are available on request from the corresponding author.

Author contributions

Conceptualization, Data curation, Formal analysis, Funding acquisition: CSK, SWK

Methodology: CSK, SYJ

Supervision: HSC, EHB, SKM, SWK

Writing – original draft: CSK

Writing – review & editing: All authors

All authors read and approved the final manuscript.

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35. Panizo N, Rubio-Navarro A, Amaro-Villalobos JM, Eigo J, More-


Safety and durable patency of tunneled hemodialysis catheter inserted without fluoroscopy

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Introduction

Ultrasound and fluoroscopy-guided punctures are recommended for safe procedures when performing catheter insertion including hemodialysis (HD) catheters. However, for unstable patients, such as those on a ventilator in an intensive care unit (ICU), transferring the patient to the fluoroscopy can be impossible or inappropriate.

Methods: From June 2019 to September 2022, 81 tunneled HD catheter insertion cases performed under ultrasound guidance without fluoroscopy and 474 cases with fluoroscopy in our institutional HD catheter cohort were retrospectively compared.

Results: Immediate complications, later catheter-associated problems, including infections and catheter dysfunction, were comparable between the two groups (p = 0.20 and p = 0.37, respectively). The patency of tunneled catheters inserted without fluoroscopy was comparable to the patency of tunneled catheters inserted with fluoroscopic guidance (p = 0.90).

Conclusion: Tunneled HD catheter insertion without fluoroscopy can be performed safely and has durable patency compared to the insertion with fluoroscopy. Therefore, this method can be considered for the selected unstable patients (e.g., ventilator care) in the intensive care unit.

Keywords: Catheters, Fluoroscopy, Intensive care units, Renal dialysis, Ultrasonography

Background: A tunneled hemodialysis (HD) catheter is preferred due to its lower incidence of infection and malfunction than non-tunneled ones. For safer insertion, fluoroscopic guidance is desirable. However, if the patient is unstable, transfer to the fluoroscopy may be impossible or inappropriate.

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Conclusion: Tunneled HD catheter insertion without fluoroscopy can be performed safely and has durable patency compared to the insertion with fluoroscopy. Therefore, this method can be considered for the selected unstable patients (e.g., ventilator care) in the intensive care unit.

Keywords: Catheters, Fluoroscopy, Intensive care units, Renal dialysis, Ultrasonography
structure is known to be effective in preventing infections. For non-tunneled HD catheters, the material is generally rather stiff for easy insertion and catheter dysfunction can occur when the catheter contacts the vessel wall during use. In contrast, the material of tunneled HD catheters is soft, and the frequency of catheter dysfunction during use is low. However, a separate instrument, such as a peel-away sheath, is required for its insertion [3]. In brief, tunneled HD catheters are less likely to be dysfunctional, are less susceptible to infection than non-tunneled ones, and can be generally considered the first choice [4]. However, due to the material nature of tunneled catheters, they require more attention for insertion, so it is desirable to insert them under fluoroscopic guidance, if possible. When the patient’s condition is unstable, we often hesitate to insert a tunneled HD catheter without fluoroscopic guidance.

In this study, we aimed to demonstrate the safety and durable patency of tunneled HD catheter insertion without fluoroscopic guidance in our institution by retrospectively comparing cases without fluoroscopy to those conducted with fluoroscopy.

**Methods**

The study protocol was approved by the Institutional Review Board of Eunpyeong St. Mary’s Hospital (No. PC22RA-SI0204), and all patients provided written informed consent. The study population was initially comprised of 1,157 consecutive cases that underwent HD catheter insertion between June 2019 and September 2022 from the HD catheter cohort at Eunpyeong St. Mary’s Hospital. We excluded cases with only acute femoral catheter use (n = 273). Those with acute jugular catheter use (n = 181), an over-the-guidewire exchange from a former acute jugular catheter to a newly tunneled jugular one (n = 53), and an over-the-guidewire exchange from a former jugular tunneled catheter to a newly tunneled jugular one (n = 66) were then excluded. De novo femoral tunneled catheter placements (n = 5) and femoral tunneled cases by the over-the-guidewire method (n = 3) were also excluded. We do not perform left-sided tunneled HD catheter insertion without fluoroscopy in our institution because the left brachiocephalic vein is tortuous, and the procedure can be associated with serious vessel damage or perforation without fluoroscopy. Therefore, left-sided tunneled HD catheter insertion cases (n = 21) were also excluded from the comparison. Finally, 81 cases of tunneled HD catheter insertion without fluoroscopic guidance and the other 474 cases of tunneled HD insertion with fluoroscopy were compared and analyzed in this study.

**Catheter insertion techniques**

The catheter insertion procedures were performed by either an interventional nephrologist or radiologist staff. Fresh frozen plasma was used in the cases with prothrombin time (PT) or activated partial thromboplastin time (aPTT) prolongation by clinician’s discretion, whereas we did not use pre-treatments to minimize uremic bleeding such as Desmopressin diacetate arginine vasopressin (DDAVP) or cryoprecipitate. The patients were sedated with intravenous midazolam and fentanyl at the interventionalist’s discretion. In fluoroscopic guidance insertion, tunneled HD catheters were placed under both ultrasound and fluoroscopic guidance in patients who were able to move to the angiography suite.

In the cases of tunneled HD catheter insertion without fluoroscopy, tunneled HD catheters were placed with only ultrasound guidance for vascular punctures in patients who were unable to move to the angiography suite, commonly in the ICU. In such a scenario, initially in the former cases (about 30 to 40 cases), the appropriate catheter length site was estimated based on the patient’s height, as well as measurements on the patient’s recent chest X-ray. In the later 50 to 60 cases, we used the manubrial-sternal angle (angle of Louis) as a topographical landmark for the carina [1,5]. The estimated insertion depth was selected by adding the distance between the puncture site and a point 5 cm below the manubrial-sternal angle. There was no difference in the development rate of catheter dysfunction between these two measurement methods. However, when measured by the latter method, the catheter tip is mostly located at a little bit higher than the former one.

We also routinely used a 0.035-inch hydrophilic straight guidewire rather than a J-tip guidewire, which was originally prepared within the catheter set, because hydrophilic guidewires rarely kink. First, under ultrasonographic guidance, the targeted internal jugular vein was punctured with a 21-gauge needle rather than an 18-gauge, which was originally prepared within the catheter set, because
a 21-gauge needle is less traumatic even in the case of an arterial puncture. After confirming good venous return, a 0.018-inch hairy guidewire was inserted, and a 4 French (F) or 5F coaxial sheath was placed. The introduction of this hairy guidewire is expected to be very smooth. If there was any abnormal resistance while downing the hairy guidewire, the wire was repositioned. If any abnormal resistance remained even after repositioning, a new puncture was sometimes made. There were eight cases where the tunneled HD catheter insertion without fluoroscopy was impossible because of the disability of downing a hairy guidewire. Therefore, the failure rate of HD catheter insertion into a right internal jugular vein without fluoroscopy was 9% (8 of 90).

In such cases, femoral non-tunneled catheters were placed under ultrasonographic guidance. The right internal jugular vein was identified in ultrasound examination in all eight cases. In two cases, right innominate vein occlusion was found in angiography later so left-sided HD catheter insertion was fulfilled under fluoroscopy. In the other four cases, subsequent angiogram showed the right innominate vein was tortuous making downing a hairy guidewire without fluoroscopy difficult. In the last two cases, the patients died before considering a new HD catheter insertion.

Next, the coaxial sheath was introduced, and the 0.035-inch hydrophilic straight guidewire was inserted next through this coaxial outer sheath under continuous cardiac monitoring to detect cardiac arrhythmia, which indicated the wire tip in the right atrium. However, because fluoroscopy was unavailable in this situation, more attention was paid to not placing the guidewire too deep within the right atrium. The venotomy site was sequentially dilated using two dilators provided in the kit. A small incision was created as an exit site, and a subcutaneous tunnel was created next. Peeling away the outer sheath combined with inner-third dilator insertion was the most attentive step in the tunneled HD catheter insertion without fluoroscopy. We did not insert the third dilator with a peel-away sheath to its full length. After a characteristic “pop” was perceived by the interventionalist when the third dilator with a peel-away sheath was inserted into the internal jugular vein, the third dilator with a peel-away sheath was inserted to 3/4 or 4/5 of its full length, leaving the distal portion (1/4 or 1/5) at the venotomy site. The third inner dilator was withdrawn, and the tunneled HD catheter was introduced into the peel-away outer sheath. The catheter was advanced by gradually peeling away the outer sheath. In addition, the peel-away outer sheath was not advanced further after retracting the third inner dilator because the tip of the separated outer sheath could damage the vessel wall. Catheter function was checked by rapidly aspirating blood with a 3-mL locking syringe to see if there was resistance or a characteristic “tuck.” A post-procedural chest X-ray was obtained to confirm the catheter configuration and distal tip location. The tunneled catheters used were Glidepath (Bard) or Palindrome (Covidien).

**Definitions**

Technical success of the tunneled HD catheter insertion was defined as the completion of at least one HD session or 24-hour continuous RRT with an adequate flow rate. The incidence of immediate complications (within 1 day of catheter insertion), such as prolonged bleeding requiring additional suturing after the procedure or hematoma, and long-term or non-immediate complications, such as infection or catheter dysfunction, were compared between the two groups. Catheter dysfunction was defined as the insufficient maintenance of the blood flow rate due to thrombi or fibrin sheath formation. Catheter patency was calculated from the insertion of the tunneled catheter until the catheter removal due to its dysfunction or infection or the final follow-up date before data collection for this study began. However, when the functional catheter was removed because the patient’s arteriovenous fistula or graft was matured or the patient died, such catheter removals were analyzed as censored data. Catheter infections requiring catheter removal included catheter-related bacteremia, resistant exit infections, and tunnel infections. In the electronic medical records, catheter-related bacteremia was regarded as positive blood cultures obtained from the catheter of a febrile patient without any other source of infection. Exit-site infection was regarded as the presence of a discharge from the exit or soreness without any tenderness over the tunnel, whereas a tunnel infection was regarded as not only the presence of a discharge from the exit or erythema but also tenderness or induration over the tunnel itself, regardless of whether the discharge yielded a positive culture.
Data collection

The demographic data collected included age, sex, cause of catheter insertion (acute kidney injury [AKI] vs. end-stage renal disease [ESRD]), and the patient status (ICU or ward). The closest laboratory data to the point of a tunneled HD catheter insertion collected included white blood cell (WBC) count, hemoglobin, platelet count, blood urea nitrogen, serum creatinine (sCr), PT, aPTT, C-reactive protein (CRP), and serum albumin level. Almost all the laboratory samples were collected on the morning of a tunneled HD catheter insertion or the day before an indexed procedure.

Statistical analysis

The results for continuous variables with a normal distribution are presented as the mean ± standard deviation, and the results for variables without a normal distribution are presented as the median and interquartile range. The Student t test or the Mann-Whitney U test was used, as appropriate, to determine the significance of differences in the continuous variables between groups. Categorical variables are presented as percentages. Pearson chi-square test or Fisher exact test was used for determining the significance of differences in the categorical variables between groups. Survival curves were estimated using the Kaplan-Meier method and compared using the log-rank test. Cox proportional-hazard regression models were used to calculate hazard ratios (HRs) with 95% confidence intervals (CIs) for catheter patency. A p-value of <0.05 was considered statistically significant. Statistical analyses were performed using IBM SPSS version 23.0 for Windows (IBM Corp.).

Results

Diabetes mellitus was more prevalent in the group with fluoroscopy compared to the group without fluoroscopy. There were more AKI and ICU patients in the group without fluoroscopy. Such group characteristics without fluoroscopy were also compatible with higher WBC counts, lower platelet counts, more prolonged PT, and more prolonged aPTT in the group without fluoroscopy. Similarly, CRP levels were also higher in the group without fluoroscopy. In contrast, sCr levels were lower in the group without fluoroscopy, consistent with the current real clinical practice where early RRT is commonly performed in AKI patients while early RRT is no longer recommended for ESRD patients (Table 1).

Table 1. Baseline characteristics of the two groups

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Without fluoroscopy group</th>
<th>With fluoroscopy group</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>81</td>
<td>474</td>
<td>0.56a</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>67 (53–74)</td>
<td>68 (56–75)</td>
<td>0.56a</td>
</tr>
<tr>
<td>Female sex</td>
<td>48 (59.3)</td>
<td>248 (52.3)</td>
<td>0.25</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>44 (54.3)</td>
<td>316 (66.7)</td>
<td>0.03</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>22.7 ± 4.1</td>
<td>23.3 ± 4.1</td>
<td>0.22</td>
</tr>
<tr>
<td>AKI (vs. ESRD)</td>
<td>44 (54.3)</td>
<td>111 (23.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ICU (vs. ward)</td>
<td>54 (66.7)</td>
<td>91 (19.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>WBC (mm³)</td>
<td>12,260 (7,818–17,283)</td>
<td>8,820 (6,789–11,975)</td>
<td>&lt;0.001a</td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>9.9 ± 1.8</td>
<td>9.6 ± 2.2</td>
<td>0.20</td>
</tr>
<tr>
<td>Platelet (mm³)</td>
<td>141,500 (75,500–234,000)</td>
<td>198,000 (149,000–264,000)</td>
<td>&lt;0.001a</td>
</tr>
<tr>
<td>BUN (mg/dL)</td>
<td>64.3 (41.4–90.4)</td>
<td>59.1 (38.6–84)</td>
<td>0.15a</td>
</tr>
<tr>
<td>sCr (mg/dL)</td>
<td>4.8 (3.2–7.5)</td>
<td>5.7 (4.0–8.1)</td>
<td>0.03a</td>
</tr>
<tr>
<td>PT (INR)</td>
<td>1.26 (1.15–1.45)</td>
<td>1.13 (1.05–1.26)</td>
<td>&lt;0.001a</td>
</tr>
<tr>
<td>aPTT (sec)</td>
<td>40.7 (32.8–61.1)</td>
<td>30.8 (26.5–38.5)</td>
<td>&lt;0.001a</td>
</tr>
<tr>
<td>CRP (mg/dL)</td>
<td>5.79 (1.27–10.56)</td>
<td>3.16 (0.75–9.2)</td>
<td>0.05a</td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>3.0 (2.5–3.5)</td>
<td>3.0 (2.5–3.4)</td>
<td>0.78a</td>
</tr>
</tbody>
</table>

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

AKI, acute kidney injury; aPTT, activated partial thromboplastin time; BMI, body mass index; BUN, blood urea nitrogen; CRP, C-reactive protein; ESRD, end-stage renal disease; ICU, intensive care unit; PT, prothrombin time; sCr, serum creatinine; WBC, white blood cell.

*aUsing the nonparametric Mann-Whitney U test.
Table 2. Comparison of immediate and long-term complication rates between the two groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>Without fluoroscopy group (n = 81)</th>
<th>With fluoroscopy group (n = 474)</th>
<th>Chi-square</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Immediate complications</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>75 (92.6)</td>
<td>456 (96.2)</td>
<td>3.27</td>
<td>0.20</td>
</tr>
<tr>
<td>Prolonged bleeding</td>
<td>5 (6.2)</td>
<td>17 (3.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hematoma</td>
<td>1 (1.2)</td>
<td>1 (0.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Long-term complications</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>72 (88.9)</td>
<td>379 (80.0)</td>
<td>4.30</td>
<td>0.37</td>
</tr>
<tr>
<td>Catheter dysfunction</td>
<td>6 (7.4)</td>
<td>62 (13.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infection</td>
<td>3 (3.7)</td>
<td>24 (5.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Catheter slippage</td>
<td>0 (0)</td>
<td>6 (1.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Catheter breakage</td>
<td>0 (0)</td>
<td>3 (0.6)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Between the two groups, immediate complications after catheter insertion and long-term complications requiring catheter replacement including dysfunction, infection, catheter slippage, and breakage, were comparable (Table 2).

The patency of tunneled catheters inserted without fluoroscopy was also comparable to that of tunneled catheters inserted with fluoroscopy (p = 0.90) (Fig. 1). When we compared among ICU patients only, we found that the two methods were still similar (p = 0.70) (Fig. 2A). Likewise, the two methods were also comparable among ward patients (p = 0.61) (Fig. 2B). Univariate and multivariate Cox regression analyses were performed to assess the effects of variables on the catheter patency, in which the potential confounders were included (Table 3). In the multivariate Cox regression analysis of catheter patency, tunneled catheter placement without fluoroscopy (vs. with fluoroscopy) also did not influence catheter patency (HR, 0.96; 95% CI, 0.44–2.11; p = 0.92).

**Discussion**

The new 2019 Kidney Disease Outcomes Quality Initiative (KDOQI) vascular guideline recommended that tunneled HD should be inserted under imaging guidance using both ultrasound and fluoroscopy as in the former KDOQI 2006 guideline for safety and correct catheter tip positioning [4,6]. However, it is not always easy to use fluoroscopy when needed if a hospital does not have its own nephrology angiography suite. Several studies previously reported the safety and comparable patency of tunneled HD catheter insertion or exchange from non-tunneled without fluoroscopy [7–12]. More recently, some authors reported the additional benefits of tunneled HD catheter insertion without fluoroscopy from the perspective of coronavirus 2019 (COVID-19) infection prevention [1,13]. Those suggested that an isolated catheter insertion procedure within the patient’s ICU room without fluoroscopy could minimize COVID-19 exposure in hospital personnel and the waste of available hospital resources. Some of those previous studies reported only the safety and technical success rate of tunneled HD catheter without fluoroscopy and did not compare it to a group with fluoroscopy [1,9–13]. However, a

**Figure 1.** Comparison of catheter patency between the two groups.
few of those studies demonstrated the safety and comparable patency of tunneled HD catheter insertion without fluoroscopy compared to a group with fluoroscopic guidance during the same period, as was analyzed in our study [7,8].

For a long time, non-tunneled HD catheters with or without ultrasound guidance have been inserted in the ICU by nephrologists or critical care physicians. The choice between non-tunneled and tunneled HD catheters remains unresolved, considering the limited life expectancy of ICU AKI patients [5,14]. However, a non-tunneled HD catheter has definite weak points compared to a tunneled one. Basically, it is designed for convenience in bedside insertion. Its relative stiffness, sometimes similar to a dilator within a catheter kit, can ease the insertion procedure via a guide wire. However, such stiffness may cause dysfunction during use when a non-tunneled catheter contacts a vessel wall. A stiff non-tunneled HD catheter remains stuck at the vessel wall without slipping. In addition, the vessel entry point is
directly open to the skin with a non-tunneled HD catheter, so the infection risk is higher compared to a tunneled one, where a vessel entry point is covered with instantly sutured skin or completely healed skin later. In contrast to a non-tunneled HD catheter, a tunneled HD catheter is created to be soft to prevent its dysfunction. When not connected to a dialysis machine, it is never stuck when it touches the vessel wall. When connected, even when it shows a tendency to approach the vessel wall due to the negative pressure of the aspirating arterial side, such a tendency is minimized because of its softness. But this soft tunneled HD catheter can also become stuck to the vessel wall if in conditions of high negative pressure. The recently developed symmetric tip HD catheter has the advantage of switching the arterial and venous lumens when the arterial lumen is stuck to the vessel wall, working well without significant blood recirculation [15].

Paradoxically, the softness of tunneled HD catheters can be an obstacle during their initial insertion, so a peel-away sheath with a third dilator is equipped within the catheter kit to facilitate soft tunneled catheter insertion. The rigid and pointed third dilator can penetrate a vessel wall, so its position should be constantly monitored under fluoroscopy if available. Even without fluoroscopic guidance, this third dilator can be advanced but should not be advanced too deeply so that it reaches the right atrium. For this, in our institution, the third dilator with a peel-away sheath is inserted to 3/4 or 4/5 considering its full length, leaving the distal portion (1/4 or 1/5 of it) at the venotomy site.

In our institution, we do not attempt to insert an HD catheter into the left internal jugular vein, either tunneled or non-tunneled, although central venous catheterization is performed using the left internal jugular vein. This is because the left brachiocephalic vein is not straight but tortuous, unlike the right brachiocephalic vein. A large-bore dilator within the HD catheter kit without fluoroscopic guidance can perforate a vessel wall if the left brachiocephalic vein is very tortuous or at an acute angle. Some serious consequences have been reported [16–18]. That is why our current study did not include left-side inserted tunneled catheters.

The interventional nephrologist in our institution who inserted tunneled HD catheters without fluoroscopy already had performed more than a thousand tunneled HD catheter insertions with fluoroscopy, so he is a very skillful interventionalist. Therefore, our study results do not simply imply that tunneled HD catheter insertion without fluoroscopy by any medical personnel is both safe and comparable to the formal method with fluoroscopic guidance. However, because many nephrologists already are used to acute HD catheter blind insertion, we think any nephrologist, who has only additional interests in HD catheter insertion using ultrasound, can perform this tunneled HD catheter insertion without fluoroscopy, especially in ICU after education and sufficient practice.

However, based on our study results, tunneled catheter insertion without fluoroscopy can be positively considered and then performed more frequently than it is currently, especially in ICU patients.

Conflicts of interest

All authors have no conflicts of interest to declare.

Funding

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Data sharing statement

The data presented in this study are available on request from the corresponding author.

Authors’ contributions

Conceptualization, Methodology, Formal analysis: DHK, HSP
Data curation: SY, THB, HSP
Supervision: BSC, BSK, CWP, CWY
Writing—original draft: DHK, HSP
Writing—review & editing: All authors
All authors read and approved the final manuscript.

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References


Effect of donor–recipient size mismatch on long-term graft survival in pediatric kidney transplantation: a multicenter cohort study

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Background: Donor–recipient size mismatching is commonly occurs in pediatric kidney transplantation (KT). However, its effect on graft survival remains unknown. This study aimed to determine the effect of donor–recipient size mismatch on the long-term survival rate of transplant kidneys in pediatric KT.

Methods: A total of 241 pediatric patients who received KT were enrolled. The medical records of all patients were retrospectively reviewed, and the correlation between donor–recipient size mismatch and graft function and long-term graft outcome was analyzed according to donor–recipient size mismatch.

Results: Recipients and donors’ mean body weight at the time of KT were 34.31 ± 16.85 and 56.53 ± 16.73 kg, respectively. The mean follow-up duration was 96.49 ± 52.98 months. A significant positive correlation was observed between donor–recipient body weight ratio (DRBWR) or donor–recipient body surface area ratio (DRBSR) and graft function until 1 year after KT. However, this correlation could not be confirmed at the last follow-up. The results of long-term survival analysis using Fine and Gray’s subdistribution hazard model showed no significant difference of the survival rate of the transplant kidney according to DRBWR or DRBSR.

Conclusion: Donor–recipient size mismatch in pediatric KT is not an important factor in determining the long-term prognosis of transplant kidneys.

Keywords: Donor, Kidney transplantation, Pediatrics, Recipient

Introduction

Kidney transplantation (KT) is the main treatment option for patients with end-stage kidney disease (ESKD). However, it is limited by the low number of donor organs [1]. Moreover, donor–recipient size mismatching is a common problem in KT given the various types of donors [2]. Donor–recipient size mismatching is divided into two main
types. The first type is when a large recipient receives a small donor’s kidney (e.g., when the recipient is an adult and the deceased donor is a child). In this case, the risk of graft loss is high because of hyperfiltration injury [3–5]. The second type is when a small child receives a kidney from an adult. In this case, various medical problems can occur, including hemodynamic imbalance, low perfusion into the transplant kidney, and increased heart burden on the recipient [2] and poor long-term prognosis of transplant kidneys [6]. Age- and size-matched pediatric donors are difficult to find in pediatric KT. Therefore, kidneys from adult donors are used in most pediatric recipients, resulting in size mismatching. Accordingly, this study aimed to determine the effect of donor-recipient size mismatch on the long-term survival rate of transplant kidneys in pediatric KT.

Methods

This study was conducted in accordance with the principles of the Declaration of Helsinki and approved by the Institutional Review Board of Kyungpook National University Hospital (No. 2021-10-005). Informed consent was waived because of the study’s retrospective design.

Study population and data collection

A total of 241 patients who received KT at three national university hospitals from 2000 to 2019 were enrolled. All patients were less than 19 years of age, followed up for more than 1 year, and had available medical data of donors. The medical records and Korean Network for Organ Sharing data of all patients were retrospectively reviewed. Information of recipients and donors including age; sex; body weight; height; body surface area (BSA); graft weight; causes of ESKD; duration and modality of dialysis before KT; cold/warm ischemic time; human leukocyte antigen (HLA) matching; maintenance immunosuppressive regimen; occurrence of delayed graft function (DGF); estimated glomerular filtration rate (eGFR) at the time of discharge during KT, 1 year after KT, and last follow-up; and renal events after KT (restart of dialysis by graft failure) was collected. The surgical method used at the time of transplantation (extraperitoneal vs. transabdominal approach) was also investigated. The Mosteller formula, square root \([(\text{height (cm)} \times \text{weight (kg)})/3,600]\), was used to calculate the BSA. Meanwhile, the revised Schwartz formula, \(0.413 \times \text{height (cm)}/\text{serum creatinine (mg/dL)}\), was used to calculate the eGFR in children receiving KT. The donor-recipient body weight ratio (DRBWR) was calculated by dividing the donor’s body weight by the recipient’s body weight at the time of KT. The donor-recipient body surface area ratio (DRBSR) was calculated by dividing the donor’s BSA by the recipient’s BSA at the time of KT.

Statistical analysis

In descriptive analysis, categorical variables were presented as frequencies and percentages, and continuous variables were presented as mean ± standard deviation or median (interquartile range). The statistical difference was evaluated using the chi-square test or Fisher exact test for categorical variables, and analysis of variance or Kruskal-Wallis test for continuous variables. The Pearson correlation coefficient and linear regression model were used for statistical analyses between two continuous variables. As survival analysis, Fine and Gray’s subdistribution hazard model was applied for estimating cumulative incidence for graft failure, considering competing risk including death not related to KT. Statistical significance was considered at p-value of <0.05. R version 4.1.1 (R Foundation for Statistical Computing) was used to conduct all statistical analysis.

Results

A total of 241 pediatric patients who received KT were enrolled. At the time of transplantation, the mean age of patients was 11.65 ± 4.63 years, and the ratio of males and females was 149:92. The age distribution was as follows: 25 patients were aged under 5 years, 60 patients were aged 5–10 years, 86 patients were aged 10–15 years, and 70 patients were aged over 15 years. Congenital anomalies of the kidney and urinary tract were the most common cause of ESKD, accounting for 42.1% of the total. The mean body weight, height, and BSA of patients at the time of transplantation were 34.31 ± 16.85 kg, 134.99 ± 25.77 cm, and 1.12 ± 0.37 m², respectively. Two patients had a history of previous KT, and 58 patients (24.1% of the total) received preemptive KT. The remaining patients underwent dialysis for an average of 21.56 ± 20.47 months before KT. Peri
Kidney transplantation (KT) was performed via the transabdominal approach in 76.3% of the total, and triple regimen including tacrolimus, mycophenolate mofetil, and prednisolone was used as the maintenance immunosuppressive regimen in 79.7% of the total. The mean cold and warm ischemic times at the time of KT were 112.55 ± 106.67 minutes and 39.35 ± 14.23 minutes, respectively, and four patients (1.7%) developed DGF. The mean follow-up duration was 96.49 ± 52.98 months (Table 1).

The mean age of donors was 34.74 ± 14.91 years, and the ratio of males and females was 105:136. Approximately 81.7%, 1.2%, and 17.0% of all transplant donors were identified as living-related, living-unrelated, and deceased donors, respectively. Among the living-related donors, the recipient’s mother and father accounted for 53.3% and 34.5% of the total, respectively. The mean body weight, height, and BSA of donors were 56.53 ± 16.73 kg, 156.22 ± 21.02 cm, and 1.56 ± 0.34 m², respectively. The mean eGFR of donors and mean weight of transplanted kidneys were 86.13 ± 41.40 mL/min/1.73 m² and 153 g, respectively (Table 2).

### Table 1. Pediatric recipients’ baseline characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of recipients</td>
<td>241 (100)</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>11.65 ± 4.63</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>149 (61.8)</td>
</tr>
<tr>
<td>Female</td>
<td>92 (38.2)</td>
</tr>
<tr>
<td>Sex by age group (yr), male:female</td>
<td></td>
</tr>
<tr>
<td>0–5 (n = 25)</td>
<td>15:10</td>
</tr>
<tr>
<td>5–10 (n = 60)</td>
<td>36:24</td>
</tr>
<tr>
<td>10–15 (n = 86)</td>
<td>56:30</td>
</tr>
<tr>
<td>&gt;15 (n = 70)</td>
<td>42:28</td>
</tr>
<tr>
<td>ESKD cause</td>
<td></td>
</tr>
<tr>
<td>CAKUT</td>
<td>101 (41.9)</td>
</tr>
<tr>
<td>Glomerulonephritis</td>
<td>65 (27.0)</td>
</tr>
<tr>
<td>Others</td>
<td>75 (31.1)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>34.31 ± 16.85</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>134.99 ± 25.77</td>
</tr>
<tr>
<td>BSA (m²)</td>
<td>1.12 ± 0.37</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>17.52 ± 3.57</td>
</tr>
<tr>
<td>Previous history of KT</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>2 (0.8)</td>
</tr>
<tr>
<td>No</td>
<td>239 (99.2)</td>
</tr>
<tr>
<td>Preemptive KT</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>58 (24.1)</td>
</tr>
<tr>
<td>No</td>
<td>183 (75.9)</td>
</tr>
<tr>
<td>Dialysis time before KT (mo)</td>
<td>21.56 ± 20.47</td>
</tr>
<tr>
<td>Dialysis type before KT</td>
<td></td>
</tr>
<tr>
<td>Hemodialysis</td>
<td>71 (29.5)</td>
</tr>
<tr>
<td>Peritoneal dialysis</td>
<td>98 (40.6)</td>
</tr>
<tr>
<td>Both</td>
<td>13 (5.4)</td>
</tr>
<tr>
<td>No dialysis</td>
<td>59 (24.5)</td>
</tr>
<tr>
<td>Drug regimen</td>
<td></td>
</tr>
<tr>
<td>Tac/MMF/Pred</td>
<td>192 (79.7)</td>
</tr>
<tr>
<td>Cyc/MMF/Pred</td>
<td>5 (2.1)</td>
</tr>
<tr>
<td>Cyc/Aza/Pred</td>
<td>2 (0.8)</td>
</tr>
<tr>
<td>Others</td>
<td>42 (17.4)</td>
</tr>
<tr>
<td>Operation approach</td>
<td></td>
</tr>
<tr>
<td>Extraperitoneal</td>
<td>57 (23.7)</td>
</tr>
<tr>
<td>Transabdominal</td>
<td>184 (76.3)</td>
</tr>
<tr>
<td>Cold ischemic time (min)</td>
<td>112.55 ± 106.67</td>
</tr>
<tr>
<td>Warm ischemic time (min)</td>
<td>39.35 ± 14.23</td>
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<tr>
<td>Delayed graft function</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>4 (1.7)</td>
</tr>
<tr>
<td>No</td>
<td>237 (98.3)</td>
</tr>
<tr>
<td>Pack cell transfusion</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>34 (14.1)</td>
</tr>
<tr>
<td>No</td>
<td>207 (85.9)</td>
</tr>
<tr>
<td>Total FU duration (mo)</td>
<td>96.49 ± 52.98</td>
</tr>
</tbody>
</table>

### Table 2. Donors’ baseline characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of donors</td>
<td>241 (100)</td>
</tr>
<tr>
<td>Donor type</td>
<td></td>
</tr>
<tr>
<td>Living-related</td>
<td>197 (81.7)</td>
</tr>
<tr>
<td>Living-unrelated</td>
<td>3 (1.2)</td>
</tr>
<tr>
<td>Deceased</td>
<td>41 (17.0)</td>
</tr>
<tr>
<td>If living-related donor (n = 197)</td>
<td></td>
</tr>
<tr>
<td>Father</td>
<td>68 (34.5)</td>
</tr>
<tr>
<td>Mother</td>
<td>105 (53.3)</td>
</tr>
<tr>
<td>Sister</td>
<td>1 (0.5)</td>
</tr>
<tr>
<td>Brother</td>
<td>1 (0.5)</td>
</tr>
<tr>
<td>Others</td>
<td>22 (11.1)</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>34.74 ± 14.91</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>105 (43.6)</td>
</tr>
<tr>
<td>Female</td>
<td>136 (56.4)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>56.53 ± 16.73</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>156.22 ± 21.02</td>
</tr>
<tr>
<td>BSA (m²)</td>
<td>1.56 ± 0.34</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>22.39 ± 3.53</td>
</tr>
<tr>
<td>eGFR (mL/min/1.73 m²)</td>
<td>86.13 ± 41.40</td>
</tr>
<tr>
<td>Graft weight (g)</td>
<td>153.06 ± 41.22</td>
</tr>
</tbody>
</table>

Data are expressed as number (%) or mean ± standard deviation, BMI, body mass index; BSA, body surface area; CAKUT, congenital anomalies of the kidney and urinary tract; Cyc, cyclosporine; ESKD, end-stage kidney disease; FU, follow-up; KT, kidney transplantation; MMF, mycophenolate mofetil; Pred, prednisolone; Tac, tacrolimus.

Aza, azathioprine; BMI, body mass index; BSA, body surface area; CAKUT, congenital anomalies of the kidney and urinary tract; Cyc, cyclosporine; ESKD, end-stage kidney disease; FU, follow-up; KT, kidney transplantation; MMF, mycophenolate mofetil; Pred, prednisolone; Tac, tacrolimus.
In the Table 3, we compared the baseline characteristics of recipients and donors according to DRBWR category (<1, ≥1 to <3, and ≥3). In the group with DRBWR of ≥3, the recipients were significantly younger and had lower body weight than that in the other groups. In addition, transabdominal approaches were widely used in the KT, but the cold ischemic time was significantly shorter than that in the other groups. On the other hand, the donors in the

Table 3. Baseline characteristics of recipients and donors according to donor–recipient body weight ratio

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>DRBWR</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of recipients</td>
<td>&lt;1</td>
<td>≥1, &lt;3</td>
</tr>
<tr>
<td>Recipient age (yr)</td>
<td>15.3 (10.8–17.2)</td>
<td>13.1 (10.6–16.6)</td>
</tr>
<tr>
<td>Recipient sex</td>
<td>Male</td>
<td>22 (59.5)</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>15 (40.5)</td>
</tr>
<tr>
<td>ESKD cause</td>
<td>CAKUT</td>
<td>15 (40.6)</td>
</tr>
<tr>
<td></td>
<td>Glomerulonephritis</td>
<td>9 (24.3)</td>
</tr>
<tr>
<td></td>
<td>Others</td>
<td>13 (35.1)</td>
</tr>
<tr>
<td>Recipient weight (kg)</td>
<td>53.5 (27.3–68.0)</td>
<td>36.7 (28.2–45.7)</td>
</tr>
<tr>
<td>Recipient BSA (m²)</td>
<td>1.5 (1.0–1.7)</td>
<td>1.2 (1.0–1.4)</td>
</tr>
<tr>
<td>Dialysis time before KT (mo)</td>
<td>17.0 (4.5–31.0)</td>
<td>14.5 (4.0–32.0)</td>
</tr>
<tr>
<td>Dialysis type before KT</td>
<td>Extrapitoneal</td>
<td>15 (40.5)</td>
</tr>
<tr>
<td></td>
<td>Transabdominal</td>
<td>22 (59.5)</td>
</tr>
<tr>
<td>Cold ischemic time (min)</td>
<td>196.0 (120.5–284.0)</td>
<td>57.0 (39.5–110.5)</td>
</tr>
<tr>
<td>Warm ischemic time (min)</td>
<td>40.1 ± 12.4</td>
<td>40.1 ± 15.8</td>
</tr>
<tr>
<td>Delayed graft function</td>
<td>Yes</td>
<td>1 (2.7)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>36 (97.3)</td>
</tr>
<tr>
<td>Pack cell transfusion</td>
<td>Yes</td>
<td>30 (81.1)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>7 (18.9)</td>
</tr>
<tr>
<td>Donor type</td>
<td>Living-related</td>
<td>21 (56.8)</td>
</tr>
<tr>
<td></td>
<td>Living-unrelated</td>
<td>0 (0)</td>
</tr>
<tr>
<td></td>
<td>Deceased</td>
<td>16 (43.2)</td>
</tr>
<tr>
<td>Donor age (yr)</td>
<td>10.0 (4.0–43.0)</td>
<td>42.0 (37.0–46.0)</td>
</tr>
<tr>
<td>Donor weight (kg)</td>
<td>38.7 (18.5–54.0)</td>
<td>58.0 (51.8–65.2)</td>
</tr>
<tr>
<td>Donor BSA (m²)</td>
<td>1.2 (0.7–1.5)</td>
<td>1.6 (1.5–1.7)</td>
</tr>
<tr>
<td>Total FU duration (mo)</td>
<td>66.4 (38.1–91.0)</td>
<td>90.7 (54.2–126.0)</td>
</tr>
</tbody>
</table>

Data are expressed as number only, median (interquartile range), number (%), or mean ± standard deviation.
BMI, body mass index; BSA, body surface area; CAKUT, congenital anomalies of the kidney and urinary tract; DRBWR, donor–recipient body weight ratio; ESKD, end-stage kidney disease; FU, follow-up; KT, kidney transplantation.
The p-value was calculated by using the chi-square test, Fisher exact test, analysis of variance, or Kruskal-Wallis test as appropriate. *p < 0.05, statistical significance.
group with DRBWR of ≥3 had the higher rate of living-related donor and higher body weight than that in the other groups.

The association between DRBWR and eGFR of transplant kidneys was analyzed at the time of discharge immediately after KT (Fig. 1A), 1 year after KT (Fig. 1B), and last follow-up (96.49 ± 52.98 months after KT) (Fig. 1C). The DRBWR was significantly positively associated with the eGFR of transplant kidneys at the time of discharge after KT (Pearson’s r = 0.578, p < 0.001) and 1 year after KT (r = 0.266, p < 0.001). This finding shows that the larger the body weight of the donor compared with the recipient, the greater the eGFR of the transplant kidney. However, this association weakened with extension of the follow-up period and could not be confirmed at the last follow-up (r = 0.066, p = 0.32). Similarly, these results were also confirmed in the association analysis between DRBSR and eGFR of transplant kidneys (Fig. 2). The DRBSR was significantly positively associated with the eGFR at the time of discharge after KT (Pearson’s r = 0.584, p < 0.001) (Fig. 2A) and 1 year after KT (r = 0.269, p < 0.001) (Fig. 2B). However, no significant association was observed at the last follow-up (r = 0.069, p = 0.30) (Fig. 2C).

The survival curves of Fine and Gray’s subdistribution hazard model were expressed as the cumulative incidence according to DRBWR category (<1, ≥1 to <3, and ≥3) (Fig. 3). No significant differences were observed between each curve (Gray test p = 0.50 in Fig. 3). The curves did not differ significantly from each other (Gray test p = 0.50) compared with the DRBWR results in the cumulative incidence curves plotted according to DRBSR category (<0.9, ≥0.9 to <1.1, and ≥1.1) (Fig. 4).

Discussion

This study showed that donor-recipient size mismatching in pediatric KT can affect the transplant kidney’s function until 1 year immediately after transplantation, but not its long-term survival rate.

The number of KT in Korea is increasing every year and an average of 48.5 cases of pediatric KT have been performed annually for the last 10 years [7]. A number of considerations need to be examined when choosing the most ideal donor for pediatric KT. For example, extended criteria donors (e.g., donation after cardiac death), donors with acute kidney injury, and HLA- or ABO-mismatched donors are usually not recommended in pediatric KT [1,8]. Moreover, pediatric recipients inevitably receive kidneys from adults because deceased pediatric donors with similar size and age as the recipients are extremely difficult to find [2]. In this study, 200 living donors (82.9% of total donors) were all adults, showing that donor-recipient size mismatch commonly occurs in pediatric KT.

During childhood, the length and volume of the kidney grow to the adult size according to age and are known to be related to the height and weight [9,10]. Based on a prospective observational study of 437 normal Korean children aged between 0 and <13 years, Oh et al. [9] reported that there were good correlations between kidney length and various somatic values, including body weight, height, and BSA and suggested the following equation for the reference values of kidney length for Korean children: kidney length of the right kidney (cm) = 0.051 × height (cm) + 2.102; kidney length of the left kidney (cm) = 0.051 × height (cm) + 2.280. In addition, Kim et al. [10] also reported that renal length and volume in Korean children showed the strongest significant correlation with their height and weight, respectively. Therefore, donor-recipient size mismatching in KT implies donor-recipient kidney size mismatching.

Various medical problems occur when a kidney from a small pediatric donor is provided to an adult recipient [3–5,11]. The same situation can be observed in the case of adolescent recipients receiving kidneys from deceased pediatric donors. In this case, glomerular hypertrophy occurs probably because of hyperfiltration damage caused by nephron underdosing, leading to a low long-term survival rate of the transplant kidney [4,5]. The risk of graft loss significantly increases when the DRBSR is less than 0.9 or the donor’s weight is 30 kg less than the recipient’s weight [12,13].

The effects of donor-recipient size mismatch on graft outcome in pediatric KT (a small pediatric recipient and a large adult donor) have been reported in previous studies [6,14–16]. According to the North American Pediatric Renal Trials and Collaborative Studies, acute tubular necrosis (ATN) occurred in 10% of infants who received adult kidneys, requiring dialysis posttransplantation, and the infants showed poor long-term survival rates [6]. In addition, ATN occurred more frequently in small children or infants who received adult kidneys than adults who received KT.
Figure 1. Association between DRBWR and eGFR at discharge. (A) After kidney transplantation (KT), (B) 1 year after KT, and (C) at the last follow-up (96.49 ± 52.98 months after KT).

DRBWR, donor–recipient body weight ratio; eGFR, estimated glomerular filtration rate.
Figure 2. Association between DRBSR and eGFR at discharge. (A) After kidney transplantation (KT), (B) 1 year after KT, and (C) at the last follow-up (96.49 ± 52.98 months after KT).

DRBSR, donor–recipient body surface area ratio; eGFR, estimated glomerular filtration rate.
Figure 3. Cumulative incidence curves and risk table using Fine and Gray’s subdistribution hazard model. Donor–recipient body weight ratio (DRBWR) of <1, ≥1 to <3, and ≥ 3 were the major exposure variables. Gray’s test showed that the curves did not differ significantly from each other.

The occurrence of ATN can theoretically be expected considering the marked hemodynamic difference between the cardiovascular system of pediatric recipients and the kidneys from adults. An adult’s cardiac output at rest is approximately 5 L/min, and both kidneys receive 20% of the cardiac output. Therefore, one kidney is supplied with 500 mL of blood per minute. On the other hand, the total blood volume of a child weighing 10 kg is about 800 mL (80 mL/kg), so one transplant kidney from an adult requires approximately 62% of the total blood volume of a pediatric recipient. Therefore, the transplant kidney from adult donors shows hypoperfusion status immediately after pediatric KT, and ATN often occurs. In 2000, according to their analysis of a single center and United Network for Organ Sharing database, Sarwal et al. [14] emphasized the importance of preventing ATN after KT. They reported that adult-size kidneys without ATN from living and deceased donors lead to remarkably better long-term graft outcomes for small children; moreover, they created protocols for ATN prevention including long-term aggressive fluid management (3,000 ± 500 mL/m²/day with mean sodium content of 10 ± 4 mEq/kg/day) for a mean of 9 months after KT and maintenance of higher blood pressure (up to the 95th percentile for age and sex) until 6 months after KT [15]. However, based on the analysis of data from 99 pediatric patients who received KT under the age of 10 years, Pape et al. [16,17] reported that the long-term survival rate of transplant kidneys was significantly lower than that in the case of donors under the age of 16 years when a kidney was transplanted from a donor aged 16 years or older; they concluded that age-matched exchange is essential for pediatric KT. Therefore, the controversy over the ideal donor in pediatric KT continued until the 2000s.

In 2010, Goldsmith et al. [18] analyzed the data from 23 low-weight pediatric patients who received KT and reported no difference in the short-term survival rate of transplant kidneys between low-weight and high-weight donors. In addition, Lee et al. [19] reported the successful graft survival rate based on single-center data in the United States, in spite of donor–recipient size mismatch in pedi-
They reported that the graft survival rate of adult-sized transplant kidney in pediatric recipients under 20 kg was 98.4%, 96.6%, and 84.2% at 1, 5, and 10 years, respectively; moreover, they emphasized the importance of careful perioperative management including adequate fluid resuscitation and use of pressors. Based on an analysis of single-center data in Europe, Amesty et al. [20] also reported that adult-sized kidneys can be successfully transplanted to children under 20 kg of weight with no differences in graft survival, GFR, proteinuria, and rejection episodes. These results were the same in comparison based on BSA. Accordingly, Lepeytre et al. [21] reported that even if size mismatch occurs, the donor shows excellent long-term survival rate if the donor is young; thus, donor age is a much stronger determinant of graft survival rate than size mismatch.

Unfortunately, although donor-recipient size mismatch was identified as a factor that adversely affected the long-term survival rate of transplant kidneys in previous reports published before 2010, the present study could not confirm the specific reasons why it did not show similar results in recent reports. In general, methods were used to minimize the ultrafiltration volume of dialysis before KT and to keep the recipient’s size over time. Survival analysis using Fine and Gray’s subdistribution hazard model showed no difference in long-term graft survival between groups with more than three times the body weight of donors, and groups with more than one times and less than three times the body weight of donors, and groups with less than one times the body weight of donors compared with recipients. These results showed that kidneys from adults with large bodies temporarily showed a relatively higher GFR compared with the recipient’s size; however, they adapted to the recipient’s size over time.
the central venous pressure and blood pressure high at the time of transplantation, but it is unclear as to what differences have led to the difference in results. Nevertheless, this study confirmed that donor-recipient size mismatch is no longer a determinant that adversely affects the long-term survival rate of transplant kidneys in pediatric KT. Thus, it is hoped that more active and safer pediatric KT can be implemented in the future.

Conflicts of interest

Hee Gyung Kang is the Associate Editors of *Kidney Research and Clinical Practice* and was not involved in the review process of this article. All authors have no other conflicts of interest to declare.

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Data sharing statement

The data presented on this study are available on request from the corresponding author.

Authors’ contributions

Conceptualization, Funding acquisition: MHC
Data curation, Formal analysis: MJP, JYS, NC, YHA, HGK
Supervision: MHC, HGK
Writing—original draft: MJP, MHC
Writing—review & editing: HSB, JYS, YHA, HGK

All authors read and approved the final manuscript.

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References


The roles of interleukin-17A in risk stratification and prognosis of patients with sepsis-associated acute kidney injury

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2Department of Clinical Laboratory, The Second Hospital of Tianjin Medical University, Tianjin, China

Background: The aim of this study was to evaluate the roles of interleukin (IL)-17A in risk stratification and prognosis of patients with sepsis-associated acute kidney injury (SAKI).

Methods: We enrolled 146 sepsis patients (84 non-SAKI and 62 SAKI patients) admitted to the emergency department from November 2020 to November 2021. Patients with SAKI were differentiated based on the severity of acute kidney injury. All clinical parameters were evaluated upon admission before administering antibiotic treatment. Inflammatory cytokines were assessed using flow cytometry and the Pylon 3D automated immunoassay system (ET Healthcare). In addition, a receiver operating characteristic (ROC) curve was utilized to determine the prognostic values of IL-17A in SAKI.

Results: The levels of creatinine, IL-2, IL-4, IL-6, IL-17A, tumor necrosis factor alpha, C-reactive protein, and procalcitonin (PCT) were significantly higher in the SAKI group than in the non-SAKI group (p < 0.05). The level of IL-17A revealed significant differences among stages 1, 2, and 3 in SAKI patients (p < 0.05). The mean levels of PCT, IL-4, and IL-17A were significantly higher in the non-survival group than in the survival group in SAKI patients (p < 0.05). In addition, the area under the ROC curve of IL-17A was 0.811. Moreover, the IL-17A cutoff for differentiating survivors from non-survivors was 4.7 pg/mL, of which the sensitivity and specificity were 77.4% and 71.0%, respectively.

Conclusion: Elevated levels of IL-17A could predict that SAKI patients are significantly prone to worsening kidney injury with higher mortality. The usefulness of IL-17A in treating SAKI requires further research.

Keywords: Acute kidney injury, Cytokines, Inflammation, Interleukin-17, Sepsis

Introduction

Sepsis-associated acute kidney injury (SAKI) is a life-threatening disease characterized by renal dysfunction through sepsis with high morbidity and mortality. Recent studies have elaborated that pathophysiological responses during
SAKI mediate kidney impairment [1], leading to inflammation, renal blood hypoperfusion, and tubular epithelial cell death. Therefore, early detection and treatment access is beneficial to the prognosis of SAKI patients in the clinic. However, there are no effective and reliable biomarkers to date to predict the risk stratification and prognosis of SAKI. Previous studies have described a vital role of tumor necrosis factor alpha (TNF-α) in the inflammatory process of SAKI, with insufficient sensitivity and specificity [2]. Therefore, it is essential to have an early, sensitive, and accurate biomarker to predict the severity and prognosis of SAKI, which could alleviate renal injury and poor outcomes.

Interleukin (IL)-17A, as one of the IL-17 family members, is mainly secreted by CD4+ T cells and can be secreted by nature killer T cells, neutrophils, CD8+ T cells, and γδ T cells [3]. Initially, IL-17A indicates a proinflammatory role in protecting against microbial infections during several inflammatory diseases. Meanwhile, IL-17A interacts with inflammatory cytokines, like IL-22, IL-1β, and TNF-α, resulting in a worse result [4]. Once infected, IL-17A can mediate neutrophil recruitment, host defense, and inflammation, leading to overt tissue damage [5]. Some studies have revealed that IL-17A produced in the peritoneal cavity by the γδ T cells at the early phase of sepsis is rapidly detected in the circulation [6]. IL-17A is released within 6 hours after the mild renal ischemia-reperfusion injury (IRI) [7]. Besides, activation of toll-like receptor (TLR) 2 facilitates the generation of IL-17A, leading to cisplatin-induced acute kidney injury (AKI) by recruiting innate effector cells. Therapeutic IL-17A antibodies have been shown to protect mice from cisplatin-induced AKI [8]. However, little is known about the contributions of IL-17A to SAKI progression in humans.

Considering the high morbidity and mortality of SAKI, it is essential to study the poorly known roles of IL-17A in risk stratification and prognosis in humans. Therefore, this research aims to evaluate the prognostic values of IL-17A in SAKI patients from the emergency department.

**Methods**

A total of 146 patients between 18 to 80 years old and hospitalized with sepsis in the emergency department from Nov 2020 to Nov 2021 were enrolled in the study. All patients admitted to the hospital completed promptly the Acute Physiology and Chronic Health Evaluation II (APACHE II) within 24 hours. Eighty-four sepsis patients without acute kidney injury who were hospitalized were included in the control group. The exclusion criteria for the study were anyone under 18 or over 80 years, chronic kidney disease, connective tissue disease, cancer, and congenital and acquired immunodeficiency. Patients were also excluded if any inflammatory cytokines were missed. The origin of infection included pneumonia, urinary infection, intraabdominal infection, soft tissue infection, and others.

The diagnostic criterion of sepsis is formulated using the Sepsis-3 definition [9]. SAKI diagnosis is usually based on AKI in the presence of sepsis, characterized by the Kidney Disease: Improving Global Outcomes (KDIGO) criteria [10]. Based on the serum creatinine or urine output, patients were divided into those diagnosed with acute kidney injury (SAKI group) and those who did not suffer from acute kidney injury (non-SAKI group). The AKI patients were divided into three groups based on the KDIGO guidelines: stages 1, 2, and 3. Furthermore, we divided SAKI patients into survival and non-survival group based on the 28-day mortality.

All the clinical parameters were evaluated on admission. Before initiating antibiotic treatment, the peripheral blood, urine, and other bodily fluid samples were collected. IL-2, IL-4, IL-6, IL-17A, TNF-α, and interferon gamma (IFN-γ) levels were assessed by FACS Calibur flow cytometer (BD Biosciences) based on the manufacturer’s instructions. C-reactive protein (CRP) and procalcitonin (PCT) were tested by Pylon 3D Automated Immunoassay System (ET Healthcare). In addition, the creatinine and white blood cell count (WBC) were evaluated by the clinical laboratory at Tianjin Medical University General Hospital.

The IBM SPSS version 19.0 (IBM Corp.) was used for statistical analyses. Numerical data with normal distribution were presented as mean ± standard deviation. The t test was used to compare two groups, and one-way analysis of variance was used to compare three or more groups. Quantitative data with non-normally distributed variables were represented as median with interquartile range. The Mann-Whitney U test was used for comparisons between two groups and the Kruskal-Wallis test was used for comparisons among three or more groups. A logistic regression analysis model was performed to assess the risk factors involved in the mortality of SAKI. The receiver operating...
characteristic (ROC) curves were implemented to analyze the area under the curve (AUC) of clinical indicators, thus assessing the prognostic values of clinical indicators in SAKI. Cox regression was utilized to evaluate the prognostic analysis. Net reclassification improvement (NRI) and integrated discrimination improvement (IDI) were used to compare the predictive accuracy of inflammatory cytokines. A p-value of <0.05 was considered statistically significant.

The study protocol was approved by the Medical Ethics Committee of Tianjin Medical University General Hospital (No. IR2021-YX-188-01) and was conducted in accordance with the Helsinki Declaration of 1964 (revised 2008). All the patients gave informed consent to enter the study.

**Results**

**Characteristics of study participants**

The demographic and clinical characteristics of the study are presented in Table 1. There was no statistical significance between the non-SAKI and SAKI groups concerning age, sex, APACHE II, WBC, and IFN-γ among all the patients. However, the levels of creatinine, IL-2, IL-4, IL-6, IL-17A, TNF-α, CRP, and PCT were significantly higher in the SAKI group than those in the non-SAKI group (p < 0.05). In addition, the mean length of hospitalization was significantly longer in the SAKI group (hospitalized for 15.5 ± 7.5 days) than in the non-SAKI group (hospitalized for 12.1 ± 6.3 days) (p = 0.02).

**Comparison of inflammatory cytokines in sepsis-associated acute kidney injury patients based on the severity**

Based on the severity, SAKI patients were divided into three groups: stage 1 (n = 25), stage 2 (n = 19), and stage 3 (n = 18). There was a significant difference in PCT, IL-4, IL-6, and IL-17A levels based on the severity of SAKI (Fig. 1). IL-4 and IL-17A levels in the stage-2 group were significantly higher than in the stage-1 group (p = 0.049 and 0.04, respectively).

**Table 1. Clinical characteristics of sepsis patients**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Non-SAKI group</th>
<th>SAKI group</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>84</td>
<td>62</td>
<td></td>
</tr>
<tr>
<td>Sex, male:female</td>
<td>52:32</td>
<td>40:22</td>
<td>0.57</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>64.7 ± 18.0</td>
<td>65.3 ± 16.3</td>
<td>0.83</td>
</tr>
<tr>
<td>Origin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumonia</td>
<td>46 (54.8)</td>
<td>36 (58.1)</td>
<td></td>
</tr>
<tr>
<td>Urinary infection</td>
<td>25 (29.8)</td>
<td>15 (24.2)</td>
<td></td>
</tr>
<tr>
<td>Intraabdominal infection</td>
<td>7 (8.3)</td>
<td>8 (12.9)</td>
<td></td>
</tr>
<tr>
<td>Soft tissue infection</td>
<td>2 (2.4)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>4 (4.8)</td>
<td>3 (4.8)</td>
<td></td>
</tr>
<tr>
<td>Hospitalization (day)</td>
<td>12.1 ± 6.3</td>
<td>15.5 ± 7.5</td>
<td>0.02</td>
</tr>
<tr>
<td>APACHE II</td>
<td>9.1 ± 3.0</td>
<td>9.7 ± 3.8</td>
<td>0.12</td>
</tr>
<tr>
<td>Creatinine (μmol/L)</td>
<td>59 (51–75)</td>
<td>80 (56–136)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>White blood cell (×10^9/L)</td>
<td>7.7 (5.7–10.8)</td>
<td>8.4 (5.7–13.2)</td>
<td>0.29</td>
</tr>
<tr>
<td>C-reactive protein (mg/L)</td>
<td>33.6 (9.3–80.7)</td>
<td>56.9 (22.0–103.4)</td>
<td>0.03</td>
</tr>
<tr>
<td>Procalcitonin (ng/mL)</td>
<td>0.09 (0.04–0.37)</td>
<td>0.25 (0.63–5.10)</td>
<td>0.002</td>
</tr>
<tr>
<td>IL-2 (pg/mL)</td>
<td>0.52 (0.30–0.80)</td>
<td>0.76 (0.49–1.14)</td>
<td>0.02</td>
</tr>
<tr>
<td>IL-4 (pg/mL)</td>
<td>0.40 (0.15–0.82)</td>
<td>0.67 (0.40–0.99)</td>
<td>0.004</td>
</tr>
<tr>
<td>IL-6 (pg/mL)</td>
<td>13.4 (5.7–38.3)</td>
<td>39.6 (8.9–133.7)</td>
<td>0.001</td>
</tr>
<tr>
<td>IL-17A (pg/mL)</td>
<td>2.4 (0.7–4.2)</td>
<td>4.8 (2.8–7.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TNF-α (pg/mL)</td>
<td>0.47 (0.23–0.87)</td>
<td>0.70 (0.43–0.94)</td>
<td>0.01</td>
</tr>
<tr>
<td>IFN-γ (pg/mL)</td>
<td>1.22 (0.81–2.43)</td>
<td>1.47 (1.07–2.72)</td>
<td>0.30</td>
</tr>
</tbody>
</table>

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

APACHE II, Acute Physiology and Chronic Health Evaluation II; IFN-γ, inflammatory factor gamma; IL, interleukin; SAKI, sepsis-associated acute kidney injury; TNF-α, tumor necrosis factor alpha.
respectively). Compared to the stage-2 group, PCT and IL-17A levels were significantly higher in the stage-3 group (p = 0.01 and 0.048, respectively). The results indicated that IL-17A was more promising than other clinical indicators in predicting the severity of SAKI.

**Association between the inflammatory cytokines and prognosis in sepsis-associated acute kidney injury**

We assessed the predictive value of inflammatory cytokines on prognosis during the 28-day mortality of SAKI and non-SAKI patients. The mortality of the non-SAKI group and SAKI group reached 25% and 50%, respectively. Non-survivors showed significantly increased APACHE II, PCT, IL-4, and IL-17A levels than survivors in the SAKI group (p < 0.05). However, there was no statistical significance in CRP, IL-2, IL-6, and TNF-α levels between the non-survival and survival groups in SAKI patients (p > 0.05) (Fig. 2). Additionally, the mean length of hospitalization also did not reveal any significant difference between the two groups (p > 0.05). Besides, the prognostic value of inflammatory cytokines in non-SAKI patients was shown in Supplementary Table 1 (available online).

**Logistic regression analysis of mortality in sepsis-associated acute kidney injury**

As shown in Table 2, logistic regression analysis was used to assess mortality risk factors in SAKI. According to the results of prognosis, the levels of IL-17A, IL-4, and PCT were analyzed as the independent variables in logistic regression analysis. It was demonstrated that IL-17A was an independent factor that could predict the 28-day mortality of SAKI (odds ratio, 1.423; 95% confidence interval, 1.102–1.839; p

![Figure 1](#). **Risk stratification of inflammatory cytokines in SAKI patients.** Levels of CRP (A), PCT (B), IL-2 (C), IL-4 (D), IL-6 (E), IL-17A (F), and TNF-α (G) in SAKI patients based on the severity. Data are expressed as mean ± standard deviation. CRP, C-reactive protein; IL, interleukin; NS, not significant; PCT, procalcitonin; SAKI, sepsis-associated acute kidney injury; TNF-α, tumor necrosis factor alpha. The p-values were calculated with the Kruskal-Wallis test; *p < 0.05, **p < 0.01, ***p < 0.001.
However, the levels of IL-4 and PCT were not the independent risk factors of SAKI ($p > 0.05$). Based on the result of logistic regression analysis, a prediction model was proposed as follows:

$$\text{Logit}(P) = -2.408 + 0.353 \times (\text{IL-17A}) + 0.114 \times (\text{IL-4}) + 0.055 \times (\text{PCT}).$$

Receiver operating characteristic analysis of the inflammatory cytokines in sepsis-associated acute kidney injury

We demonstrated that IL-17A had higher and superior sensitivity and specificity than other inflammatory cytokines in predicting the prognosis of SAKI ($p > 0.05$). Based on the result of logistic regression analysis, a prediction model was proposed as follows: $-2.408 + 0.353 \times (\text{IL-17A}) + 0.114 \times (\text{IL-4}) + 0.055 \times (\text{PCT})$.

Table 2. Logistic regression analysis of 28-day mortality in SAKI patients

<table>
<thead>
<tr>
<th>Inflammatory cytokine</th>
<th>$\beta$</th>
<th>OR</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-17A</td>
<td>0.353</td>
<td>1.423</td>
<td>(1.102–1.839)</td>
<td>0.007</td>
</tr>
<tr>
<td>IL-4</td>
<td>0.114</td>
<td>1.121</td>
<td>(0.229–5.479)</td>
<td>0.90</td>
</tr>
<tr>
<td>Procalcitonin</td>
<td>0.055</td>
<td>1.057</td>
<td>(0.994–1.123)</td>
<td>0.08</td>
</tr>
<tr>
<td>Constant</td>
<td>-2.408</td>
<td>0.09</td>
<td>-</td>
<td>0.002</td>
</tr>
</tbody>
</table>

Logit$(P) = -2.408 + 0.353 \times (\text{IL-17A}) + 0.114 \times (\text{IL-4}) + 0.055 \times (\text{PCT}).$

CI, confidence interval; IL, interleukin; OR, odds ratio.

Table 3. Predictive values of IL-17A, IL-4, and PCT for prognosis of SAKI patients

<table>
<thead>
<tr>
<th>Inflammatory cytokine</th>
<th>AUC</th>
<th>SE</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-17A</td>
<td>0.811</td>
<td>0.054</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>IL-4</td>
<td>0.665</td>
<td>0.069</td>
<td>0.03</td>
</tr>
<tr>
<td>PCT</td>
<td>0.652</td>
<td>0.070</td>
<td>0.04</td>
</tr>
</tbody>
</table>

IL, interleukin; PCT, procalcitonin; AUC, area under the curve; SE, standard error.

Receiver operating characteristic analysis of the inflammatory cytokines in sepsis-associated acute kidney injury

We demonstrated that IL-17A had higher and superior sensitivity and specificity than other inflammatory cytokines in predicting the prognosis of SAKI. The AUC-ROC curve for sepsis prognosis in IL-17A was 0.811 (Table 3). The sensitivity was 77.4%, and the specificity was 71.0%, at a 4.7 pg/mL cutoff value. Therefore, the ROC curve revealed that of all the inflammatory cytokines assessed, IL-17A had the most potential in the prognosis of SAKI (Fig. 3A). The
survival curves were established based on the cutoff value of 4.7 pg/mL of IL-17A (Fig. 3B). There was a significant difference in survival rates of SAKI as stratified based on the IL-17A on the day of admission. Patients with higher IL-17A levels showed worse outcomes than low levels.

**Net reclassification improvement and integrated discrimination improvement of the inflammatory cytokines in sepsis-associated acute kidney injury**

Compared with an IL-4 model, the IL-17A model resulted in an NRI of 0.26 (p < 0.05) and an IDI of 0.20 (p < 0.01), indicating a positive improvement. Compared with the PCT model, the IL-17A model had an IDI of 0.17, indicating the IL-17A model could increase the predictive accuracy by 0.17 (p < 0.05). However, NRI showed no significant difference between IL-17A and PCT models (p = 0.19).

**Discussion**

In recent years, many studies have revealed that a dysfunctional inflammatory response could result in organ dysfunction, wherein inflammatory indicators, primarily cytokines, play a crucial role in developing kidney injury during sepsis [11]. Various biomarkers have been utilized to diagnose and predict the mortality of SAKI. However, most conventional biomarkers are released and detected at a later phase of SAKI with low sensitivity and specificity. Previous meta-analyses suggested that urinary IL-18 had also been studied to predict AKI in severe sepsis patients with a low AUC [12]. Serum neutrophil gelatinase-associated lipocalin (NGAL) failed to discriminate AKI from non-AKI in sepsis patients [13]. PCT was not associated with mortality in critically ill patients with low sensitivity and specificity [14]. Therefore, an early and reliable biomarker could be essential to assess the severity and prognosis of SAKI clinically. In our studies, we demonstrated that IL-17A is more capable of predicting the severity and mortality at the early stage of SAKI.

The role of IL-17A had been previously studied in infectious and renal diseases [15,16]. However, the potential role of IL-17A in SAKI was rarely reported, especially the clinical ability to predict the severity and prognosis. The increasing level of IL-17A is detected in plasma and tissues of animal models during sepsis associated with organ damage [17,18]. There is evidence that TLR9 activated the myeloid dendritic cells to produce IL-23, which induced γδ T cells to synthesize IL-17A in septic mice and contributed to septic AKI development [19]. IL-17A is elevated in animal models of acute tubular injury and cisplatin-induced AKI [20]. The signal pathways of IL-17A and IFN-γ activated by upstream IL-23 and IL-12 promoted inflammatory response in mice with renal IRI [21]. Moreover, IL-17 knockout mice can defend against SAKI by decreasing the proinflammatory cyto-
kine levels and reducing neutrophil infiltration followed by apoptosis of tubular epithelial cells [22].

Our study indicated that IL-17A could assess the severity of SAKI. PCT, IL-4, IL-6, and IL-17A levels were significantly different based on the severity of SAKI (p < 0.05). Compared with the other cytokines evaluated, IL-17A efficiently predicted the severity in SAKI patients. Liu et al. [23] reported that increasing IL-17A was associated with significantly worse disease severity and unfavorable prognosis in sepsis patients, concurrent with our results. The high levels of IL-17A in septic shock activated the proinflammatory cytokines (IL-1β, TNF-α, and IL-6) and chemokines [24]. Besides, IL-17A levels correlated with disease severity in patients having lupus nephritis, in which cytokines like TNF-α, could attract inflammatory cells into the kidney [25]. A previous study showed that IL-17A served as an optimal biomarker to determine the severity and prognosis of sepsis-induced acute respiratory distress syndrome (ARDS) [26]. Furthermore, tubular damage and interstitial infiltration were alleviated in the IL-17A knocked-out mice [20,27]. In contrast, Thorenz et al. [7] demonstrated that IL-17A deficiency or treatment of IL-17A antibody could not attenuate renal fibrosis after severe IRI in mice.

Our study also indicated that IL-17A had the highest sensitivity and specificity to predict the prognosis of SAKI compared to IL-4 and PCT. Most of the initial IL-17A in the kidney was secreted by neutrophils, directly damaging kidney and tubular cells [19]. Moreover, IL-17A induced neutrophil infiltration and tubular cell apoptosis [22]. IL-17A acted as a driver of developing AKI in septic shock patients and was found to be deposited heavily in the glomeruli by renal biopsies of patients, who died of dengue fever [27,28]. Mikacenic et al. [3] had also shown that increased circulating levels of IL-17A were potential indicators of organ dysfunction in ARDS. Similar to the report by Ahmed et al. [18], we found that non-survivors had significantly elevated levels of IL-17A compared with survivors among SAKI patients, demonstrating that high levels of IL-17A were associated with mortality and poor outcomes in SAKI patients. However, we only studied the patients who suffered from SAKI and not poly-trauma. In animal experiments, Naito et al. [19] confirmed that the knockout of IL-17A improved outcomes post-cecal ligation and puncture (CLP) and attenuated the septic AKI. Moreover, the role of IL-17A in sepsis mortality might depend on the microbe that initiated the infection. IL-17A elevated the recruitment of neutrophils, which were unable to phagocytose the bacteria [29]. On the contrary, some animal experiments had revealed that IL-17 played a protective role in less severe CLP models. Compared to IL-17–/– mice, wild-type mice had significantly higher survival after CLP [30,31]. Therefore, more well-conducted trials are required to assess the role of IL-17A in SAKI.

There are several limitations to our study. First, it is a retrospective study and involves a small size of patients from a single center. Secondly, IL-17A was measured at baseline only within 24 hours after admission and dynamic monitoring was not presented, which might make the results imperfect. Thirdly, some other biomarkers, such as NGAL and IL-18, were not included in the study, which might have a potential effect on the results.

In conclusion, elevated IL-17A might indicate poor mortality in SAKI patients. Further studies are needed to elucidate better the usefulness of IL-17A in the therapy of SAKI.

Conflicts of interest

All authors have no conflicts of interest to declare.

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Data sharing statement

All the data supporting the findings of this study are included in the article.

Authors’ contributions

Conceptualization: YZ, AM
Data curation: WW, YZ, AM, KS, XL
Formal analysis: KS
Funding acquisition: HJ
Investigation: WW, KS
Methodology: XL, YZ
Project administration: HJ, QL, SS, YZ
Software: WW, YZ, AM, QL
Supervision: HJ, SS, YZ
Validation: SS
Writing–original draft: WW, YZ
Writing–review & editing: HJ, SS
All authors read and approved the final manuscript.

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References


Background: Patients with chronic kidney disease (CKD) should be educated about their condition so that they can initiate dialysis at the optimal time and make an informed choice between dialysis modalities. Shared decision-making (SDM) empowers patients to select their own treatment and improves patient outcomes. This study aimed to evaluate whether SDM affects the choice of renal replacement therapy among CKD patients.

Methods: This is a multicenter, open-label, randomized, pragmatic clinical trial. A total of 1,194 participants with CKD who are considering renal replacement therapy were enrolled. The participants will be randomized into three groups in a 1:1:1 ratio: the conventional group, extensive informed decision-making group, and SDM group. Participants will be educated twice at months 0 and 2. Videos and leaflets will be provided to all patients. Patients in the conventional group will receive 5 minutes of education at each visit. The extensive informed decision-making group will receive more informed and detailed education using intensive learning materials for 10 minutes each visit. Patients in the SDM group will be educated for 10 minutes each visit according to illness perception and item-based analysis. The primary endpoint is the ratio of hemodialysis to peritoneal dialysis and kidney transplantation among the groups. Secondary outcomes include unplanned dialysis, economic efficiency, patient satisfaction, patient evaluation of the process, and patient adherence.

Discussion: The SDM-ART is an ongoing clinical study to investigate the effect of SDM on the choice of renal replacement therapy in patients with CKD.

Keywords: Chronic renal insufficiency, Peritoneal dialysis, Renal dialysis, Shared decision making
Introduction

The number of patients with chronic kidney disease (CKD) and kidney failure with replacement therapy (KFRT) is rapidly increasing due to longer life expectancy and a higher prevalence of chronic diseases including diabetes and hypertension [1,2]. CKD progression heavily increases socioeconomic burden [3]. When CKD patients approach KFRT, they must choose a renal replacement therapy (RRT) that usually includes dialysis or kidney transplantation (KT). KT provides superior survival outcomes and long-term cost-effectiveness compared to dialysis [4]. However, lack of available donated kidneys in addition to socioeconomic limitations can lead patients to choose dialysis treatment, of which there are two types: hemodialysis (HD) and peritoneal dialysis (PD).

HD and PD are complementary and have several advantages and disadvantages. When patients choose a dialysis modality, various medical and socioeconomic factors should be considered, and the decision to go with one modality over another should be made on a patient-centered basis. In Korea, the proportion of HD patients is increasing while the proportion of PD patients is decreasing, and most KFRT patients have recently undergone HD [2]. In particular, the percentage of patients who selected HD as their initial RRT increased from <70% before 2008 to >80% after 2014 [2]. However, improvements in PD patient survival have led to similar mortality rates between PD and HD in Korea [2,5]. In other countries, PD mortality rates were lower than those of HD prior to 2000, but the survival rates between the two groups are similar now [6–8]. Quality of life is also comparable between the PD and HD groups [9,10].

Shared decision-making (SDM) is an approach in which clinicians and patients make decisions together using the best available evidence [11]. An understanding of treatment goals, advantages and disadvantages of treatment options, and the likelihood of achieving desired outcomes are all important to patients [12]. Additionally, SDM increases patients’ quality of life and maintains their autonomy [13]. International guidelines recommend that all patients with CKD be educated at the predialysis stage to improve their knowledge and understanding of their own condition, and to make an informed choice among the RRT options [12,14–16]. SDM is a recommended model to follow when choosing the preferred treatment for patients with advanced CKD [12,14–16]. Despite these recommendations, many patients feel unprepared and ill-informed about the initiation of dialysis and available treatment options [17]. This may lead to a situation where the patient loses the opportunity to make their own choices, resulting in emergency dialysis or a dialysis modality that is not suitable.

CKD patients have the right to choose RRT modalities that are appropriate for them through sufficient communication with clinicians, but how to guide the patient through the decision-making process is not well-established. Therefore, this study aims to evaluate whether SDM has an effect on RRT choice among CKD patients.

Methods

Study design

This study is an investigator-initiated, multicenter, open-label, randomized, pragmatic clinical trial occurring over a 12-month period. Patients with CKD who have not received RRT will be screened to participate, and those who meet all inclusion and exclusion criteria will be eligible for enrollment. After participants provide written informed consent and are enrolled, they will be randomized into the three study arms. Participants will receive education twice during months 0 and 2, and clinical follow-up will be performed at months 4, 6, 8, 10, and 12 (Fig. 1).

Study participants

Participants will be recruited from the following 19 tertiary university hospitals in Korea: Seoul National University Bundang Hospital, Seoul National University Hospital, Seoul National University Boramae Medical Center, Severance Hospital, The Catholic University of Korea Seoul St. Mary’s Hospital, Ewha Woman’s University Seoul Hospital, Samsung Medical Center, The Catholic University of Korea Eunpyeong St. Mary’s Hospital, Korea University Guro Hospital, Kyung Hee University Hospital at Gangdong, Dongguk University Ilsan Hospital, Gachon University Gil Medical Center, Yonsei University Wonju Severance Christian Hospital, Daejeon Eulji Medical Center, Ulsan University Hospital, Kyungpook National University Hospital, Pusan National University Hospital, Chonnam National
University Hospital, and Kyungpook National University Chilgok Hospital. The inclusion and exclusion criteria are presented in Table 1. The estimated glomerular filtration rate (eGFR) was calculated using the four-variable Modification of Diet in Renal Disease equation as follows [18]:

eGFR (mL/min per 1.73 m²) = 175 × [serum creatinine (mg/dL)]⁻¹.154 × [age]⁻⁰.⁰⁸⁵ × [0.⁷⁴² if female] × [1.⁴³ if black].

Table 1. Inclusion and exclusion criteria

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Patients with chronic kidney disease whose nephrologist predicts initiation of renal replacement therapy within 12 months:</td>
<td>1. Patients who have a contraindication to perform peritoneal dialysis due to abdominal surgery</td>
</tr>
<tr>
<td>a) Patients with stage 5 chronic kidney disease (defined as a creatinine-based eGFR of &lt;15 mL/dL/1.73 m² at least two times at intervals of 2 weeks or longer)</td>
<td>2. Patients whose life expectancy is less than 6 months due to underlying diseases</td>
</tr>
<tr>
<td>b) Patients with cystatin-C–based eGFR of &lt;15 mL/dL/1.73 m² at least once if the creatinine-based eGFR does not accurately evaluate patient kidney function due to patient characteristics</td>
<td>3. Patients who have enrolled in other clinical trials within 3 months or plan to participate in other clinical trials during this clinical trial period</td>
</tr>
<tr>
<td>c) Patients whose nephrologist requires renal replacement therapy within 12 months due to the patient’s comorbidities even when eGFR is ≥15 mL/dL/1.73 m²</td>
<td>4. Patients judged by the investigator to be inappropriate for participation in this clinical trial</td>
</tr>
</tbody>
</table>

2. Patients between 19 and 80 years old |
3. Patients who understand the study |
4. Patients who have no permanent access device for long-term maintenance dialysis |

eGFR, estimated glomerular filtration rate.

Ethics approval and consent to participate

All participants provided informed consent prior to enrollment. This study obtained the approval from Institutional Review Board (IRB) at all 19 participating sites (Additional information). The trial protocol was registered at ClinicalTrials.gov (http://www.clinicaltrials.gov; NCT04976166) on July 26, 2021. Recruitment began in March 2021 and 215 patients were randomized by December 2021. Recruitment in this study is ongoing. The protocol version number is 3.1 dated December 2021.

Randomization

The randomization process is conducted using a web-based program. A list of random numbers will be generated by a computerized random allocation system operated by the Medical Research Collaborating Center at Seoul National University Hospital. Eligible participants will be randomized into three groups in a 1:1:1 ratio: the conventional group, extensive informed decision-making (EIDM) group, and SDM group. Randomization will be stratified based on the institution and diabetes status. All patients are provided with an educational leaflet and a QR code to view a 12-minute video describing the importance of informed decision-making when choosing dialysis therapy, and the advantages and disadvantages of the dialysis modalities. Participants will receive education twice, once during...
month 0 and once during month 2 and will then decide on their preferred dialysis modality. Dialysis education will be provided by the doctors at each hospital. Patients in the conventional group will receive education as usual in the form of leaflets for 5 minutes at months 0 and 2. Patients in the EIDM group will be provided with education consisting of intensive learning materials for more than 10 minutes at months 0 and 2. Patients in the SDM group will receive education using a self-developed counseling calendar (Supplementary Fig. 1, available online) for more than 10 minutes and will complete self-assessment items and illness perception at month 0 [19]. Self-assessment consists of 35 items in three categories: dialysis environment, health, and lifestyle (Supplementary Table 1, available online). Illness perception is a 10-item questionnaire using a scale from 1 to 5 (Supplementary Table 2, available online). Then, patients will be educated for more than 10 minutes according to their values and preferences through illness perception and items-based analysis at month 2 (Fig. 2).

**Primary endpoint**

The primary endpoint is the proportion of HD versus non-HD (PD and KT) treatments among the groups. HD is defined as dialysis via arteriovenous fistula (AVF) or arteriovenous graft (AVG), or 8 weeks after arteriovenous vascular surgery. PD is defined as starting PD or 4 weeks after PD catheter insertion. KT is defined as a KT operation.

**Secondary endpoints**

The secondary endpoints include unplanned dialysis, economic efficiency, patient satisfaction, patients’ evaluation of the SDM process, and patient adherence.

Unplanned dialysis events will be compared to planned dialysis. Planned dialysis is defined as starting dialysis if the patient has a permanent access device such as AVF/AVG and PD catheter already in place. If dialysis is started 4 weeks after PD catheter insertion or 8 weeks after arteriovenous vascular surgery, planned dialysis should be re-

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**Figure 2. Education methods and materials provided to each group.**

EIDM, extensive informed decision-making; SDM, shared decision-making.

aPatients filled out illness perception and self-assessment items at month 0 and were educated according to illness perception and item-based analysis at month 2.
Economic efficiency will be assessed using a cost-utility analysis from a healthcare sector perspective. Healthcare, patient, and family costs are tallied using a survey at months 2 and 12. Healthcare costs include the medical costs for CKD treatment. Additionally, patient and family costs include a caregiver and transportation, among others. For utility, study participants will be asked to fill out the 5-level EQ-5D version (EQ-5D-5L) of the EuroQol group and the Korean Health-Related Quality of Life Instrument with 8 items (HINT-8) [20] at months 0, 2, and 12. We will calculate quality-adjusted life year (QALY) by multiplying the EQ-5D index by the follow-up duration in each arm. Finally, the incremental cost-utility ratio for SDM groups is calculated as the ratio of differences in costs and utilities among the three groups.

Patient satisfaction will be assessed using the patient satisfaction questionnaire (ZUF-8) at months 0, 2, and 12 [21]. The ZUF-8 questionnaire, “Fragebogen zur Patientenzufriedenheit,” is an eight-item questionnaire that assesses patient satisfaction using a scale from 1 to 4. Originally, ZUF-8 used a 4-point scale, but in this study, we further extended the scoring system of this questionnaire from four to five incremental stages of perceived satisfaction ranging from 1 to 5 [22]. The minimum and maximum values were 8 and 40, respectively. Higher scores indicated better outcomes.

Patients’ evaluation of the SDM process will be assessed using the nine-item Shared Decision Making Questionnaire (SDM-Q-9) at months 0, 2, and 12 [23]. The original instrument (SDM-Q) consisted of 26 items with items rated on a 4-point scale. The SDM-Q-9 is a major revision from the original wherein the response scale was adjusted from 4-point to 6-point ratings to include greater extremes (“completely disagree” and “completely agree”) to counter high ceiling effects [24]. In this study, six response options are converted into five incremental stages ranging from 1 to 5. To calculate the total scale score, items are summed, resulting in a total range from 9 to 45. Higher scores reflect a patient’s level of participation in SDM regarding their treatment. The translated version of SDM-Q-9 reported excellent reliability and validity [24–26].

Patient adherence will be assessed using the eight-item Morisky Medication Adherence Scale (MMAS-8) at months 0, 2, and 12 [27]. The MMAS-8 is an eight-item questionnaire and the scale includes seven items with yes/no response options and one item with a 5-point Likert scale option [28]. The cumulative score based on eight items is used to obtain a final adherence score ranging from 0 to 8. Adherence is defined as low (score 0-5), medium (score 6-7), or high (score 8).

Participants will visit the outpatient clinic or receive a phone call for a survey on economic efficiency, patient satisfaction, and patient adherence 12 months after the end of the study.

**Clinical and laboratory evaluations**

A physical examination, comorbidity assessment, and medication review will be performed, including the following laboratory evaluations: complete blood count (hemoglobin, hematocrit, white blood cells, and platelets), sodium, potassium, chloride, total CO₂, glucose, protein, albumin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, gamma-glutamyl transferase, blood urea nitrogen (BUN), creatinine, calcium, phosphorous, total bilirubin, uric acid, total cholesterol, low-density lipoprotein cholesterol triglyceride, and eGFR. Complete blood count, sodium, potassium, chloride, protein, albumin, AST, ALT, BUN, creatinine, calcium, phosphorous, and eGFR evaluations will be conducted every 2 months during the study. The self-assessment questionnaire will be completed by the SDM group only at month 0 and in all groups at month 12. The study schedule is shown in Fig. 3. Participants will visit the outpatient clinic or receive a phone call for a survey on “illness perception” 12 months after the end of the study.

**Sample size calculations**

We estimated a 10% increase in the proportion of non-HD patients in the EIDM or SDM groups compared with those in the conventional group. It is estimated that the proportion of non-HD patients in the conventional group will be 15% and 25% in the EIDM or SDM groups. We calculated the required sample size for a two-sided level of significance of α = 0.05, a power of 90%, and one interim analysis. The number of participants required was 358 per group. Based on the assumption of a dropout rate of 10%, a total of 1,194 participants were included in the analysis. Interim
analysis will be performed at 50% study progress, and the significance levels used in the interim analysis will be \( p = 0.003 \). The final analysis will be completed after the last participant’s treatment. The O’Brien-Fleming alpha spending function will be used to test the primary outcomes in the interim analysis and final analysis.

### Safety issues and adverse events

The trial itself is not expected to pose any medical risk to the participants. The safety assessments include laboratory tests (hematology and blood chemistry), blood pressure, heart rate, and body weight. Any adverse events (AEs) will be assessed every visit after randomization. All AEs will be summarized and presented according to their severity and outcome.

### Data collection and management

All participants’ information will be recorded by the investigators and clinical research coordinators (CRCs) at the participating hospital using electronic case report forms.
(eCRF) from a web-based database (Korea National Institute of Health; http://icreat.nih.go.kr). Records will only be accessed by authorized personnel to ensure confidentiality. The data will be handled confidentially and anonymously. Study participants will only be recognized by their study ID, and their personal identifiers will not be recorded or stored. Investigators and CRCs at the participating hospitals will monitor the completeness of the eCRF. An independent data management team separate from the investigators will conduct data management. A data validation plan will be prepared to review the consistency, validity, and completeness of the eCRF data. Through this iterative process, the data will be cleaned and the final database will be locked. All database backups of the eCRF will be performed in real time. A data monitoring committee board is not needed because this study is a minimal-risk study.

To modify protocols, approval will be required during an investigator meeting. Any planned amendments in this trial will be communicated to the trial site staff in person and reported to the IRB and sponsor. The investigators will also update the protocol in the clinical trial registry.

Statistical analyses

All primary and secondary endpoints and serious AEs will be analyzed by investigators at participating hospitals. The differences among the groups will be analyzed using one-way analysis of variance and Kruskal-Wallis rank sum tests for continuous variables, and chi-square and Fisher exact tests for categorical variables. Repeated measures data will be compared using a mixed model. The primary endpoint, HD versus non-HD, was analyzed using a logistic regression model among the groups. A logistic regression model was used to analyze stratification factors (institutions and diabetes) and factors with a standardized difference of 10% or more because of randomization. For the secondary endpoints, a mixed model will be used to analyze whether there is a difference over time among groups, or if there is a different pattern among groups according to time by correcting for stratification factors (institutions and diabetes) and factors with a standardized difference of 10% or more because of randomization. If the measurement data are not repeated, logistic regression analysis or linear regression analysis will be used according to stratification factors and covariates.

The statistical analyses will be conducted on an intention-to-treat (ITT) and per-protocol (PP) basis. For the ITT analysis, all participants who are enrolled and randomized to one of the three groups and who complete the first visit will be included. For PP analysis, all participants who complete the study will be included to evaluate the primary and secondary outcomes.

The final dataset will be available for researchers who are interested in related topics after the research team has disseminated the main findings of the research aims. Permission from the primary investigator is required for all publications and dissemination efforts.

Dissemination plans

The research progress will be regularly reported to the National Evidence-based Healthcare Collaborating Agency and will be presented at the Korean Society of Nephrology conference. We will also disseminate the study results at national and international conferences and in scientific peer-reviewed journals.

Discussion

This study compares RRT choice among patients with CKD according to the level of SDM. It also compares the differences in unplanned dialysis, economic efficiency, patient satisfaction, patients’ evaluation of the process, and patient adherence.

SDM is an important component of patient-centered care. The physician provides quality information about treatment options, the patient provides his or her values and preferences, and together they make the best decision [29]. SDM increases the quality of decision-making and acceptability of patients during the treatment process because they feel a responsibility for their own treatment. In the past, patients relied on physician judgment and decisions alone when deciding on a treatment plan [30]. However, in recent years due to improvements in medical care, various treatments for the same disease have been made available, and communication technology has facilitated easy acquisition of health and medical information. The patient has a right to know their treatment options and the associated risks and benefits, which often means more in-depth information is required. However, extensive
information can be exhausting and distressing for patients, many of whom ultimately end up on dialysis without feeling they have actually made an appropriate decision [30]. Moreover, some comorbidities are related to the choice of dialysis modality, and this choice might not lead to the best outcomes in the real-world [31]. Therefore, patients are changing the way they participate in the treatment decision-making process.

This study divides patients into three groups according to education method and decision aids. The differences among the groups are the quality and quantity of information provided and the extent to which patients and doctors share their opinions. In the conventional group, the necessity of starting dialysis and the advantages and disadvantages of the dialysis methods are briefly explained twice within 5-minute sessions, after which the patient decides on the start date and dialysis method. The EIDM group receives more information, including intensive learning materials, and the patient undergoes a session that is 5 minutes longer than the conventional group’s education. However, while KFRT patients prefer to receive information, this does not always translate into active involvement in decision-making [32]. Thus, in the SDM group, the doctor explains the necessity of starting dialysis and describes the different dialysis methods to the patient, and then refers to the self-assessment responses. The patient is then educated according to their answers to the self-assessment items, with a particular focus on patient illness perceptions. Afterward, the patient makes a treatment decision based on the doctor’s recommendations as well as their values and preferences.

Illness perceptions are the organized beliefs patients have about their disease and are defined by identity, cause, timeline, consequences, control, and emotional responses [33,34]. Within KFRT, illness perceptions have been shown to be related to a variety of health outcomes including quality of life [35], depression [36,37], and mortality [38,39]. In this respect, an investigation into the illness perceptions of people with kidney disease is important and may serve as an interventional target for treatment engagement, adherence, and health outcomes [40]. A recent study showed that understanding the illness perception of CKD patients was crucial in the SDM communication process [19]. The illness perception of HD and PD patients was different, and it affected patients’ perception and satisfaction with SDM [19]. When patients report that they have participated in SDM, they are likely to enjoy better affective-cognitive outcomes such as improved satisfaction and less decisional conflict [41]. The challenging point is that it is not clear what leads a patient to report a decision as having been shared. Thus, to foster SDM and its associated benefits in practice, more effort should be given to finding links between SDM and patient behavioral and health outcomes. The primary endpoint in this study is the proportion of HD versus non-HD treatments. It is very important to choose long-term RRT for KFRT patients. KT is the best choice for RRT, but lack of available donated kidneys or poor socioeconomic status can lead a patient to choose HD or PD. The reason why “8 weeks after vascular surgery” was added to the definition is that 8 weeks is the period during which the patient can be considered to have decided on their dialysis method through HD, and they are ready to start HD. This means that they have no chance to change their dialysis modality. Also, the reason why “4 weeks after PD catheter insertion” was added to the definition is that 4 weeks is the period during which the patient can be considered to have decided on their dialysis method through PD. Various medical and socioeconomic factors influence decisions regarding dialysis modality selection. The importance of health and dialysis environmental factors is more emphasized in HD patients, while lifestyle factors may be considered more important in PD patients [19]. PD patients were found to have been provided with sufficient information and were more informed about dialysis modalities than HD patients [42,43]. A recent study reported that SDM implementation for long-term RRT led to more KFRT patients receiving living KT and entering PD rather than HD [44]. The incidence of HD patients is increasing to >80% in Korea [2]. The sample size in this study was calculated assuming that the ratio of non-HD patients increased by 10%.

The secondary endpoints are unplanned dialysis, economic efficiency, patient satisfaction, patient evaluation of the SDM process, and patient adherence. Implementing SDM and providing sufficient information on RRT may lead to a situation in which the patient has the ability to make an informed choice. This results in more planned dialysis treatments and increases patient satisfaction and adherence. This study also compares the differences in economic efficiency. Control and treatment of CKD and RRT impose a large economic burden on the healthcare system and its
patients. Korea has higher HD costs than PD costs—5-year costs were $16,335 and $12,398 for HD and PD, respectively [3]. The cost per QALY gained was RM (Malaysian ringgit) 46,595 for HD and RM41,527 for PD in Malaysia, and increasing PD as the initial dialysis modality would be more cost-effective [45]. With regard to medication adherence, a recent study in China reported that patient adherence was positively correlated with perceived necessity and negatively correlated with concern [46]. Among 283 PD hypertensive patients who completed the MMAS-8 questionnaire, the proportion of medium-to-high drug adherence to anti-hypertensive therapy was 89.8% [47].

In summary, the SDM-ART study is a multicenter, open-label, randomized, pragmatic trial to evaluate the effect of SDM on RRT choice in patients with CKD. The results of this trial could help better equip patients to choose the right RRT modality and could be useful in reducing unplanned dialysis, decreasing economic burden, and increasing overall patient satisfaction and adherence.

Additional information

The approval numbers from the Institutional Review Boards of all 19 participating sites are as follows: Gachon University Gil Medical Center, GAIRB2021-122; Seoul National University Bundang Hospital, B-2103/672-405; Seoul National University Hospital, H-2011-164-1176; Seoul National University Boramae Medical Center, 20-2021-31; Severance Hospital, 4-2021-0459; The Catholic University of Korea Seoul St. Mary’s Hospital, XC21EID10046; Ewha Woman’s University Seoul Hospital, SEUMC 2021-03-007-008; Samsung Medical Center, SMC 2021-02-040-005; The Catholic University of Korea Eunpyeong St. Mary’s Hospital, XC21EID10046; Korea University Guro Hospital, 2021GR0188; Kyung Hee University Hospital at Gangdong, KHNMC 2021-03-003-001; Dongguk University Ilsan Hospital, DUH2021-03-034-007; Yonsei University Wonju Severance Christian Hospital, CR320200; Daejeon Eulji Medical Center, EMC 2021-03-001-001; Ulsan University Hospital, UUH 2021-05-009; Kyungpook National University Hospital, KNUH 2021-02-027-001; Pusan National University Hospital, 2103-022-101; Chonnam National University Hospital, BTMP-2021-063; and Kyungpook National University Chilgok Hospital, KNUCH2021-03-021-002.

Conflicts of interest

All authors have no conflicts of interest to declare.

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Data sharing statement

The data presented in this study are available on request from the corresponding author.

Authors’ contributions

Conceptualization, Data curation, Formal analysis, Methodology: YCK, Soojin K, MWJ, Sejoong K
Funding acquisition: Sejoong K
Investigation, Methodology, Resources: JHC, SHS, Soojin K, MWJ, Sejoong K
Writing—original draft: JHC, SHS, Soojin K, MWJ, Sejoong K
Writing—review & editing: JHC, SHS, Soojin K, MWJ, Sejoong K

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**References**


Acquired ectopic kidney

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An 80-year-old man was referred to the nephrology clinic for evaluation of chronic kidney disease with proteinuria. His past medical history was consistent with diabetes mellitus, hypertension and obesity. He also had Crohn disease since 1971 and had been operated on several times, resulting in an abdominal eventration. The eventration had been treated with a prosthesis, which had to be removed in 2013 due to an infection, with no possibility of reintervention (Fig. 1A). His medication consisted in adalimumab, irbesartan/hydrochlorothiazide and dapaglifozine. Clinical examination revealed morbid obesity (body mass index, 45.1 kg/m\textsuperscript{2}) and a voluminous eventration with no signs of occlusion. Biologically, plasma creatinine was 97 μmol/L (1.1 mg/dL; estimated glomerular filtration rate, 70 mL/min/1.73 m\textsuperscript{2}) with protein-to-creatinine ratio of 0.2 g/mmol (normal range, <0.03) without hematuria nor leukocyturia. An abdominal computed tomography scan was performed to evaluate the possibility of performing a renal biopsy (Fig. 1B, C). Over time, right kidney had localized within the eventration taking on a subcutaneous position. Finally, kidney biopsy was not performed, as proteinuria remained stable over time without kidney impairment and

Figure 1. Axial views of abdominal computed tomography scans. (A) Voluminous abdominal eventration with normal kidney localization in 2015, 2 years after prosthesis removal. Subcutaneous intrahernial localization of right kidney in 2023 (B), while the left kidney remains in normal anatomical position (C).
because of the risk of the procedure.

**Conflicts of interest**

All authors have no conflicts of interest to declare.

**Data sharing statement**

The data presented in this study are available on request from the corresponding author.

**Authors’ contributions**

Conceptualization: All authors
Data curation, Formal analysis, Visualization: HL
Supervision: ET
Writing-original draft: HL
Writing-review & editing: All authors
All authors read and approved the final manuscript.

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An intradialytic aerobic exercise program ameliorates frailty and improves dialysis adequacy and quality of life among hemodialysis patients: a randomized controlled trial

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Hemodialysis patients with chronic kidney disease commonly exhibit physical deconditioning in line with protein-energy wasting and frailty [1]. Enhancing physical activity improves body composition and preserves muscle mass in hemodialysis patients [2]. Intradialytic exercise modulates the metabolic balance by stimulating anabolic activity in muscle tissues with anabolic nutritional support in patients undergoing dialysis [3]. In contrast to previous literature, this study did not detect any beneficial effects on body composition parameters, including skeletal muscle mass, lower leg muscle mass, and body fat mass, after 40 to 70 minutes of ergometer cycling during each hemodialysis session, three times a week for 12 weeks, despite improvements in frailty, dialysis adequacy, and quality of life (QoL) [4]. These results suggest that the authors did not consider the effect of nutritional factors on body composition profiles [1,4].

Nutritional support or exercise training is associated with an increase in serum albumin and pre-albumin [1]. The serum albumin concentration is a crucial dialysis-related nutritional factor that reflects protein-energy wasting, muscle strength, and physical function in connection with intradialytic exercise training [2,4,5]. However, there is insufficient evidence of intradialytic aerobic exercise combined with nutritional factors to improve body composition parameters [5]. Therefore, this study hypothesized that an intradialytic aerobic exercise program combined with the nutritional factor of the serum albumin concentration affects frailty, dialysis adequacy, body composition parameters, and QoL among hemodialysis patients. The exercise group completed a 12-week program of intradialytic aerobic exercise and a single education session (n = 18), whereas the control group completed only the education session (n = 21). The serum albumin value was classified as low level (≤3.8 g/dL), or normal level (>3.8 g/dL) based on previous reports that low serum albumin (cutoff value of...
3.8 g/dL) reflects protein-energy wasting that is concomitant with low body mass index, reduced muscle mass, and unintentional low dietary intake [6]. Moreover, it is evident that serum albumin higher than 3.8 g/dL is associated with a greater increase in renal urea clearance, normalized protein catabolic rate, lower mortality, and reduced cardiovascular death among hemodialysis patients [7,8]. In this study, the mean albumin value was 3.82 ± 0.38 g/dL. Cases of low albumin levels in the exercise and control groups were 50.0% (n = 9) and 57.1% (n = 12), respectively (χ² = 0.20, p = 0.75). Although there was no significant difference in the baseline mean albumin value between the exercise and control groups (3.87 ± 0.18 g/dL vs. 3.77 ± 0.49 g/dL, t = 0.92, p = 0.37), the frailty score classified exercise and albumin level had a significant difference (p = 0.02) (Table 1). As we did not achieve selection balance, the dialysis vintage [4] and baseline frailty score should be considered confounding variables to determine the interaction effects. There was a significant interaction between groups and albumin levels in dialysis efficacy at week 12 (p = 0.02). The exercise group with albumin >3.8 g/dL exhibited the highest Kt/V of 1.88 ± 0.32 with a large effect size (f = 0.41) among the four subgroups (Table 1). The two-way analysis of covariance for changes in frailty, Kt/V, short physical performance battery, and quality of life (QoL) was conducted to assess the interaction between groups and albumin level (Table 1).

### Table 1. Effect of frailty, dialysis adequacy, body composition parameters, and QoL according to intradialytic aerobic exercise and serum albumin levels

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Albumin ≤ 3.8 g/dL (n = 21)</th>
<th>Albumin &gt; 3.8 g/dL (n = 18)</th>
<th>Two-way ANCOVA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Exercise group (n = 9)</td>
<td>Control group (n = 12)</td>
<td></td>
</tr>
<tr>
<td>Frailty (score, 0–5)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>1.89 ± 0.93</td>
<td>2.91 ± 0.67</td>
<td></td>
</tr>
<tr>
<td>Week 12</td>
<td>1.11 ± 0.93</td>
<td>3.33 ± 0.98</td>
<td></td>
</tr>
<tr>
<td>Kidney-to-Urea Clearance (Kt/V)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>1.58 ± 0.18</td>
<td>1.69 ± 0.18</td>
<td></td>
</tr>
<tr>
<td>Week 12</td>
<td>1.64 ± 0.25</td>
<td>1.70 ± 0.15</td>
<td></td>
</tr>
<tr>
<td>SPPB (0–12, score)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>11.11 ± 0.93</td>
<td>9.42 ± 2.31</td>
<td></td>
</tr>
<tr>
<td>Week 12</td>
<td>11.11 ± 0.67</td>
<td>9.83 ± 2.41</td>
<td></td>
</tr>
<tr>
<td>Skeletal Muscle Mass (kg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>25.57 ± 3.85</td>
<td>24.03 ± 2.90</td>
<td></td>
</tr>
<tr>
<td>Week 12</td>
<td>24.98 ± 4.40</td>
<td>22.59 ± 3.08</td>
<td></td>
</tr>
<tr>
<td>Body Fat (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>20.57 ± 7.18</td>
<td>21.51 ± 8.07</td>
<td></td>
</tr>
<tr>
<td>Week 12</td>
<td>22.02 ± 8.32</td>
<td>22.66 ± 8.67</td>
<td></td>
</tr>
<tr>
<td>Lower Leg Muscle Mass (kg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>16.01 ± 2.09</td>
<td>14.85 ± 3.55</td>
<td></td>
</tr>
<tr>
<td>Week 12</td>
<td>13.39 ± 2.34</td>
<td>12.36 ± 1.95</td>
<td></td>
</tr>
<tr>
<td>Quality of Life (QoL)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>44.12 ± 6.29</td>
<td>43.18 ± 7.95</td>
<td></td>
</tr>
<tr>
<td>Week 12</td>
<td>52.62 ± 4.76</td>
<td>41.47 ± 8.60</td>
<td></td>
</tr>
<tr>
<td>Physical Component Summary (PCS)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>50.60 ± 12.20</td>
<td>48.08 ± 10.29</td>
<td></td>
</tr>
<tr>
<td>Week 12</td>
<td>53.06 ± 6.96</td>
<td>48.92 ± 9.65</td>
<td></td>
</tr>
</tbody>
</table>

Values are presented as mean ± standard deviation.

G, group (exercise vs. control); LLM, lower leg muscle mass; MCS, mental component summary; PCS, physical component summary; QoL, quality of life; SMM, skeletal muscle mass; SPPB, short physical performance battery. Kt/V: K = dialyzer’s capacity to clear urea at the blood flow rate, t = treatment time, and V = distribution volume of urea.

°F-score calculated using two-way analysis of covariance (ANCOVA) adjusted by dialysis vintage at baseline; †F-score calculated using two-way ANCOVA adjusted by dialysis vintage, and baseline frailty score at week 12.
battery score, body composition profiles, and QoL revealed that the exercise group with albumin > 3.8 g/dL exhibited a significant improvement in the short physical performance battery score of 1.67 (p = 0.05) with a moderately high effect (f = 0.35) (Table 2). The change in lower leg muscle mass in the albumin > 3.8 g/dL group was significantly lower than that in the albumin ≤ 3.8 g/dL group (p = 0.02) (Table 2).

This study did not find any significant interaction between exercise training and serum albumin levels with regard to an improvement in body composition profiles. Additional research is needed to determine whether aerobic exercise with various sessions, durations, and intensities, or nutritional support might be useful for improving body composition profiles in hemodialysis patients. The present study had several limitations that warrant consideration. First, we included only patients undergoing treatment at a single hemodialysis center, and the results might not be generalizable to other centers and patient populations [4]. Second, the small sample size could indicate a risk of bias to use of factorial statistics for the exercise and nutritional factors. Lastly, because the effects of intradialytic aerobic exercise on body composition have been controversial, this discrepancy should be verified through further research by modifying the duration, time, and intensity of the intra-

Table 2. Interaction effects between the intradialytic aerobic exercise and serum albumin level in the changes of frailty, dialysis adequacy, body composition parameters and QoL.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Albumin ≤ 3.8 g/dL (n = 21)</th>
<th>Albumin &gt; 3.8 g/dL (n = 18)</th>
<th>Two-way ANCOVA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frailty (score, 0-5)</td>
<td>Exercise group (n = 9)</td>
<td>Control group (n = 12)</td>
<td>Group</td>
</tr>
<tr>
<td></td>
<td>-0.78 ± 0.11</td>
<td>0.42 ± 0.79</td>
<td>48.58 &lt;0.001</td>
</tr>
<tr>
<td>Dialysis adequacy (Kt/V urea)</td>
<td>Exercise group (n = 9)</td>
<td>Control group (n = 9)</td>
<td>Group</td>
</tr>
<tr>
<td></td>
<td>0.06 ± 0.11</td>
<td>0.01 ± 0.13</td>
<td>6.92 0.01</td>
</tr>
<tr>
<td>SPPB (0-12, score)</td>
<td>0.67 ± 1.00</td>
<td>0.42 ± 0.79</td>
<td>15.38 &lt;0.001</td>
</tr>
<tr>
<td>SMM (kg)</td>
<td>Exercise group (n = 9)</td>
<td>Control group (n = 9)</td>
<td>Group</td>
</tr>
<tr>
<td></td>
<td>-0.59 ± 1.06</td>
<td>-1.43 ± 1.14</td>
<td>2.64 0.11</td>
</tr>
<tr>
<td>Body fat (%)</td>
<td>Exercise group (n = 9)</td>
<td>Control group (n = 9)</td>
<td>Group</td>
</tr>
<tr>
<td></td>
<td>1.46 ± 3.24</td>
<td>1.15 ± 2.87</td>
<td>2.21 0.15</td>
</tr>
<tr>
<td>LLM (kg)</td>
<td>Exercise group (n = 9)</td>
<td>Control group (n = 9)</td>
<td>Group</td>
</tr>
<tr>
<td></td>
<td>-2.62 ± 1.24</td>
<td>-2.49 ± 2.90</td>
<td>0.12 0.73</td>
</tr>
<tr>
<td>PCS</td>
<td>Exercise group (n = 9)</td>
<td>Control group (n = 9)</td>
<td>Group</td>
</tr>
<tr>
<td></td>
<td>8.50 ± 6.46</td>
<td>-1.71 ± 11.18</td>
<td>6.46 0.02</td>
</tr>
<tr>
<td>MCS</td>
<td>Exercise group (n = 9)</td>
<td>Control group (n = 9)</td>
<td>Group</td>
</tr>
<tr>
<td></td>
<td>2.46 ± 9.18</td>
<td>0.83 ± 10.89</td>
<td>1.49 0.23</td>
</tr>
</tbody>
</table>

Values are presented as mean ± standard deviation. G, group (exercise vs. control); LLM, lower leg muscle mass; MCS, mental component summary; PCS, physical component summary; QoL, quality of life; SMM, skeletal muscle mass; SPPB, short physical performance battery. Difference = value at the 12th week – value at baseline Kt/V. K = dialyzer’s capacity to clear urea at the blood flow rate, t = treatment time, and V = distribution volume of urea.

*F-score calculated using two-way analysis of covariance (ANCOVA) adjusted by dialysis vintage and baseline frailty score.
dialytic aerobic exercise program and nutritional support program in a larger, multicenter population.

**Conflicts of interest**

All authors have no conflicts of interest to declare.

**Funding**

None.

**Data sharing statement**

The data presented in this study are available on request from the corresponding author.

**Authors’ contributions**

Conceptualization, Data curation, Investigation, Methodology: all authors
Formal analysis: SK, HJP
Writing–original draft: all authors
Writing–review & editing: all authors
All authors read and approved the final manuscript.

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**References**

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새로운 점면승부

· 심혈관계 사망 위험 38% 감소
· 우수한 HbA1c 강하 효과

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자다인듀오(Empagliflozin/metformin-HCl) 25mg(Empagliflozin 25mg, Metformin-HCl 500mg)
자다인듀오(Empagliflozin/metformin-HCl) 50mg(Empagliflozin 50mg, Metformin-HCl 1,000mg)
자다인듀오(Empagliflozin/metformin-HCl) 75mg(Empagliflozin 75mg, Metformin-HCl 1,500mg)
자다인듀오(Empagliflozin/metformin-HCl) 100mg(Empagliflozin 100mg, Metformin-HCl 2,000mg)
자다인듀오(Empagliflozin/metformin-HCl) 150mg(Empagliflozin 150mg, Metformin-HCl 2,500mg)
자다인듀오(Empagliflozin/metformin-HCl) 200mg(Empagliflozin 200mg, Metformin-HCl 3,000mg)

자다인(Diabetes mellitus) 10mg, 25mg
자다인듀오(Empagliflozin/metformin-HCl) 10mg, 25mg(Empagliflozin 10mg, Metformin-HCl 300mg)
자다인듀오(Empagliflozin/metformin-HCl) 25mg(Empagliflozin 25mg, Metformin-HCl 500mg)
자다인듀오(Empagliflozin/metformin-HCl) 50mg(Empagliflozin 50mg, Metformin-HCl 1,000mg)
자다인듀오(Empagliflozin/metformin-HCl) 75mg(Empagliflozin 75mg, Metformin-HCl 1,500mg)
자다인듀오(Empagliflozin/metformin-HCl) 100mg(Empagliflozin 100mg, Metformin-HCl 2,000mg)
자다인듀오(Empagliflozin/metformin-HCl) 150mg(Empagliflozin 150mg, Metformin-HCl 2,500mg)
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References

미쎄라®와 렌벨라®가 한독으로 하나가 되었습니다.
1. The 1st launched medicine of Calcium polystyrene sulfonate in Korea

2. The most prescribed treatment agent of Hyperkalemia in Korea

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2. 2019 MAT IQVIA DATA 기준(국내 고갈혈증 치료제 판매량)

카랄리메트 산과실

【해설】해설 그리고설명 부분으로 3개의 아래의 내용을 추가합니다. 1. 치료사례에 상관없이 체증과 신장질환에 대해 2. 치료사례에 상관없이 체증과 신장질환에 대해 3. 치료사례에 상관없이 체증과 신장질환에 대해.

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Biweekly

Monthly

INDICATIONS
1. Normoanemia
2. Chemotherapy-induced anemia in solid cancer patients

DOSEAGE AND ADMINISTRATION
- Normoanemia patients
  - Initial dose: The usual dose of NESP in adults 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 11-40 µg as darbepoetin alfa (parenteral reconstituted), to be administrated as a single intravenous injection once weekly. If elevation of anemia is maintained by once weekly injection, the frequency of administration can be changed to once every two weeks with an initial dose set to be two-fold of the dose in the once weekly injection. In this case, the usual dose in adult patients is 30-120 µg administrated as a single intravenous injection once every two weeks. In all cases, the dose should be adjusted in view of the degree of anemic symptoms and the patient's age, and should not exceed 180 µg as a single injection. The target of anemia correction is around 11 g/dL of hemoglobin level.

- Dialysis patients and patients with chronic kidney disease not on dialysis
  - Initial dose: When correction of anemia is achieved, the usual dose of NESP in adult patients is 0.2-0.5 µg/kg as darbepoetin alfa (parenteral reconstituted), to be administrated as a single intravenous injection once weekly. If elevation of anemia is maintained by once weekly injection, the frequency of administration can be changed to once every two weeks with an initial dose set to be two-fold of the dose in the once weekly injection. In this case, the usual dose in adult patients is 30-120 µg administrated as a single intravenous injection once every two weeks. In all cases, the dose should be adjusted in view of the degree of anemic symptoms and the patient's age, and should not exceed 180 µg as a single injection. The target of anemia correction is around 11 g/dL of hemoglobin level.

- Hemodialysis patients and patients with chronic kidney disease not on dialysis
  - Initial dose: When correction of anemia is achieved, the usual dose of NESP in adult patients is 30-120 µg as darbepoetin alfa (parenteral reconstituted), to be administrated as a single intravenous injection once every two weeks. If elevation of anemia is maintained by once every two weeks injection, the frequency of administration can be changed to once every four weeks with an initial dose set to be two-fold of the dose in the once every two weeks injection. In this case, the usual dose in adult patients is 0.07-0.35 µg/kg as darbepoetin alfa (parenteral reconstituted), to be administrated as a single intravenous injection once every four weeks. If elevation of anemia is maintained by once every four weeks injection, the frequency of administration can be changed to once every two weeks with an initial dose set to be two-fold of the dose in the once every four weeks injection. In this case, the usual dose in adult patients is 30-120 µg administrated as a single intravenous injection once every two weeks. In all cases, the dose should be adjusted in view of the degree of anemic symptoms and the patient's age, and should not exceed 180 µg as a single injection. The target of anemia correction is around 11 g/dL of hemoglobin level.

- Precautions related to Dose and Administration
1. Initial dose at the switching from erythropoiesis preparations: When NESP is started in substitution for an erythropoiesis preparation, the dose and the frequency of administration should be determined on the basis of the dose of the erythropoiesis preparation that has been used. See the table (package insert).
2. Patients who have been treated with an erythropoiesis preparation twice weekly or three times weekly: Calculate the total dose of the erythropoiesis preparation administrated during the week before the switching, and then determine the initial dose of NESP according to the table below. The treatment should be started on once weekly basis. See the insert insert.
3. Dose adjustment: If dose adjustment is required (for example, when the appropriate increase in the hemoglobin concentration or the hematocrit levels can not be achieved in correction phase, or when the hemoglobin concentration or the hematocrit level deviates from the target range for successive two weeks in maintenance phase), the dose should be increased or decreased according to the table below. Any dose increase should be performed step by step in principle.

PRECAUTIONS
See the package insert.

STORAGE
Store in a tightly closed container at 2-8 °C and avoid freezing.

PACKAGING
1 µg/bag, 10 µg/bag, for NESP 20µg, 50µg, 100µg, 120µg, respectively.

MANUFACTURED BY:
Thea Pharmaceutical Co., Ltd.
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Kyowa Hakko Kirin Co., Ltd.
120-1 Nagahara-machi, Takada-ku, Gunma, Japan

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