Intestinal microbiota and kidney diseases
Nephrotoxicity of novel cancer agents
Copeptin levels and treatment responses in patients with symptomatic hyponatremia
Urinary exosomal microRNA profiling in type 2 diabetes patients
The role of hemodiafiltration in hemodialysis patients
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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Fighting COVID-19: The role of a COVID-19 Task Force Team

Hayne Cho Park, Young-Ki Lee, Jang-Hee Cho, Sang-Ho Lee, Dong Ki Kim, Seong Nam Kim, Chul-Woo Yang; on behalf of the Korean Society of Nephrology COVID-19 Task Force Team

The image on the front cover: Cho et al showed the expression patterns of urinary exosomal miRNAs from nondiabetic controls and type 2 diabetic participants who were grouped according to their medication with DPP4i or sulfonyluria. Please see the text for more details (pp. 383-391).
Arginine vasopressin (AVP) is a major regulating hormone in the body fluid homeostasis. Disorders of body fluid homeostasis may result in hyper- or hypoosmolar conditions. A typical example of hyper-osmolar disorders related to AVP is a diabetes insipidus, which is caused by impaired AVP synthesis (central diabetes insipidus) or impaired action in the kidney (nephrogenic diabetes insipidus). Hypoosmolar disorders include heterogeneous disease entities, such as syndrome of inappropriate antidiuresis (SIAD), and are largely related to dysregulated secretion of AVP. As disorders of body fluid homeostasis are closely related to AVP secretion imbalance, direct measurement of AVP to delineate the underlying pathophysiology has been tried. Indeed, plasma AVP levels substantially improve the diagnostic accuracy in a certain clinical context [1]. Nevertheless, the direct measurement of AVP has not been adopted in routine practice, mainly because of difficulties in specimen handling [2,3].

Copeptin is secreted from the posterior pituitary as a precursor protein pre-provasopressin together with AVP and neurophysin II [4]. Copeptin is a peptide consisting of 39-amino acids, with a molecular weight of approximately 5 kDa [4,5]. Copeptin is very stable ex vivo, and easy to measure with sandwich immunoassay [5]. The main stimuli of the copeptin secretion are the same as those of AVP—the osmotic and other nonosmotic stimuli [6]. Although its physiological function is uncertain, the role of copeptin as a surrogate of AVP has been highlighted, as it is secreted in an equimolar amount to AVP. The use of copeptin is best illustrated in the differential diagnosis of polyuria-polydipsia syndrome (central and nephrogenic diabetes insipidus, and primary polydipsia), which has been suggested by Timper et al. [1]. Combined measurement of random and hypertonic saline-stimulated copeptin provides high diagnostic accuracy of 96% in the differential diagnosis of central diabetes insipidus from primary polydipsia, suggesting the diagnostic value of copeptin in hyperosmolar conditions [1]. On the other hand, the use of copeptin in the hypoosmolar disorder has been not been established until now.

In this regard, Go et al. [7] conducted analyses from a total of 100 participants in a prospective cohort to investigate the role of copeptin as a biomarker for the diagnosis and
prognosis in hypoosmolar disorders. All participants were defined as having symptomatic hyponatremia (corrected serum sodium of ≤125 mmol/L) and were treated with hypertonic saline, where mean serum sodium and median copeptin levels were 117.9 and 16.9 pmol/L, respectively. In the analyses to evaluate the copeptin levels as a marker for responses to hypertonic saline treatment in hyponatremic patients, low (below-median) copeptin levels at the baseline were associated with a significantly higher target correction rate in 6 hours (adjusted odds ratio [OR], 2.97; 95% confidence interval [CI], 1.16–7.64; p = 0.02) and 24 hours (adjusted OR, 6.21; 95% CI, 1.67–23.09; p = 0.006) after treatment start. Meanwhile, low copeptin levels at 24-hour after treatment was associated with a significantly higher overcorrection rate in 48-hour after treatment (adjusted OR, 18.00; 95% CI, 1.59–203.45; p = 0.02). The authors presented a plausible explanation for these findings that low baseline copeptin may indicate less chance of previous hyperosmolar or hypovolemic stimuli, thereby enhancing the response to a hypertonic saline infusion (Table 1). The authors also suggested that a low copeptin level at 24 hours after treatment may indicate that a greater excretion of free water can occur to augment the effect on serum sodium level by the same amount of hypertonic saline (Table 1).

In the current study, Go et al. [7] also investigated the usefulness of copeptin for differentiating etiologies of hyponatremia. The participants were classified into five categories, based on the patient’s history, physical examination, and laboratory test results: (1) decreased extracellular fluid (ECF) volume due to renal Na loss (e.g., diuretics, especially thiazides); (2) decreased ECF volume due to nonrenal sodium loss (e.g., gastrointestinal Na loss or third spacing: vomiting, diarrhea, or malnutrition); (3) increased ECF volume (e.g., heart failure, liver cirrhosis, and nephrotic syndrome); (4) normal ECF volume with adrenal insufficiency; and (5) normal ECF volume fulfilling the essential criteria for SIAD. Although the ratio of copeptin-to-urine sodium improved the differential diagnosis of hyponatremic patients with insufficient effective circulatory volume from the others, the authors were not able to present any cutoff values of copeptin levels to discriminate the etiologies of hyponatremia, due to widely overlapping copeptin levels among the different etiologies of hyponatremia and large variability within a single category. This finding is in agreement with a previous report [8] and seems clear that hyponatremia is not solely dependent on inappropriate AVP secretion, but also other factors, such as medications, volume status, or stress [9].

The cost-effectiveness of copeptin measurement in hyponatremic patients is a remaining question, which should be considered for routine practice. As it is still important to repeatedly measure serum sodium level in the treatment of hyponatremic patients, copeptin should be measured in addition to serum sodium measurement. Further, although osmotic demyelination syndrome is obviously a dreaded complication of overcorrection in the treatment of hyponatremia, its frequency is rare [10]. Hence, it should be validated whether the cost of routine copeptin measurement could be balanced by the prevention of osmotic demyelination syndrome.

In summary, Go et al. [7] suggested a novel role of copeptin as a biomarker for the prediction of treatment response in hyponatremia. The authors demonstrated that low copeptin levels at the baseline are associated with a significantly higher target correction rate in 6 and 24 hours after hypertonic saline treatment start, and that low copeptin levels at 24-hour after hypertonic saline treatment is associated with a significantly higher overcorrection rate in the next 24 hours. The cost-effectiveness of copeptin measurement in hyponatremic patients is a remaining question requiring further consideration.

Table 1. Interpretation of plasma copeptin level during hypertonic saline treatment of hyponatremic patients, suggested by Go et al. [7]

<table>
<thead>
<tr>
<th>Plasma copeptin</th>
<th>Low</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>Putative status of plasma AVP</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>Interpretation</td>
<td>• Baseline: Less chance of previous hyperosmolar or hypovolemic stimuli → Enhanced response to a hypertonic saline infusion</td>
<td>• Baseline: More chance of previous hyperosmolar or hypovolemic stimuli → Poor response to a hypertonic saline infusion</td>
</tr>
<tr>
<td></td>
<td>• 24-hour after hypertonic saline treatment: Greater excretion of free water → Increased risk of overcorrection by the same amount of hypertonic saline</td>
<td>• 24-hour after hypertonic saline treatment: Less excretion of free water → Decreased risk of overcorrection by the same amount of hypertonic saline</td>
</tr>
</tbody>
</table>

Note that low and high copeptin levels indicate below and above median copeptin level (16.9 pmol/L), respectively.

AVP, arginine vasopressin.
Conflicts of interest

All authors have no conflicts of interest to declare.

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References

Online hemodiafiltration (HDF) is the most technologically advanced renal replacement therapy, combining convective and diffusive solute removal. Online HDF removes a larger volume of small and middle molecule uremic toxins compared to conventional hemodialysis (HD). Recent clinical trials demonstrated that HDF improves patient survival when adequate convection volumes are achieved [1,2]. Online HDF is more complex than conventional HD. Various modes of online HDF, differing by the site of replacement fluid infusion, are in use. The replacement fluid can be infused into the tubing downstream of the dialyzer (postdilution), upstream of the dialyzer (predilution), both upstream and downstream (mixed dilution), or into the middle of the dialyzer blood pathway (mid-dilution). Each has its strengths and limitations (Table 1).

Postdilution mode is the most common method of fluid substitution in online HDF. Postdilution HDF is the most effective method in terms of solute removal. However, it can increase the viscosity of the blood before fluid substitution, which results in deposition of plasma proteins on the membrane surface, clogging of membrane pores, increased transmembrane pressure (TMP), and occlusion of dialyzer blood channels [1]. Hemoconcentration generally limits the filtration fraction to 20%–25% of the blood flow rate in postdilution HDF [3]. However, modern HDF machines have the option to run TMP-controlled mode during HDF by adapting the substitution flow according to the blood viscosity in the dialyzer [4]. Filtration fraction up to 30% can be achieved with TMP-controlled mode without excessive hemoconcentration. However, the probabilities of clotting and protein deposition are increased when blood flow is interrupted. For that reason, a high blood flow rate (typically ≥350 mL/min) and a well-functioning vascular excess (arteriovenous fistula blood flow of ≥600 mL/min) are prerequisites for successful high-volume postdilution HDF [5].

On the other hand, the hemoconcentration associated with postdilution HDF can be avoided by infusing the replacement fluid upstream of the dialyzer in predilution HDF [6]. This reduces the risks of clotting and protein deposition and allows much higher ultrafiltration rates up to 100% of the blood flow rate [3]. Despite achieving higher...
ultrafiltration rates, predilution HDF reduces the efficiency of both diffusive and convective solute removal because predialysis solute concentrations are decreased or diluted by upstream infusion of substitution volume. For equivalent clearance with the postdilution method, the ultrafiltration rate needs to be increased in predilution HDF at least two times greater than that of postdilution HDF.

In mixed dilution HDF, replacement fluid is substituted both upstream and downstream of the dialyzer. This combines the beneficial effects of both predilution and postdilution modes to optimize solute removal. The TMP-controlled mode automatically adjusts and controls the infusion ratio between predilution and postdilution as well as the total infusion volume. Mixed dilution HDF can maximize the total infusion volume while reducing blood hyperviscosity. Mixed dilution HDF results in higher convective removal of small and middle molecule uremic toxins than predilution HDF while maintaining the optimal pressure conditions within the dialyzer. Therefore, mixed dilution HDF can be a good alternative to compensate for the drawbacks of predilution or postdilution HDF modes. Despite these advantages of mixed dilution HDF, few studies have compared the efficacy of mixed dilution HDF versus other HDF modes.

In this issue of *Kidney Research and Clinical Practice*, Park et al. conducted a randomized controlled trial to compare convection volume and solute clearance between predilution HDF and mixed dilution HDF in patients receiving maintenance HD. The mixed dilution mode was not inferior to the predilution mode considering effective convection volume (51.5 ± 9.0 L/session vs. 41.0 ± 10.3 L/session, respectively). In addition, mixed dilution HDF showed higher clearance of β2-microglobulin compared to predilution HDF. The solute removal rate correlates well with convection volume when performing HDF. Although the absolute convection volume was greater in predilution HDF, the effective convection volume from mixed dilution HDF was approximately 20% higher than that of predilution HDF. Since predilution HDF uses twice as much replacement fluid as the postdilution mode, the effective convection volume for mixed dilution HDF can be calculated as follows as the authors suggested: effective convection volume = substitution volume in predilution mode + (2 × substitution volume in postdilution mode) + ultrafiltration volume.

In this regard, the effective convection volume can be used instead of absolute convection volume when comparing the convection volumes between predilution and mixed dilution HDF.

Previous studies well demonstrated an inverse relationship between the convection volume during HDF and the mortality risk. In postdilution HDF, the substitution volume of ≥23 L/session is currently recommended. Recently, a few studies evaluated the optimal dose of substitution volume for predilution HDF for improving patient survival. The study conducted by the Japanese Society for Dialysis Therapy found that predilution HDF was associated with improved survival compared to conventional HD with a trend toward improved cardiovascular survival. Patients treated with high substitution volumes (≥40 L/session) had improved all-cause and cardiovascular survival compared to those treated with lower substitution volumes (<40 L/session). The optimal substitution volume associated with improved overall survival was estimated to be 50.5 L per session for predilution HDF. However, the optimal convection volume for mixed dilution HDF remains unknown.

| Table 1. Strengths and limitations of online HDF modes |
|-----------------|-----------------|-----------------|
| **Mode of HDF** | **Postdilution** | **Predilution** | **Mixed dilution** |
| **Advantages**  | • Effective in solute clearance & removal | • Decrease hematocrit and TMP | • Avoid shortcomings of both predilution & postdilution modes |
|                 | • Decrease consumption of replacement solution | • Reduce the risks of clot formation and protein deposition in dialyzer | |
|                 | • Decrease consumption of replacement solution | • Is available in relatively low blood flow rate | |
|                 | • Decrease consumption of replacement solution | • Reduce membrane stress | |
| **Disadvantages** | • Increase hematocrit and TMP | • Reduce solute clearance and removal | • Require specific HDF machine with two infusion pumps |
|                 | • Increase the risks of clot formation and protein deposition in dialyzer | • Increase consumption of replacement solution | • Require specific blood tubing set |
|                 | • Require relatively high blood flow rate | | |
|                 | • Increase membrane stress (potential albumin leakage) | | |

HDF, hemodiafiltration; TMP, transmembrane pressure.
since no studies have examined clinical outcomes according to convection volume.

Meanwhile, HDF can lead to significant albumin loss into the dialysate, especially with a highly permeable membrane and high convection volume. Data on albumin loss during HDF are limited and conflicting. Although the serum albumin levels were not different between the predilution and mixed dilution groups, the exact amount of albumin loss via the dialyzer was not evaluated in this study. However, a previous study by Potier et al. [10] demonstrated a higher level of albumin loss in mixed dilution mode compared to predilution mode. Although the degree of albumin loss can be greater in mixed dilution mode, it was within the safety margin (<5 g/session).

High-volume HDF is indicated for patients with end-stage renal disease. The clinical benefits of high-volume HDF, particularly postdilution HDF, include improved patient survival and cardiovascular outcomes, better intradialytic hemodynamic stability, less inflammation-related or dialysis-related complications, improved derangement in calcium-phosphate homeostasis and less vascular calcification, better preservation of residual renal function, and improved quality of life [1]. Theoretically, postdilution HDF is the most efficient mode for solute removal. However, successful postdilution HDF depends on high blood flow rates, reliable vascular access, adequate anticoagulation throughout the procedure, and the absence of any condition that increases blood viscosity (high hematocrit, cryoglobulinemia, and gammopathies) [3]. When the prerequisites for postdilution HDF are unavailable, predilution or mixed dilution HDF may be the more appropriate modes. Therefore, predilution or mixed dilution HDF may be the preferable option for patients in Asian countries, such as Korea or Japan, who have relatively lower blood flow of arteriovenous access compared to Caucasians.

The optimal dialysis strategy for patients with end-stage renal disease may differ by country and may not be driven by the best evidence but by experience and local center performance. More evidence for a survival benefit of high-volume HDF is still needed. Currently, the mode of HDF should be decided based on the characteristics and needs of the individual patient.

Conflicts of interest

All authors have no conflicts of interest to declare.

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References

Intestinal microbiota and kidney diseases

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Large microbial communities reside in the gut as an endogenous organ and interact with the host physiology through symbiotic relationships, affecting health. Recent advances in high-throughput sequencing techniques have made it possible to better understand these complex microbial communities and their effects on hosts. Animal and clinical studies have provided considerable evidence to show that the microbiota plays an important role in chronic kidney disease, acute kidney injury, nephrolithiasis, and kidney transplantation by altering the functions of the intestinal barrier, regulating local and systemic inflammation, controlling production of metabolic components, and affecting immune responses. Although the exact mechanism underlying the microbial shift and its impact on disease progression remains uncertain, the kidney-gut interaction clearly plays a significant role in onset and progression of kidney disease and, therefore, holds promise as a therapeutic target. Here, we review recent literature pertaining to the bidirectional relationship between microbes and humans in various kidney diseases and discuss the future direction of microbial research in nephrology.

Keywords: Acute kidney injury, Chronic kidney disease, Microbiota, Nephrolithiasis, Transplantation

Introduction

Over 100 trillion microorganisms including bacteria, fungi, and protozoa (collectively called the microbiota) form colonies in the human gut and interact in a complex manner with their host, directly or indirectly affecting host health [1,2]. Microbial species are transferred first from the vaginal canal at birth, and these microbial communities keep changing in response to various environmental stimuli including diet, stress, and antibiotic use. The intestinal microbiota is characterized by significant diversity; however, the microbial composition remains relatively stable over time and is similar within families as well as in individuals from a region with common dietary habits [3,4].

The structure of the microbiota is balanced functionally by commensal or adversarial relationships with the host. Therefore, changes in intestinal microbial balance, known as dysbiosis, are associated with an unbalanced intestinal microbiota with quantitative and qualitative changes in the composition and metabolic functions. Dysbiosis can contribute to pathogenesis in various diseases, including obesity, cancer, diabetes, inflammatory bowel disease, asthma, and cardiovascular disease [5]. In this review, the emerging roles of the intestinal microbiota in various kidney diseases and the future of microbiome research are discussed.
The intestinal microbiota as an endogenous organ

The intestinal microbiota exerts a variety of functions while maintaining a symbiotic relationship with the host. Colonic microbiota ferment non-digestible carbohydrates including dietary fibers, cellulose, and resistant starch to produce short-chain fatty acids (SCFAs; acetate, propionate, butyrate, etc.). SCFAs function as an energy source for colonicocytes, strengthen intestinal barrier integrity, and exert potent anti-inflammatory and immunomodulatory functions [6–8]. The microbiota is involved in the synthesis of various vitamins (vitamin B12, thiamine, riboflavin, and vitamin K) and the metabolism of amino acids [9].

The intestinal microbial community contributes to the development and maturation of the immune system. Defects in the development of gut-associated lymphoid tissue, Peyer’s patches, and mesenteric lymph nodes in germ-free mice indicate the important role of the microbiota in immune system development. Germ-free mice also displayed defective immunoglobulin A production and increased susceptibility to and mortality from certain pathogenic bacteria, suggesting that the microbiota is important in normal physiological immune response [10]. Epithelial cells and immune cells crosstalk with the microbiota and recognize pathogenic microorganisms or their metabolic products and subsequently increase the production of antimicrobial proteins and inflammatory cytokines through activation of the nuclear factor kappa B (NF-kB) pathway. Sustained immune activation by intestinal bacteria acts as a key immune modulator, activating both proinflammatory and counter-regulatory, anti-inflammatory pathways, and the balance among these signals through the induction of various immune cells is important for the maintenance of normal physiology. Homeostasis of immune response signals exchanged between the microbiota and the host is important for development of secondary lymphoid organs [11–14].

Microbial-epithelial interactions also serve to protect and maintain the intestinal barrier by several mechanisms, including preventing pathogens from attaching to intestinal epithelial cells [15], activating anti-inflammatory pathways [16], and regulating mucus properties [17]. The colonization of germ-free mice with a mixture of Lactobacillus strains has been shown to enhance barrier integrity, suggesting that the microbiota is important in maintaining barrier integrity [18]. In addition to metabolic and immune functions, the intestinal microbiota has been shown to contribute to development of the complex enteric nervous system [19].

In summary, as an endogenous organ, the gut and microbiota perform multiple physiological roles in the host, including metabolism, maintenance of barrier integrity, development of the immune system, immune modulation, and maturation of the enteric nervous system. This knowledge has led to the idea that dysbiosis contributes to the pathogenesis of not only intestinal diseases, but also of various metabolic diseases, cancer, inflammatory diseases, and cardiovascular diseases, and that strategies targeting the microbiota hold promise in prevention and treatment of these diseases.

Intestinal microbiota and chronic kidney disease

Several studies have shown the presence of dysbiosis in animal models and humans with chronic kidney disease (CKD) [20,21]. In CKD patients, uremia, intestinal edema, prolonged colonic transit time, dietary restriction of fiber, metabolic acidosis, and frequent use of antibiotics can directly or indirectly contribute to dysbiosis and an altered intestinal environment [21–26].

In an early study, Vaziri et al. [20] found significant differences in the abundance of 190 bacterial operational taxonomic units between end-stage kidney disease (ESKD) and healthy controls. They showed that the abundance of saccharolytic microorganisms such as Lactobacillus and Bifidobacteria decreases in ESKD, whereas that of proteolytic microorganisms such as Clostridium and Bacteroides increases. Although urea supplementation was unable to provoke similar dysbiosis in a mouse model of CKD, accumulation of uremic toxins could negatively affect the growth of commensal bacteria and might be responsible for dysbiosis [21]. A recent study on Chinese ESKD patients reported a reduction of butyrate-producing bacteria including Roseburia, Faecalibacterium, Coprococcus, and Prevotella [27]. Wong et al. [28] showed the relative expansion of bacterial families producing urease, indole, and p-cresol forming enzymes, while the bacterial families producing SCFAs were reduced. Given the toxic effects of these metabolites and the beneficial effects of SCFA, dysbiosis in patients with ESKD is likely to play certain roles in the development of systemic inflammation and uremic symptoms.

The intestinal barrier, composed of a single epithelial lining...
and mucus layer, prevents transmigration of luminal contents while permitting selective absorption of nutrients, water, and electrolytes. Dysbiosis in CKD has been shown to be associated with barrier disruption that potentially leads to transmigration of bacteria or their metabolites [29–32]. Studies have shown the increased permeability to exogenous polyethylene glycol or increased circulating endotoxin levels in patients with CKD, suggesting enhanced transmigration through a disrupted barrier [29,30]. Urea directly provokes a decrease in transepithelial resistance of cultured enterocytes, and intestinal edema and regional ischemia in CKD could lead to development of leaky gut [31]. At the molecular level, intestinal barrier disruption has been associated with decreased expression of heat shock protein 70 (HSP70) and claudin-1, increased expression of pore-forming claudin-2, and epithelial apoptosis in the colon of a mouse model of CKD [31,32]. In a recent study on CKD, dysbiosis and barrier disruption were found to be linked to an altered mucosal immune response through activation of inflammatory macrophages with production of inflammatory cytokines [32]. This could potentially lead to systemic inflammation and aggravated cardiovascular/renal complications [30,32–34].

Uremic toxins derived from the gut are associated with poor outcomes of CKD. Protein-bound uremic toxins such as p-cresyl sulfate or indoxyl sulfate, produced by fermentation of tyrosine or tryptophan by intestinal bacteria, are excreted by tubular secretion in the kidney, leading to elevated blood levels in patients with CKD. Indoxyl sulfate has been reported to increase transforming growth factor-β expression and oxidative stress, promote smooth muscle cell calcification, and cause endothelial cell dysfunction. These protein-bound uremic toxins ultimately lead to increased risk of cardiovascular diseases, mortality, and CKD progression [35–38]. Trimethylamine N-oxide (TMAO), another uremic toxin derived from bacterial metabolism of quaternary amines, has been reported to be associated with increased mortality in patients with CKD [39,40].

Based on these findings, therapeutic strategies targeting the microbiota, including prebiotics, an indigestible food ingredient that induces activation of microorganisms; probiotics, living microorganisms; synbiotics, a combination of prebiotics and probiotics; and adsorbents, which adsorb toxic substances, might be useful in the treatment of CKD. AST-120, an insoluble enteric carbon adsorbent that can suppress the accumulation of indoxyl sulfate, has been shown to delay dialysis initiation and to slow the reduction in glomerular filtration rate despite negative results shown in a recent double-blind controlled trial [41–44]. Probiotic supplementation has recently been shown to improve glucose homeostasis with a decrease of markers of inflammation and oxidative stress in diabetic hemodialysis patients [45]. In a randomized, double-blind, placebo-controlled crossover trial on patients with CKD, synbiotics showed beneficial effects on serum p-cresyl sulfate reduction associated with favorable modifications of fecal microbiota [46]. However, clinical research published to date does not provide strong evidence of the efficacy of pre- or probiotics in patients with CKD, possibly owing to the limited number of studies and small sample sizes [47].

Intestinal microbiota and acute kidney injury

Unlike CKD, few studies have analyzed the kidney-gut crosstalk in acute kidney injury (AKI). In a recent study by Yang et al. [49], intestinal dysbiosis, characterized by an increase in Enterobacteriaceae and a decrease in Lactobacilli and Ruminococcaceae, was induced on day 1 in a mouse ischemia/reperfusion injury (IRI) model. Furthermore, the authors showed that germ-free mice transplanted with feces from IRI mice developed more severe postischemic kidney injury compared to controls. These results show that sudden changes in kidney function or injury are sufficient to provoke dysbiosis in a short time period, and the changes in microbial composition might serve as an important modifier.
of AKI. In support of these findings, the authors also showed that depletion of the microbiota using a combination of nonabsorbable antibiotics before IRI significantly reduced posts ischemic injury. In the same study, the authors showed that kidney IRI-induced dysbiosis is associated with leaky gut, bacterial translocation, and reduced fecal SCFA levels as well as activation of both innate and adaptive immune responses. Neutrophils and proinflammatory macrophages were shown to accumulate in the lamina propria of the large intestine, and the Th17 pathway was shown to be activated in the small intestine. Microbial depletion led to inhibition of Th17 activation and decreased proinflammatory macrophage accumulation in the intestine; simultaneously, it increased the levels of regulatory T cells and M2 macrophages in both the kidney and large intestines. These data suggest that an altered mucosal immune response associated with dysbiosis is an important player in the kidney-gut crosstalk in AKI [49]. Additionally, the data also indicate a shift in the microbiota and in mucosal immunity toward dysbiosis and proinflammatory changes in IRI-induced AKI, which could further aggravate kidney injury.

The gut-kidney crosstalk in AKI is supported by several recent studies that demonstrated the renoprotective effects of probiotics or gut microbiota-derived metabolites [50,51]. Lactobacillus salivarius BP121 was shown to mitigate cisplatin-induced kidney injury by decreasing kidney inflammation, oxidative stress, and serum levels of uremic toxins [50]. Among gut microbiota-derived metabolites, administration of SCFAs (acetate, propionate, and butyrate) mitigated kidney injury, and the renoprotective effects of these molecules were associated with increased autophagy, decreased inflammation, and decreased oxidative stress [51]. In a study by Nakade et al. [52], gut microbiota-derived D-serine was shown to attenuate tubular damage in AKI. Altogether, these data suggest that the gut microbiota is important and could serve as a therapeutic target in AKI. However, further studies that enhance our understanding of the complex kidney-gut interplay are necessary to apply these findings in the treatment of human AKI.

Intestinal microbiota and nephrolithiasis

Nephrolithiasis is a relatively common kidney disease reported in 6.0% of the male population and 1.8% of the female population in Korea [53]. The incidence of the disease increases approximately three fold in individuals with a family history of the disease [54]. The genetic predisposition or environmental conditions shared by family members can influence disease pathophysiology. The concentrations of urinary calcium, oxalate, phosphate, and uric acid play an important role in stone formation, and emerging evidence indicates active participation of the gut/microbiome in the pathogenesis of nephrolithiasis. Oxalate, which is a constituent of the most common type of kidney stone, is excreted via the urine after absorption in the intestine. Lack of commensal bacteria with oxalate-degrading activity has been shown to be associated with stone formation. In uric acid excretion, one-third of the uric acid is degraded by intestinal uricolyis, also suggesting the possible role of intestinal microbiota in the pathogenesis of uric acid stones. Observations have shown that the overall microbial composition in patients with kidney stones is considerably different from that in healthy controls, which further support the intestinal microbiota as an important contributor to stone formation [55-56]. According to a recent systematic review of 25 studies, increase in Enterobacteriaceae and Streptococcaceae and decrease in Prevotellaceae, Prevotella, and Roseburia are characteristic of the microbiota in patients with stone formation [56]. Oxalobacter formigenes are gram-negative, anaerobic bacteria that degrade and, therefore, reduce absorption and subsequent urinary excretion of oxalate, leading to a potential protection against calcium oxalate stone formation [57,58]. A case-controlled study in which 47 patients with recurrent calcium oxalate stones were compared with 259 controls showed that colonization with O. formigenes reduced the risk of recurrent calcium oxalate stone formation by approximately 70% [58]. However, even though that preliminary study conducted in a small sample size showed that supplementation with O. formigenes significantly reduced urinary or plasma oxalate level, a recent randomized trial on patients with primary hyperoxaluria reported no beneficial effects of O. formigenes supplementation [59,60].

Although single microbial strains might not sufficiently lower the pathological risk of oxalate metabolism, therapeutic trials on microbiota modulation strategies, such as treatment with a combination of different microbial strains, diet control, and fecal transplantation, hold promise [61-63], and the intestinal environment can be considered a novel therapeutic target in nephrolithiasis.
Intestinal microbiota and kidney transplantation

Dysbiosis in patients with CKD has emerged as an important contributing factor in chronic inflammation and increased cardiovascular risk. However, considering the more complex clinical conditions of transplant recipients, such as improvement of uremia, administration of immunosuppressive drugs, and frequent use of antibiotics, understanding the role of the intestinal microbiota and its interaction with the host immune system or patient outcomes poses a significant challenge [64]. Fricke et al. [65] reported drastic changes in the microbiota in patients in the first month after kidney transplantation (KT) in association with improvement of renal function upon administration of prophylactic antibiotics and high-dose immunosuppressants. However, persistent exposure to immunosuppressants and various posttransplant complications can lead to substantial longitudinal changes in microbial composition [66].

In KT recipients, the balance between activation of alloimmune immune responses and suppression using immunosuppressants is a key factor in determining graft outcomes. Therefore, considering the important immune-modulatory role of intestinal microbiota and various immune cells, it is possible that alterations in the number and composition of microbiota could have a huge impact on graft outcome including transplant rejection and posttransplant infection.

Lee et al. [67] reported that the abundance of Enterococcus in rectal stool samples was associated with urinary tract infection, and the absence of Bacteroides, Ruminococcus, Coprococcus, and Dorea was associated with post-renal transplant diarrhea. In addition to intestinal microbiota, Diaz et al. [68] have demonstrated that long-term administration of immunosuppressants facilitates oral colonization of opportunistic pathogens, leading to increased posttransplant secondary infections.

Other observations in which microbial distance between donor and recipient showed a significant negative correlation with 6-month estimated glomerular filtration rate, suggesting that intestinal microbiota similarity might affect graft outcome [69]. In the same study, the dissimilarity of microbiota between donor and recipient was associated with increased posttransplant infection rate. Moreover, certain microbial species have been shown to affect the blood levels of immunosuppressants by modulating drug pharmacokinetics, which might explain the interindividual differences in tacrolimus dose administered for achieving therapeutic efficacy [70].

The presence of certain species in the microbiota prior to KT has been reported to be significantly associated with subsequent rejection, suggesting a possible role for microbiota in immune modulation [66]. However, despite growing evidence, the effects exerted by the microbial community on immune activation, rejection, or pharmacokinetics remain largely unknown. Future studies assessing the impact of longitudinal changes in individuals and the role of specific microbes in a larger population will help elucidate the role of the microbiota in KT.

Conclusions

Advances in high-throughput sequencing technology have provided unprecedented insights into the complex microbial communities of the various mucosal surfaces. Similar to several other metabolic and chronic inflammatory conditions including diabetes, obesity, or rheumatoid arthritis, emerging data have demonstrated that alteration of intestinal microbiota is associated with a variety of kidney diseases. Dysbiosis and associated barrier dysfunction, bacterial translocation, and an altered immune response were shown to play important roles in both AKI and CKD. Several strains of bacteria participating in degradation of oxalate have been shown to be associated with oxalate stone formation, and recent studies also suggest the presence of more complex interactions between the microbiota and kidney in transplantation recipients (Fig. 1). However, many of these studies only show a correlation, and causal relationship remains largely unclear. To develop microbiota-targeted therapeutics, further studies unraveling the mechanisms underlying the shifts of microbiota, metabolites, and their impact on disease pathogenesis are needed.

Despite promising data from several clinical trials testing the effect of pre-, pro-, and symbiotics in various kidney diseases, they are derived from studies that enrolled only small numbers of patients; also, the results are inconsistent and limited. Various factors such as individual genetic characteristics, race, and environmental factors complicate the interaction between the microbial community and the host, and targeting a single microbial community might not provide sufficient control over complex host and microbial interactions.
Nevertheless, the microbiota of mucosal surfaces is a previously unrecognized factor that can potentially modify pathogenesis and outcome in various kidney diseases. A better understanding of the molecular mechanisms linking altered microbiota and its crosstalk with hosts, as well as improved animal models and analytical techniques, should be developed to facilitate translation of these findings to humans.

**Conflicts of interest**

All authors have no conflicts of interest to declare.

**Authors’ contributions**

Conceptualization: MGK, SKJ
Writing—original draft: MGK, SKJ
Writing—review & editing: All authors
All authors read and approved the final manuscript.

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Nephrotoxicity of cancer therapeutic drugs: Focusing on novel agents

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Kidney injury caused by anticancer agents is a common problem that can interfere with and affect the dose intensity of anticancer therapy, thus restricting patient survival. Recent advances in targeted and immunotherapeutic agents have transformed the landscape of medical oncology, and these agents have been widely employed in clinical practice. While typically associated with favorable toxicity profiles, several novel anticancer drugs present distinctive nephrotoxicities. It remains urgent to closely monitor renal injuries associated with these agents, and medical practitioners should be familiar with general principles for managing nephrotoxicity associated with novel cancer drugs. This review provides an in-depth investigation of the literature and guidelines regarding the prevalence, clinical presentations, mechanisms, and management of nephrotoxicity for each drug.

Keywords: Acute kidney injury, Immune checkpoint inhibitors, Molecularly targeted therapy, Neoplasms, Renal insufficiency

Introduction

In recent decades, advances in cancer chemotherapeutics have improved both the survival and quality of life of patients with cancer. Novel chemotherapeutic agents, such as targeted molecular agents and immunotherapeutics, have been developed and widely adopted in clinical practice [1,2]. Compared to cytotoxic agents, these drugs present fewer conventional adverse events such as alopecia, nausea/vomiting, fatigue, and bone marrow suppression. However, drug-induced kidney injury remains a frequent challenge. A variety of renal complications can occur among patients with malignancy, and these drugs can affect every structural component of the kidney, including the glomerulus, tubules, interstitium, or renal microvasculature via distinct mechanisms, presenting with clinical manifestations ranging from asymptomatic elevation of serum biochemical markers (e.g., creatinine or cystatin C) and electrolyte imbalances to acute kidney injury (AKI) or chronic kidney disease necessitating renal replacement therapy [3]. Furthermore, the nephrotoxic potential of these agents may limit their therapeutic efficacy and increase patient morbidity and mortality. Thus, under-
standing the nephrotoxicity of cancer therapeutics is critical for effectively managing oncologic patients.

The mechanisms underlying drug-induced nephrotoxicity associated with most cancer therapeutic drugs have not been thoroughly investigated or established. Hence, generating appropriate strategies to prevent or minimize nephrotoxic injuries, and to maintain the dose intensity of agents, can be challenging. In the present review, we collate the incidence, risk factors, clinical features, and management of drug-related nephrotoxicity of specific anticancer drugs based on the currently available literature, focusing on targeted molecular therapies and immunotherapies. With the growing usage of novel cancer therapies, oncologists and nephrologists should be aware of the attributes and characteristics of each chemotherapeutic drug. Table 1 summarizes the indications, mechanisms of action, and types of renal involvement of novel anticancer drugs.

### Targeted therapy-induced nephrotoxicity

Molecular targeting anticancer therapies have been developed to exploit the oncogenic addictive nature of cancer and explicitly block the growth and spread of cancer by inhibiting specific molecules or pathways. Typically, these agents are associated with higher response rates than those by cytotoxic agents, with fewer adverse events. However, they have also been associated with various renal injuries.

### Epidermal growth factor receptor inhibitors

Epidermal growth factor receptor (EGFR) is a transmembrane protein, and the binding of EGFR to its ligand results in phosphorylation of the EGFR tyrosine kinase domain, thus activating downstream pathways [4]. The most widely used agents that interfere with EGFR pathways are EGFR

<table>
<thead>
<tr>
<th>Drug</th>
<th>Target or mode of action</th>
<th>U.S. FDA-approved indication</th>
<th>Renal manifestations</th>
<th>Need for dosage adjustment in renal insufficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gefitinib, erlotinib, afatinib, osimertinib, dacomitinib</td>
<td>EGFR TKI</td>
<td>NSCLC</td>
<td>Minimal change disease, membranous nephropathy (rare)</td>
<td>No</td>
</tr>
<tr>
<td>Cetuximab, panitumumab</td>
<td>EGFR mAb</td>
<td>Head and neck cancer, colorectal cancer</td>
<td>Hypomagnesemia</td>
<td>No</td>
</tr>
<tr>
<td>Crizotinib, ceritinib, brigatinib, alectinib, lorlatinib</td>
<td>ALK TKI</td>
<td>NSCLC</td>
<td>Renal cyst (crizotinib), pseudo or true AKI, Acute tubular necrosis</td>
<td>Yes in severe cases</td>
</tr>
<tr>
<td>Imatinib</td>
<td>BCR-ABL and PDGFR TKI</td>
<td>Chronic myelogenous leukemia, gastrointestinal stromal tumor</td>
<td>AKI</td>
<td>Yes</td>
</tr>
<tr>
<td>Dasatinib</td>
<td>BCR-ABL and PDGFR, VEGF TKI</td>
<td>Chronic myelogenous leukemia</td>
<td>AKI, proteinuria, TMA</td>
<td>No</td>
</tr>
<tr>
<td>Bevacizumab, ramucirumab, aflibercept</td>
<td>VEGF ligand binding inhibition</td>
<td>Colorectal cancer, NSCLC</td>
<td>Proteinuria, TMA, hypertension, AKI, glomerulonephropathy</td>
<td>No</td>
</tr>
<tr>
<td>Sunitinib, sorafenib, axitinib, pazopanib</td>
<td>VEGF receptor TKI</td>
<td>RCC, hepatocellular carcinoma</td>
<td>Proteinuria, hypertension, AKI, glomerulonephropathy, TMA</td>
<td>No</td>
</tr>
<tr>
<td>Everolimus, temsirolimus</td>
<td>mTOR inhibitor</td>
<td>RCC, breast cancer, neuroendocrine tumor</td>
<td>Proteinuria, hypertension, AKI, glomerulonephropathy, acute tubular necrosis</td>
<td>No</td>
</tr>
<tr>
<td>Dabrafenib, vemurafenib</td>
<td>BRAF inhibitor</td>
<td>Melanoma</td>
<td>AKI, hypokalemia, hyponatremia</td>
<td>No</td>
</tr>
<tr>
<td>Pembroizumab, nivolumab</td>
<td>PD-1 inhibitor</td>
<td>NSCLC, SCLC, melanoma, RCC, bladder cancer, and so on</td>
<td>AKI, glomerulonephropathy, acute interstitial nephritis</td>
<td>No</td>
</tr>
<tr>
<td>Atezolizumab, durvalumab, avelumab</td>
<td>PD-L1 inhibitor</td>
<td>NSCLC, SCLC, RCC, bladder cancer, and so on</td>
<td>AKI, glomerulonephropathy, acute interstitial nephritis</td>
<td>No</td>
</tr>
<tr>
<td>Ipilimumab</td>
<td>CTLA-4 inhibitor</td>
<td>Melanoma, NSCLC, RCC</td>
<td>AKI, glomerulonephropathy, acute interstitial nephritis</td>
<td>No</td>
</tr>
</tbody>
</table>

AKI, acute kidney injury; ALK, anaplastic lymphoma kinase; BCR-ABL, breakpoint cluster region-Abelson leukemia; BRAF, v-Raf murine sarcoma viral oncogene homolog B; CTLA-4, cytotoxic T-lymphocyte antigen-4; EGFR, epidermal growth factor receptor; mAb, monoclonal antibody; mTOR, mammalian target of rapamycin; NSCLC, non-small cell lung cancer; PD-1, programmed cell death protein-1; PD-L1, programmed death-ligand 1; PDGFR, platelet-derived growth factor receptor; RCC, renal cell carcinoma; SCLC, small cell lung cancer; TKI, tyrosine kinase inhibitor; TMA, thrombotic microangiopathy; U.S. FDA, U.S. Food and Drug Administration; VEGF, vascular endothelial growth factor.
tyrosine kinase inhibitors (EGFR-TKIs) targeting EGFR mutations in non-small cell lung cancer (NSCLC), including gefitinib, erlotinib, afatinib, dacomitinib, osimertinib, and the recently developed lazertinib [5]. EGFR mutations reportedly account for more than 40% of Asian NSCLC cases and approximately 20% of NSCLC cases in Western countries [6]. EGFR-TKIs predominantly undergo hepatic metabolism, with less than 4% undergoing renal excretion; thus, these agents can be safely used in patients with decreased renal function without necessitating dose adjustment [7,8]. In some case reports, these drug families have been safely used in patients with end-stage renal disease receiving hemodialysis [9,10]. Despite their excellent safety profile, rare glomerular injuries such as minimal change disease and membranous nephropathy associated with gefitinib have been reported in a case report series [11,12]. Although these events were mainly reported in Asian patients, whether ethnic differences or specific EGFR-TKIs can be linked to these events remains unknown.

EGFR monoclonal antibodies targeting EGFR, such as cetuximab, panitumumab, or necitumumab, are indicated in patients with colon cancer, NSCLC, and head and neck squamous cell carcinoma; typically, these agents are not associated with a decline in renal function [13]. However, EGFR monoclonal antibodies are well known for their capacity to induce magnesium wasting as these agents prevent EGFR activation in the distal tubule, thus resulting in renal magnesium wasting [14]. One meta-analysis study (n = 3,081) reported that the overall incidence of hypomagnesemia in patients treated with cetuximab was 36%, presenting grade 3 or more hypomagnesemia (5.6%) [15]. Furthermore, the frequency of hypomagnesemia was reportedly higher with panitumumab therapy and was associated with other adverse events such as diarrhea or dehydration. However, hypomagnesemia was not related to serious irreversible complications [16].

**Anaplastic lymphoma kinase inhibitors**

Anaplastic lymphoma kinase (ALK) fusions have been observed in various malignancies, including NSCLC, Hodgkin lymphoma, anaplastic large-cell lymphoma, and sarcoma. ALK fusions have been observed in 4% to 6% of NSCLC cases, and the advent of ALK inhibitors has profoundly altered the management of ALK-positive NSCLC. Currently, ALK inhibitors approved by the U.S. Food and Drug Administration (FDA) include crizotinib, ceritinib, alectinib, brigatinib, and lorlatinib, and these agents are known to be associated with renal cysts, pseudo or true AKI, peripheral edema, and hypophosphatemia.

Although the mechanism implicated in the growth of renal cysts remains to be clarified, crizotinib has been shown to result in renal cysts and to induce renal cyst progression. According to a safety database of 1,375 patients, 9% of patients treated with crizotinib acquired new cysts within 6 months of treatment initiation [17]. Furthermore, 2% of patients with preexisting cysts developed new cysts or experienced enlargement of preexisting cysts. Additionally, the risk of renal cyst formation or progression was increased in Korean patients [17]. As these phenomena have not been observed with other ALK inhibitors, including ceritinib, brigatinib, and lorlatinib, they have been considered specific to crizotinib. However, a recent case described alectinib usage and renal cyst development [18]. As these lesions can be easily mistaken for lung cancer progression or development of primary renal cell carcinoma (RCC), clinical awareness is essential to avoid cessation of an otherwise efficacious drug. Generally, close monitoring of renal cyst development is recommended without dose adjustment or interruption, and most patients can continue ALK inhibitor treatment.

Another interesting observation related to ALK inhibitors is the presence of pseudo or true AKI. A large retrospective analysis of 1,868 patients reported an acute decline in renal function within 2 weeks of crizotinib initiation, with minimal cumulative effects and was mostly reversible after treatment discontinuation [19]. Camidge et al. [20] suggested that the decline in creatinine clearance reflects creatinine excretion rather than true renal injury, thus termed pseudo AKI. An *in vitro* study demonstrated that crizotinib impeded renal creatinine excretion by the organic cation transporter 2 in the proximal tubule [21]. Some patients demonstrate normal glomerular filtration rates when non-creatinine-based measurements (iothalamate assessment) of glomerular filtration rate are performed [20]. Therefore, most patients with elevated serum creatinine levels can continue crizotinib without dose adjustment under close monitoring. However, ALK-TKIs can also induce true kidney injury associated with acute tubular necrosis; thus, the use of a non-creatinine-based assessment of renal function should be considered before the final decision [22,23].
**Breakpoint cluster region-Abelson leukemia and KIT tyrosine kinase inhibitors**

Imatinib mesylate was the first approved TKI that targets the gene product of breakpoint cluster region-Abelson leukemia (BCR-ABL) in chronic myeloid leukemia, with additional activity on KIT and platelet-derived growth factor receptor (PDGFR). Several cases of imatinib-related nephrotoxicity have been reported [24]. Two possible mechanisms have been proposed; tumor lysis syndrome and toxic tubular damage, and tubular damage possibly associated with PDGFR inhibition by imatinib. Among 105 patients treated with imatinib and a median follow-up of 4.5 years, 7% of patients reportedly experienced AKI, with 12% of patients presenting with chronic kidney disease [25]. Treatment duration may be a determinant of the declining glomerular filtration rate. Oncologists and nephrologists should be aware that long-term treatment with imatinib may cause an irreversible and clinically significant decrease in the glomerular filtration rate, as well as chronic kidney disease. Close attention should be paid to avoid the concomitant use of nephrotoxic agents and dehydrating conditions, and clinicians in charge of these patients should regularly monitor renal function.

Dasatinib, a second-generation TKI indicated for chronic myelogenous leukemia, is known to inhibit vascular endothelial growth factor (VEGF), along with BCR-ABL and PDGFR. In a phase I trial (n = 33), 12% of patients developed proteinuria, with 3% presenting grades 3 and 4; the proposed underlying mechanisms include VEGF co-inhibition or podocyte disruption [26–28]. Ochiai et al. [29] reported that dasatinib induced nephrotic syndrome, with complete recovery observed after switching to nilotinib. Switching to imatinib or nilotinib, which are believed to be unrelated to proteinuria development, is currently a popular management strategy for dasatinib-associated proteinuria.

**Vascular endothelial growth factor inhibitors**

VEGF A and VEGF receptors (VEGFR) play a major role in angiogenesis, promoting cancer cell proliferation, migration, and invasion. There are two kinds of VEGF pathway inhibitors: VEGF ligand inhibitors, such as bevacizumab, ramucirumab, and aflibercept; and tyrosine kinase inhibitors that block the VEGFR intracellular kinase domain, including sunitinib, sorafenib, and axitinib. Various renal effects have been observed following treatment with VEGF pathway inhibitors.

Notably, the occurrence of proteinuria after inhibiting VEGF signaling pathways represents the importance of the VEGF pathway in normal kidney functions. Both monoclonal antibodies and TKIs are known to induce proteinuria, with frequency and severity differing slightly between drugs. Among these agents, bevacizumab has been extensively investigated, and frequencies of all proteinuria grades were 21% to 62%, with individuals presenting with grade 3 or more proteinuria comprising 2% to 6.5% [30–32]. The severity of proteinuria appears to be dose-dependent and generally reversible. However, persistent proteinuria is not unusual. Thus, in the case of nephrotic syndrome, bevacizumab must be discontinued permanently [30,33,34]. Underlying diseases, such as chronic kidney disease and RCC, may increase the risk of proteinuria. Furthermore, the combination of cytotoxic chemotherapy may worsen the degree of proteinuria. Regular monitoring via urinary analysis of proteinuria prior to each cycle is recommended [34]. Table 2 summarizes the management of proteinuria. Common glomerulopathies associated with VEGF inhibition include intraglomerular thrombotic microangiopathy, minimal change disease, and focal segmental glomerulosclerosis (FSGS) [35]. The use of angiotensin receptor blockers or angiotensin-converting enzyme inhibitors may be recommended for renoprotection. However, these agents have not been investigated in randomized placebo-controlled prospective trials for the management of VEGF inhibitor-associated proteinuria or glomerulonephropathy [34].

Hypertension has been observed in 8% to 36% of patients, with grade 3 or 4 hypertension ranging from 1.8% to 22% [32,36,37]. Increased risk of hypertension might be dose-dependent and associated with cancer types such as RCC, NSCLC, and pancreatic cancer [37]. Recent data suggest that patients who develop hypertension during VEGF inhibition might experience more effective VEGF antagonism, resulting in superior anticancer activity. The development of hypertension is associated with better tumor control and survival [38–40]. The management of hypertension is summarized in Table 2, and blood pressure should be monitored and managed when hypertension is detected [34]. Except for patients in hypertensive crisis, clinicians should attempt continuing VEGF inhibitor treatment without interruption by administering suitable antihypertensive drugs. There are
no evidence-based guidelines for selecting the most appropriate antihypertensive agents to manage and treat VEGF inhibitor-induced hypertension [41].

**Mammalian target of rapamycin inhibitors**

A serine/threonine protein kinase, termed mammalian target of rapamycin (mTOR), is implicated in RCC [42]. mTOR inhibitors, everolimus and temsirolimus, are known to be associated with proteinuria, hypertension, and renal failure, and their proposed mechanisms include VEGF pathway disruption [43]. Large prospective everolimus studies reported proteinuria ranging from 10% to 14% and grade 3 or more of proteinuria occurred approximately 1% or 2% [44,45]. However, there have been no reports of nephrotic syndrome. These studies also reported that the frequencies of all grades of hypertension were 8% to 10% and that patients with hypertension grade 3 or more comprised 1% to 4%. In the case of temsirolimus, the incidence of proteinuria has not been formally reported, but Izzedine et al. [46] reported four patients with acute kidney injuries, along with biopsy-proven acute tubular necrosis during mTOR inhibitor treatment with everolimus and temsirolimus. Moreover, FSGS was observed in a patient receiving temsirolimus [47]. Worsening AKI was reported in 57% of patients (with grade 3 to 4 AKI in approximately 3% of patients) in temsirolimus treatment [48]. As patients with RCC may be elderly and many have undergone previous nephrectomy, such patients are at high risk of developing renal failure. Thus, although the incidence is low and most cases are mild, regular monitoring of high blood pressure, proteinuria, and worsening renal function are recommended for mTOR inhibitor treatment, especially in patients with RCC.

**The BRAF inhibitor**

The v-Raf murine sarcoma viral oncogene homolog B (BRAF), one of three members of the RAF kinase family, plays an essential role in the carcinogenesis pathway [49]. The BRAF\(^{V600E}\) mutation, which substitutes glutamic acid for

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**Table 2. Guidelines for the management of proteinuria and hypertension in patients receiving VEGF inhibitors**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Grade*</th>
<th>Description</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proteinuria</td>
<td>1</td>
<td>1+ proteinuria; urinary protein $\geq$ ULN to $&lt;1.0$ g/24 hr</td>
<td>Continue VEGF inhibitors</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>2+ and 3+ proteinuria; urinary protein $1.0$ to $&lt;3.5$ g/24 hr</td>
<td>Give VEGF inhibitors and collect 24-hr urine</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>4+ proteinuria; urinary protein $\geq 3.5$ g/24 hr</td>
<td>Resume VEGF inhibitor if less than $2$ g/24 hr</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1</td>
<td>SBP 120–139 mmHg or DBP 80–89 mmHg</td>
<td>Continue VEGF inhibitors</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>SBP 140–159 mmHg or DBP 90–99 mmHg if previously WNL; change in baseline medical intervention indicated; recurrent or persistent (≥24 hr); symptomatic increase by $&gt;20$ mmHg (DBP) or to $&gt;140/90$ mmHg; monotherapy indicated initiated</td>
<td>Continue VEGF inhibitors with antihypertensive agents</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>SBP $\geq 160$ mmHg or DBP $\geq 100$ mmHg; medical intervention indicated; more than one drug or more intensive therapy than previously used indicated</td>
<td>Hold VEGF inhibitors and control hypertension with antihypertensive agents</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>Life-threatening consequences (e.g., malignant hypertension, transient or permanent neurologic deficit, hypertensive crisis); urgent intervention indicated</td>
<td>Discontinue VEGF inhibitors and control hypertension with antihypertensive agents</td>
</tr>
</tbody>
</table>

*Grading follows the National Cancer Institute-Common Toxicity Criteria (NCI-CTC) version 5.0.

DBP, diastolic blood pressure; SBP, systolic blood pressure; ULN, upper limit of normal; VEGF, vascular endothelial growth factor; WNL, within normal limits.

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valine at codon 600, accounts for 40% to 60% of melanoma and 1% of NSCLC cases [50,51]. Dabrafenib and vemurafenib are standard treatments for metastatic BRAF<sup>V600E</sup>-mutant melanoma [52]. Although renal insufficiency has not been reported in large prospective trials and the true incidence might be very low, AKI related to vemurafenib has been noted in several case series [53–55]. The Food and Drug Administration Adverse Event Reporting System (FAERS) database, maintained by the U.S. FDA, has recorded 132 and 13 AKI cases following treatment with vemurafenib and dabrafenib, respectively, between 2011 and 2014 [56]. Vemurafenib seems to induce greater nephrotoxicity than dabrafenib. Hypokalemia and hyponatremia were also observed at an extremely low frequency. Based on available data, renal function should be monitored during BRAF inhibitor treatment.

**Nephrotoxicity of immunotherapies**

The expanding use of immune checkpoint inhibitors (ICIs), including programmed cell death protein-1 (PD-1)/programmed death-ligand 1 (PD-L1) inhibitors and cytotoxic T-lymphocyte antigen-4 (CTLA-4) inhibitors, has altered the treatment paradigms for several cancer types [57]. Compared with conventional cytotoxic chemotherapy, immunotherapy has a favorable safety profile, with most patients experiencing only mild adverse events. However, unusual phenomena have been observed—so-called immune-related adverse events (irAEs)—including immune-mediated pneumonitis, hypothyroidism, hyperthyroidism, infusion reaction, colitis, myositis, and rashes [58]. Generally, the incidence and severity of irAEs are higher with CTLA-4 inhibitor monotherapy and ICI combination than those with PD-1/PD-L1 blockade monotherapy [59]. This autoimmune activity also involves the kidneys, but at a lower incidence than other organs, such as the thyroid, lung, or colon. Renal irAEs include AKI, proteinuria, and electrolyte imbalance [60]. In a meta-analysis of 11,482 patients in 48 PD-1 inhibitor clinical trials, the overall AKI incidence was 2.2%, with hypocalcemia observed in 1.0% [61]. In patients with AKI treated with PD-1 inhibitors, the estimated rate of interstitial nephritis was 16.6%. In one series that included 574 melanoma patients treated with nivolumab, the overall incidence of nephrotoxicity was 2%, with a median onset time of 15.1 weeks after treatment initiation [62]. In another series of 3,695 patients treated with various ICIs, the overall incidence of AKI was 2.2%, and it was more frequent in patients receiving combination therapy with ipilimumab and nivolumab (4.9%) than that in patients receiving ipilimumab (2.0%), nivolumab (1.9%), and pembrolizumab (1.4%) [63]. Wanchoo et al. [64] reported that acute interstitial nephritis (AIN) occurs 6 to 12 weeks and 3 to 12 months after initiation of CTLA-4 and PD-1 inhibitors, respectively. These data suggest that the incidence of nephrotoxicity in ICI treatment is generally low, but higher incidence can be observed following combination therapy. Interestingly, ICI-induced AKI sometimes follows other extrarenal irAEs, such as rash, thyroiditis, and colitis [65,66]. The concomitant use of proton pump inhibitors and lower baseline glomerular filtration rate have been indicated as potential risk factors [63,65–67]. According to the current literature, the most common kidney lesion is AIN, followed by minimal change disease, thrombotic microangiopathy, lupus-like nephritis, and FSGS [63,67–70]. ICI-induced AIN is characterized by its variable onset and frequent relapse when compared with traditional drug-induced AIN, highlighting a unique mechanism of action for ICIs [63]. Additionally, ICI-induced AIN is characterized by its excellent response to steroids. However, its frequent relapsing nature requires long-term corticosteroid therapy [71].

The precise mechanisms of immune-related nephrotoxicity remain unknown. However, self-antigen-specific T cell activation involving various components of the kidney is one suggested mechanism [64]. Data regarding the management of ICI-induced nephritis are limited, but glucocorticoids are the mainstay of treatment. ICI therapy should be withheld following grade 2 or more nephritis. Although the optimal dose and duration remain unclear, prednisone 0.5 to 2 mg/kg/day is recommended in guidelines [72,73]. Table 3 summarizes the management of ICI-induced nephrotoxicity [72].

An important issue in clinical practice is administering ICIs to patients with solid organ transplants, especially renal allografts. In several prospective clinical trials involving ICI, patients with organ transplantation have been excluded, and their safety in organ transplant recipients is not well defined and established [57,58]. However, a high incidence of renal allograft rejection (40.9%) was reported in 44 kidney transplant patients administered ICIs, with a higher rate recorded in those receiving PD-1/PD-L1 inhibitors (40.7%) than in those administering CTLA-4 inhibitors (22.2%). Among these 44 patients, 15 (34.1%) experienced allograft failure and 8 (18.1%) died [74]. Based on the observed implications of PD-1/PD-L1 signaling in solid organ transplant,
blockade of the PD-1/PD-L1 pathway may result in a higher rate of graft rejection than CTLA-4 blockade [75]. Another case series of 23 patients reported a similar renal allograft rejection rate of 47%, with 81% graft loss and 46% death [76]. The median time from ICI initiation to acute rejection was less than a month in both reports [74,76]. At present, the exact mechanism of graft rejection remains to be elucidated. Graft rejection is a complex process involving both humoral immunity and cellular immunity, and both the CTLA-4 and PD-1 pathways are implicated in the immune tolerance of transplanted organ [77]. Since their positions in the immune tolerant context differ, the proposed mechanisms are considered distinct between PD-1 inhibitors and CTLA-4 inhibitors [60]. PD-L1 is known to be essential for peripheral graft tolerance and protection from chronic rejection and its pathway inhibition produces the activation of cellular immunity via the effector T cell and the downregulation of regulatory T cell, subsequently inducing allograft rejection. On the other hand, the suggested mechanism of CTLA-4 inhibition is that CTLA-4 inhibitor could prime and generate new donor-specific T cell activation and cytotoxicity, and guard alloreactive T cells against apoptotic death, ultimately prompting rejection [78]. Despite a paucity of data, prior history of rejection, presence of donor-specific antibodies, and PD-L1 expression in transplant patients have been associated with increased risk of rejection [79,80].

Table 3. Management of renal immune-related adverse events of immune checkpoint inhibitor

<table>
<thead>
<tr>
<th>General principles</th>
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<tr>
<td>For suspected immune-related kidney injury, exclude other causes such as urinary tract obstruction, sepsis, dehydration, or other concomitant nephrotoxic agents.</td>
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<tr>
<td>Monitor renal function of patients at regular intervals.</td>
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<tr>
<td>Routine urinalysis is not recommended.</td>
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<tr>
<td>If there are no other potential causes of acute kidney injury, biopsy and use of immune suppressive therapy (mainly glucocorticoid) should be considered.</td>
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<tr>
<th>Grading*</th>
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<tbody>
<tr>
<td>Grade 1, mild: creatinine 1.5–2× above baseline; creatinine level increase of ≥0.3 mg/dL</td>
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<tr>
<td>Consider temporal holding immunotherapy</td>
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<tr>
<td>Closely monitor renal function and urine analysis</td>
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<tr>
<td>Grade 2, moderate: creatinine 2–3× above baseline</td>
</tr>
<tr>
<td>Hold immunotherapy</td>
</tr>
<tr>
<td>Consult to nephrologists</td>
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<tr>
<td>Consider renal biopsy</td>
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<tr>
<td>Start prednisone 0.5–1 mg/kg/day or its equivalent if other causes ruled out</td>
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<tr>
<td>If worsening or no improvement, increase prednisone to 1–2 mg/kg/day or its equivalent</td>
</tr>
<tr>
<td>If improved to grade 1 or less, taper glucocorticoid slowly over 4–6 wk</td>
</tr>
<tr>
<td>Grade 3, severe: creatinine &gt; 3× above baseline or 4.0 mg/dL</td>
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<tr>
<td>Consult to nephrologists</td>
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<tr>
<td>Consider renal biopsy</td>
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<tr>
<td>Grade 4, life-threatening: dialysis indicated</td>
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<tr>
<td>Start prednisone to 1–2 mg/kg/day or its equivalent</td>
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<tr>
<td>If no improvement, consider adding other immunosuppressive agents (azathioprine, cyclophosphamide, cyclosporine, infliximab, mycophenolate)</td>
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</table>

Other types of immunotherapies include chimeric antigen receptor T (CAR-T) cell therapy and cytokine therapy. Exogenous cytokines gained popularity in the 1980s, and only two cytokines, interferon-alpha (IFN-α) and high-dose interleukin-2 (IL-2), received the U.S. FDA approval for indications such as malignant melanoma, RCC, and chronic myelogenous leukemia [81]. IFN-α triggers T cell-mediated responses and results in renal inflammation, and is thus complicated by several types of kidney injury [82]. Minimal change disease, FSGS, and thrombotic microangiopathy are associated with IFN-α treatment and have been reported in select cases [71]. Prompt recognition and treatment discontinuation remain critical measures [83]. Another approved cytokine, high-dose IL-2, causes moderate to severe hypotension, with a frequency of 60% to 90%. Capillary leak syndrome can also occur, which can induce intravascular volume depletion, hypotension, and kidney injury following IL-2 therapy [84]. Thus, capillary leakage can bring about prerenal AKI, and severe hypotension can contribute to acute tubular injury [71]. Appropriate fluid therapy should be employed with IL-2 therapy [85]. However, the absence of biomarkers, low overall response rates, and high frequency of severe adverse events have replaced the use of cytokine anticancer treatment with ICIs [60].

The incidence of nephrotoxicity of another novel immunotherapeutic, CAR-T cell therapy, has been less well established. In one series of 46 patients with non-Hodgkin lymphoma, the incidence of AKI was 30% [86]. Another report revealed that AKI incidence in 78 patients with diffuse large B-cell lymphoma was 19% (15 patients), including six acute tubular necrosis events. Hypophosphatemia, hypokalemia, and hyponatremia reportedly occurred in more than 50% of patients [87]. Currently, no direct glomerular or tubular injuries have been reported [86]. However, systemic toxicities, including tumor lysis syndrome and cytokine release syndrome associated with hypotension, liver dysfunction, cardiac dysfunction, and intravascular volume depletion can cause AKI and electrolyte imbalances [71]. Early recognition and appropriate fluid therapy are crucial for managing CAR-T therapy-associated kidney injury [86].

**Summary**

Chemotherapy-induced kidney injury is a common problem encountered by medical oncologists and nephrologists. The advent of novel anticancer drugs such as targeted molecular agents and immune checkpoint modulators has improved patient survival while simultaneously increasing the prevalence of renal injuries. Despite their relatively low incidence, it is crucial for medical oncologists and nephrologists to be familiar with possible renal toxicities and complications and regularly monitor renal function in patients exposed to these agents.

**Conflicts of interest**

The author has no conflicts of interest to declare.

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In kidney transplantation (KT), overcoming donor shortage is particularly challenging in patients with preexisting donor-specific antibodies (DSAs) against human leukocyte antigen (HLA), called HLA-incompatible KT (HLAi KT), carrying the risk of rejection and allograft loss. Thus, it is necessary to accurately evaluate the degree of sensitization before HLAi KT, and undertake appropriate pre-treatment strategies. To determine the degree of sensitization, complement-dependent cytotoxicity has been the only method employed; the development of a method using flow cytometry further improved the test sensitivity. However, these tests present disadvantages, including the need for living cells, with a solid-phase assay developed to resolve this problem. Currently, the method using Luminex (Luminex Corp.) is widely used in clinical practice. As this method measures DSAs using single antigen beads, it is possible to classify immunological risks by measuring the type and amount of DSAs. Furthermore, there have been major advances in methods that involve DSA removal before HLAi KT. In the early stages of desensitization, plasmapheresis and intravenous immunoglobulins were the main treatment methods employed; however, the introduction of CD20 monoclonal antibody and proteasome inhibitors further increased the success rate of desensitization. Currently, HLAi KT has been established as an important transplant method, but an understanding of DSAs and a novel desensitization treatment are warranted.

Keywords: Alloantibodies, Bortezomib, HLA antigens, Kidney transplantation, Plasmapheresis, Rituximab

Introduction

Kidney transplantation (KT) is a well-known treatment strategy that best improves the quality of life and survival outcomes in patients with end-stage kidney disease (ESKD) [1]. However, although the number of patients with ESKD is markedly increasing worldwide, the number of living donors is limited, resulting in a growing number of patients on waiting lists for transplantation [2,3]. To overcome this donor shortage, KT in ABO-incompatible (ABOi) or sensitized patients has been attempted to increase the potential living donor pool. In the Republic of Korea, ABOi KT was initiated in 2007 and has been rapidly increasing [4]. Furthermore, a case of successful KT was reported in the Republic of Korea.
in 2002 after plasmapheresis was performed in a patient who had a positive crossmatch test with a living donor [5], and KT in highly sensitized recipients is currently being actively implemented across several centers.

KT in recipients with alloantibodies to donor human leukocyte antigens (HLAs) is termed HLA-incompatible (HLAi) KT. The presence of alloantibodies against HLAs of potential donors was previously considered a major barrier to KT [6]. However, as new technologies for measuring the characteristics and strength of these donor-specific antibodies (DSAs) have emerged since the early 2000s, immunologic risk stratification has been possible in highly sensitized recipients [7] along with advances in desensitization treatment. Accordingly, a highly sensitized status as a barrier to KT is being surpassed by these developments, which are being actively implemented to overcome donor shortage [8].

In this review, we describe the pretransplant alloantibody detection, desensitization treatment, allograft and patient outcomes, and our center’s experiences and outcomes in HLAi KT.

**Alloantibody detection**

To evaluate highly sensitized recipients and to implement appropriate treatment regimens, it is crucial to first understand the various tests for immunologic risk stratification. Successful KT can be achieved by identifying preformed DSAs through complement-dependent cytotoxicity (CDC) crossmatch, flow cytometry crossmatch (FCXM), and solid-phase binding assay (SPA), and reaching the appropriate target antibody range before transplantation [9]. As large differences in sensitivity and specificity exist between these tests, individualized immunologic risk stratification is generally performed by employing a combination of test results [10].

**Complement-dependent cytotoxicity crossmatch**

CDC crossmatch is a traditional test that was first employed as a pretransplant immunological test and remains a routinely performed test until now [6]. This test can detect whether complement-fixing immunoglobulin (Ig) M and IgG antibodies targeting donor lymphocytes are present in the recipient’s serum [11]. Typically, the test result is positive only when there are sufficient antibodies that can bind to the donor antigen and activate the complement cascade; hence, the sensitivity of CDC crossmatch is relatively inferior when compared with other tests [12].

The CDC crossmatch has several limitations. This test can only detect complement-fixing antibodies, requires viable donor lymphocytes for testing, and the sensitivity may vary depending on the rabbit complement batch. To overcome these limitations, various techniques have been employed [12]. Prolonging the incubation time to 120 minutes after adding the complement can increase the test sensitivity. The Amos wash technique is used to increase test sensitivity and detect only clinically meaningful IgG antibodies by removing anticomplementary factors and low-affinity IgM antibodies by washing the unbound antibodies from the cell suspension before adding complement [13]. The anti-human globulin (AHG) augmentation method is widely used to increase test sensitivity by adding an anti-kappa light chain. AHG enhances complement activation via the proximity of the Fc portion of the antibody. Therefore, detection of low-titer anti-HLA antibodies and non-complement-fixing antibodies is feasible [14]. Pretreatment of patient serum with dithiothreitol or dithioerythritol removes disulfide bonds from the IgM pentamer, but IgG remains relatively intact; hence, IgG and IgM antibodies can be distinguished [15].

Despite these efforts, CDC crossmatch is a reaction between a patient’s serum and donor lymphocytes; hence, the specific profile of the antibody cannot be identified, and false positives may be demonstrated by non-HLA antibodies that are not pathogenic [16]. Furthermore, this test may be affected by drugs or the patient’s underlying disease, with false positives detected owing to the patient’s autoantibodies [17]. Moreover, rituximab can be detected in a patient’s serum for more than 3 months; hence, the B-cell CDC crossmatch can produce false positives during this period [18]. Nevertheless, the CDC crossmatch test remains meaningful as it can stratify high immunologic risks and can be used to reevaluate pretransplant immunologic risks after appropriate desensitization treatment.

**Flow cytometry crossmatch**

Although CDC crossmatch is effective in avoiding hyperacute rejection, several transplant patients have revealed poor clinical outcomes such as primary non-function and delayed graft function. This could be attributed to low-titer DSA, which is lower than the detection threshold of
conventional CDC crossmatch in sensitized patients. Garovoy et al. [19] identified low-titer IgG DSAs by the FCXM method, which was not observed in CDC crossmatch. FCXM is a more sensitive test than CDC crossmatch, and it was reported that the incidence of delayed graft function, acute rejection, and graft failure was higher in the case of FCXM-positive with CDC crossmatch-negative than that of both negatives before transplantation, suggesting that weak and sublytic DSAs play a pathogenic role [20].

FCXM is a cell-based method in which donor lymphocytes react with the recipient serum, similar to CDC crossmatch. However, unlike CDC crossmatch, in this method, the flow cytometer signal is read by adding fluorochrome-conjugated antibodies rather than by employing a cytotoxic response [21]. In some laboratories, donor lymphocytes are pretreated with pronase to remove Fc receptors and CD20 from the B-cell surface. By removing the Fc receptor on the B-cell surface, background noise that may occur due to binding of non-HLA antibodies can be removed; removal of CD20 can reduce the effect of rituximab on B-cell FCXM [22].

As a significant proportion of patients reportedly presented an uneventful clinical course, although they were FCXM-positive, FCXM is considered a test with high sensitivity and low specificity in early graft dysfunction and antibody-mediated rejection (ABMR) [23]. Furthermore, FCXM can be impacted by several variable factors, including flow cytometers, fluorochrome reagents, cell-to-serum ratio, and incubation conditions, rendering standardization difficult. It is necessary to establish individual cutoff values for each laboratory [24]. Moreover, the problem of false positives induced by non-HLA antibodies, autoantibodies, and rituximab tends to persist, which are disadvantages associated with traditional CDC crossmatch [23].

FCXM results must be interpreted together with the CDC crossmatch results (Table 1). For example, when only T-cell CDC and T-cell FCXM results are positive, this may indicate T cell-specific antibody but probably not IgG HLA class I antibody; T-cell FCXM-negative and only B-cell FCXM-positive may indicate the presence of class II DSAs, low-titer class I DSAs, autoantibodies, or antibodies against major histocompatibility complex class I-related chain A [25]. Therefore, CDC and FCXM test results must be interpreted in combination with the SPA test described later to obtain accurate information regarding immunologic risks in sensitized patients.

### Solid-phase binding assays

Advances in the SPA method have greatly contributed to the increased sensitivity and specificity of HLA antibody detection [7]. The first SPA techniques were enzyme-linked im-

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**Table 1. Interpretation of CDC crossmatch and FCXM results**

<table>
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<tr>
<th>CDC-AHG</th>
<th>FCXM</th>
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AHG, anti-human globulin; CDC, complement-dependent cytotoxicity; DSA, donor-specific antibody; DTT, dithiothreitol; FCXM, flow cytometry crossmatch; HLA, human leukocyte antigen; SPA, solid-phase immunoassay.
munosorbent assay and flow cytometry, but recently, these have been largely superseded by “Luminex” technology (Luminex Corp., Austin, TX, USA), which uses polystyrene microbeads with attached purified HLA proteins. The panel reactive antibody (PRA) test is a method to screen anti-HLA antibodies present in the recipient’s serum using a pooled antigen panel composed of microbeads of HLA class I or class II antigens, obtained from multiple donors. A single antigen bead (SAB) panel is the most sensitive test method because each bead is coated with only one HLA allelic antigen, presenting the advantage of being able to detect specific DSAs [26]. Therefore, it is recommended that highly sensitized recipients perform at least one SAB assay before transplantation [24].

Antigen-coated microbeads are incubated with the recipient’s serum, followed by addition of fluorescent-labeled anti-human IgG. If anti-HLA antibodies are present in the recipient’s serum, they bind to the microbeads, and as fluorescent-labeled anti-human IgG binds sequentially to anti-HLA antibodies, it can be detected using a dual-laser instrument [24]. Luminex SAB provides semiquantitative information regarding the anti-HLA antibody titer through median fluorescence intensity (MFI) values, which are used as important information in pretransplant immunologic risk assessment [27]. Luminex SAB may present false-positive or false-negative results owing to IgM or various inhibitory factors present in the recipient’s serum. However, these limitations can be overcome through hypotonic dialysis, heat inactivation, or pretreatment with dithiothreitol or ethylenediaminetetraacetic acid [28].

However, as Luminex SAB is a semiquantitative test, results should be interpreted by utilizing professional knowledge rather than absolute values. In particular, as the coefficient of variance of the MFI values exceeds 25%, a change of less than 1,000 or less than 25% of the MFI values should not be interpreted as clinically significant [27]. Additionally, the prozone phenomenon may occur at markedly high antibody titers. The high titer of antibodies interferes with the formation of the antibody-antigen complex, resulting in a false-negative result. This is clinically indicated by a strong positive CDC crossmatch result, with a negative SAB assay result. In this case, when the recipient’s serum is diluted, the SAB assay results in an increase in the MFI values, allowing antibody detection [29]. The presence of antibodies against the shared epitope in the recipient’s serum may result in false-positive results for multiple microbeads representing HLA antigens [30]. Furthermore, the SAB assay is an extremely sensitive test and does not show ABMR or poor allograft survival in all patients with detected DSAs [31,32]. Therefore, to detect cytotoxic DSAs, a modified test method (C1q binding assay, C3d binding assay) that detects antibodies capable of complement activation is currently being implemented [33].

As the SAB assay can detect specific antibodies, calculated PRA (cPRA) can be derived. cPRA is an index that evaluates the actual degree of sensitization by reflecting the HLA antigen frequencies of the population and can be extremely important in counseling the waiting time of highly sensitized recipients waiting for deceased donors [34]. Furthermore, virtual crossmatching is possible by comparing the recipient’s specific anti-HLA antibodies and donor HLA typing results. The deceased donor allocation time can be reduced by allowing the compatible donor-recipient combination to be checked in advance before the actual crossmatch test [35]. In addition, the SAB assay can be used for monitoring de novo DSA, allowing proper patient management after transplantation [36].

Individualized pretransplant immunologic risk assessment is possible by using the results of previously described CDC crossmatch, FCXM, and SAB assays collectively. By interpreting these test results together, the immunologic risk of sensitized patients can be stratified into the high-risk group (the probability of hyperacute rejection is high if antibody reduction therapy is not performed owing to high-titer DSAs), the intermediate-risk group (the probability of hyperacute rejection is low, with a higher probability of ABMR and poor allograft outcome), and the low-risk group (the incidence of rejection may be high owing to low-titer DSAs, but the evidence for poor allograft outcome is insufficient) [10] (Table 2). At our center, as immunologic risk evaluation, crossmatch and PRA are used as screening tests to identify the presence of anti-HLA antibodies; if the screening test is positive, the SAB assay is performed to identify specific DSAs (Fig. 1).

Future direction

As the development of the SAB assay allows the identification of specific DSAs, there has been great progress in evaluating the degree of sensitization. However, some challenges...
Complement-binding assays determine whether DSA can activate the complement cascade. This has been reported as a valuable test for pretransplant immunologic risk stratification, predicting ABMR and graft loss occurrence \[38, 39\]. Several studies have reported that complement-binding DSA has a strong correlation with high antibody titers (high MFI levels) \[40, 41\]. However, since the antibody titer can change dynamically, the complement-binding assay can show inconsistent results \[40\]. In addition, in a previous study, ABMR with DSA did not show complement fixation \textit{in vitro}, but 40% of them showed C4d-positive histology \textit{in vivo} \[42\]; thus, further research is needed on this.

It is thought that the mechanism of alloimmune response is different depending on the IgG subclass. IgG1 and IgG3 subclasses are known to have stronger complement-fixing properties than IgG2 and IgG4 subclasses \[43\]. Furthermore, previous studies have reported that IgG1 and IgG3 subclasses are strongly related to acute rejection and graft loss \[44, 45\]. However, there is a technical limitation that the currently used IgG subclass-specific reagents cannot classify subclass-
es in 10% to 20% of total IgG-positive HLA antibodies [44]. In addition, IgG2 and IgG4 are also known to have some correlation with rejection [46]; therefore, further research is warranted.

Progress is being made in uncovering the outside-in signal transduction pathway by DSA. As the mechanistic target of rapamycin signaling axis is revealed as a pathway for activation of endothelial cells by HLA class II molecules [47], research on the development of diagnostic tools and drugs using this is expected. In addition, the relationship between the Fc receptor genotype and HLA subclass in leukocyte recruitment and microcirculation inflammation has been reported [48], and the pathological mechanisms for this are expected to be uncovered in the future.

DSA is not observed, but the presence of previously sensitized memory B/T cells may induce a rapid alloimmune response after transplantation [49]. Therefore, attempts are being made to discover these memory B/T cells before transplantation. Test methods such as flow cytometric HLA-binding memory B-cell assay, in vitro differentiation of memory B-cell assay, donor-specific interferon-γ secreting T-cell assay, follicular helper T-cell assay, immunophenotypic bulk memory T-cell assay have been attempted, but there are no tests showing clinically useful predictable power to date [50–54].

HLA alloreognition by B/T cells is more likely to occur as recipient HLA and donor HLA molecules are more different [55]. Currently, computational algorithms can be used to quantify the HLA molecule mismatch (mMM) between the recipient and donor. Commonly used methods are HLA Matchmaker, Electrostatic Mismatch Score, Predicted Indirectly ReCognizable HLA Epitopes Matching, and simple counting of amino acid mismatches [56–58]. In previous studies, the HLA-DR or -DQ mMM score was an independent risk factor for de novo DSA, and it has been reported that both simple HLA type mismatch and mMM are important for pretransplant immunologic risk stratification [59]. However, since various mMM calculation systems currently exist, standardization is required. Moreover, some mMMs have been reported to have stronger immunogenicity than other mMMs, necessitating further research on this [57,60].

**Desensitization treatment**

Currently, desensitization is performed by removing preexisting antibodies and inhibiting the production of antibodies (Fig. 2). Plasmapheresis, immunoadsorption, high-dose intravenous immunoglobulin (IVIG), and plasmapheresis with low-dose IVIG methods are available to remove existing antibodies [61]. With the introduction of drugs that inhibit the production of antibodies, the success rate of desensitization treatment has increased. As such, CD20 monoclonal antibody that removes B cells or a proteasome inhibitor, which induces apoptosis of plasma cells, can be employed. The most widely used method for desensitization treatment worldwide is plasmapheresis with low-dose IVIG [62] in

**Figure 2.** Basic concept of desensitization treatment in highly sensitized recipients. IVIG, intravenous immunoglobulin.
conjunction with rituximab [8]. Our center also uses a desensitization protocol based on plasmapheresis with low-dose IVIG with rituximab (Fig. 3A) [63]. If T-CDC-AHG is positive or if there is no appropriate DSA MFI titer reduction even after three or more plasmapheresis sessions, a bortezomib-added protocol is performed (Fig. 3B) [64]. In the case of PRA ≥ 50% alone (with crossmatch-negative and DSA MFI titer < 3,000), only rituximab is administered 7 days before transplantation without plasmapheresis [65].

**Plasmapheresis or immunoadsorption**

Plasmapheresis or immunoadsorption is a method that physically removes immunoglobulins from the recipient’s serum. As a desensitization method, plasmapheresis is mainly performed in the United States, and immunoadsorption is mainly performed in Europe. As in the United States, plasmapheresis is currently the main method undertaken in the Republic of Korea. Plasmapheresis is not specific to the removal of alloantibodies, and hence, all plasma proteins, including albumin and blood coagulation factors, are lost, which need to be replaced with albumin or fresh frozen plasma. Immunoadsorption utilizes columns that selectively remove the immunoglobulin, preventing excessive loss of coagulation factors [66]. Reportedly, one treatment session with plasmapheresis or immunoadsorption can result in an alloantibody reduction between 15% and 20%, and alloantibody levels are reduced by more than 90% with 3 to 6 treatment sessions. However, rebound anti-HLA antibody titers can be detected within 4 weeks after the completion of plasmapheresis or immunoadsorption [67].

**Intravenous immunoglobulin**

IVIG is a preparation that is produced by separating the gamma globulin fraction of pooled human plasma and is employed to treat various autoimmune diseases or hypogammaglobulinemia. The mechanism of action of IVIG in desensitization treatment remains unclear, but it is considered that IVIG modulates the immune response through various pathways [68]. These complex mechanisms could involve the neutralization of cytokines and antibodies, inhibition of B/T cells through the saturation of Fc receptors, increased regulatory T cells, inhibition of immune complex formation, and inhibition of dendritic cell activity [69]. In a retrospective study that directly compared high-dose IVIG (2 g/kg) and plasmapheresis with low-dose IVIG (100 mg/kg) as desensitization treatment in T-CDC crossmatch-positive recipients, the proportion of patients who achieved crossmatch negativity was 38% in the high-dose IVIG group and 84% in the plasmapheresis with low-dose IVIG group [70]. The incidence of ABMR was 80% in the high-dose IVIG group and 37% in the plasmapheresis with low-dose IVIG group; hence, plasmapheresis with low-dose IVIG was reported to be a better desensitization treatment method [70]. However, in another large-scale study, the comparable success rate of high-dose IVIG and rituximab combination therapy has also been reported [8], and high-dose IVIG can have an advantage over plasmapheresis, as there is no concern regarding the loss of other plasma proteins. Currently, at our center, highly sensitized patients waiting for deceased donors are undergoing high-dose IVIG therapy (1 g/kg/day for 4 days [at day 1, day 2, day 30, day 31]) for the removal of anti-HLA antibodies.

**Anti-CD20 monoclonal antibody**

Rituximab is a monoclonal antibody against CD20 expressed on the surface of B cells and their progenitor cells. It removes B cells present in the peripheral blood and spleen and inhibits their differentiation into plasma cells, thereby suppressing antibody production. In highly sensitized patients, administration of rituximab significantly reduced re-elevation of anti-HLA antibody titers after KT [71]. However, as plasma cells do not express CD20, they cannot be removed with rituximab, and hence, the effect of rituximab may be insufficient in plasma cells that continuously generate antibodies [71]. Nevertheless, to date, rituximab is the most widely used agent to inhibit antibody production during desensitization treatment.

**Proteasome inhibitor**

Bortezomib is a reversible 26S proteasome inhibitor that inhibits the migration of nuclear factor-kappa B to the cell nucleus, thereby inducing apoptosis of plasma cells [72]. The bone marrow niche resident long-lived plasma cells are known to continuously produce anti-HLA antibodies, which do not express CD20 and are not removed by rituximab [73]. Therefore, desensitization treatment via additional admin-
Figure 3. The desensitization protocol of Seoul St. Mary’s Hospital. (A) Standard desensitization protocol. The target goals were T-CDC and T-FCXM-negative conversion, DSA MFI titer less than 3,000, and C1q binding assay negative conversion. (B) Bortezomib-based desensitization protocol. If T-CDC or T-AHG is positive, or if there is no adequate DSA reduction after three or more PP/IVIG sessions, bortezomib-based protocol is performed. The target goals were T-CDC and T-FCXM-negative conversion, DSA MFI titer less than 3,000, and C1q binding assay negative conversion.

AHG, anti-human globulin; ATG, antithymocyte globulin; CDC, complement-dependent cytotoxicity; D, day; DSA, donor-specific antibody; FCXM, flow cytometry crossmatch; KT, kidney transplantation; MFI, median fluorescence intensity; IVIG, intravenous immunoglobulin; PP, plasmapheresis; XM, crossmatch.

*Basiliximab is administered at 20 mg/day on days 0 and 4. ATG is administered at a dose of 1.5 mg/kg/day from day 0 to day 4 for 5 days.
istration of bortezomib targeting plasma cells has been attempted when conventional desensitization treatment does not respond sufficiently, or the antibody titer is markedly high [74]. Carfilzomib is a second-generation irreversible proteasome inhibitor. In a recent study, it was reported that the carfilzomib monotherapy-based desensitization protocol showed acceptable safety and toxicity with significant bone marrow plasma cell depletion and DSA reduction [75]. In highly sensitized patients awaiting a deceased donor, it has been reported that the chance of deceased donor KT was increased by lowering the DSA titer through desensitization using high-dose IVIG, rituximab, and bortezomib [76]. Our center has also been performing this desensitization protocol since 2019, and to date, three deceased donor KTs have been successfully performed.

**Novel agents**

Eculizumab is a monoclonal antibody against complement C5 that prevents the separation of C5a and C5b, and finally inhibits the formation of the membrane attack complex C5b–C9. Therefore, it could prevent allograft damage by inhibiting the complement cascade. In a study comparing an eculizumab treatment group and the historical control group in crossmatch-positive recipients, the incidence of acute ABMR after KT was significantly lower in the eculizumab treatment group than in the historical control group [77]. However, a large-scale study is still lacking, and further studies are needed.

C1-esterase inhibitor (C1-INH), another complement inhibitor, inhibits the classical and lectin complement pathways by inhibiting C1r and C1s. A randomized phase I/II study compared C1-INH with placebo to prevent acute ABMR in HLAi KT. Twenty recipients who underwent IVIG, rituximab, with or without plasmapheresis before KT, were compared by dividing them into C1-INH and placebo groups. There was no ABMR in the C1-INH group, but one ABMR was reported in the placebo group [78]. It is thought that C1-INH, to some extent, contributes to the prevention of ABMR in highly sensitized patients, but further studies are needed.

Interleukin-6 is a cytokine that induces inflammation through various mechanisms, including the differentiation of B cells into plasma cells. In a previous study using an anti-interleukin-6 receptor blocker (tocilizumab) as desensitization treatment, it was revealed that successful desensitization was possible when tocilizumab was administered to patients who failed to be desensitized following high-dose IVIG and rituximab [79]. Additionally, in KT recipients with chronic ABMR, a significant decrease in the DSA titer was observed when tocilizumab was administered in patients whose DSA titer did not decrease following standard therapy (IVIG + rituximab with or without plasmapheresis). Tocilizumab is expected to contribute not only to desensitization but also to chronic ABMR treatment [80].

Belatacept is a fusion protein that inhibits costimulatory signals in T-cell activation by binding to CD80/CD86 molecules of antigen-presenting cells. It is attracting attention as a new maintenance immunosuppressant [81]. In a recent human *in vitro* study, it was reported that belatacept inhibits plasmablast differentiation and immunoglobulin production by acting independently on B cells [82]. In a recent retrospective cohort study of highly sensitized recipients (cPRA ≥ 98%), the belatacept group showed a significant decrease in HLA class I antibodies, suggesting that belatacept may be an option for desensitization.

The IgG-degrading enzyme of *Streptococcus pyogenes* (IdeS) is a cysteine endopeptidase that divides IgG into F(ab’)2 and Fc to neutralize antibodies. It reportedly acts rapidly and neutralizes most of the IgG within 4 hours of administration [83]. In the United States and Sweden, 24 out of 25 highly sensitized recipients reported successful deceased donor KT after IdeS administration. One patient presented with hyperacute rejection, but it was presumed to be caused by unrecognized IgM, IgA, or non-HLA antibodies as no detectable IgG DSAs were observed after IdeS administration [84]. IdeS is currently being investigated in a clinical trial and is expected to play an important role as a desensitization tool in highly sensitized recipients in the future.

**Alternative to desensitization (kidney paired donation)**

Kidney paired donation (KPD) is a method of performing KT without desensitization in highly sensitized recipients through compatible recipient-donor pair matching in recipient and donor pool [85]. The KPD program has been developed in many countries over the past 30 years, and recent data from KPD registries in Australia and Canada reported that the KT match rates of recipients with cPRA between 50% and 96% and recipients with cPRA < 50% were similar.
In a recent study comparing the KPD network program (National Kidney Registry) and all national transplants registry (United Network for Organ Sharing) in the United States, KT performed through the KPD network program showed a higher proportion of retransplantation and highly sensitized recipients (cPRA > 80%) [87]. In a study that analyzed how highly sensitized recipients received KT in the United States from 2009 to 2017, it was observed that living donor KT through KPD gradually increased, which is thought to be due to the development of the KPD program [88].

Allograft and patient outcomes

Table 3 summarizes the studies on HLAi KT to date. As highly sensitized recipients present preexisting alloantibodies before KT, the ABMR incidence was higher than in those without alloantibodies [89]. Consequently, HLAi KT has a significantly lower allograft survival rate than HLA-compatible KT (HLAc KT), which has been reported to be significantly reduced from 1 year of transplantation (89.9% in HLAi KT vs. 97.6% in HLAc KT) [90].

HLAi KT poses concerns regarding increased rejection and worse allograft outcomes, as well as increased infection and malignancy risks due to desensitization treatment. Until now, most studies on the risk of desensitization treatment have been short-term studies; hence, the impact of the long-term risk of desensitization treatment remains unclear. Inconsistent results have been reported on the effect of desensitization treatment on infection risk [91–94]. Kahwaji et al. [93] reported that there were no differences in bacterial, viral, and fungal infection rates between the rituximab with high-dose IVIG group and the non-administered group over 18 months after transplantation. Conversely, Ko et al. [92] reported that desensitization treatment was an independent risk factor for infection-related mortality (adjusted hazard ratio, 3.40; p = 0.002) in a nationwide cohort study in the Republic of Korea. In a recent phase 2 randomized controlled trial comparing the eculizumab-added group and the standard desensitization (plasmapheresis + IVIG or plasmapheresis alone) group in HLAi KT, it was reported that the overall infection rate was numerically higher in the eculizumab-added group (62.7% in the eculizumab group vs. 49.0% in the standard desensitization group) [95]. Few studies have highlighted the malignancy risk associated with desensitization treatment in HLAi KT. In previous studies, nonmelanoma skin cancer and lymphoproliferative disorder were common in the desensitization treatment group [96], with urothelial carcinoma particularly common in the Asian population [97].

DSA titers at the time of transplantation and allograft survival were found to be correlated [63,98]. In an observational study of living donor KT patients at 22 centers of United States, the overall graft survival rates at 1 year and 5 years of transplantation were highest in HLAc KT, the second in the positive SAB (Luminex) assay with negative FCXM (PLNF) group, the third in the positive FCXM with negative CDC crossmatch (PFNC) group, and the lowest in the positive CDC crossmatch (PCC) group. The authors reported that the higher the intensity of sensitization before transplantation, the higher the overall allograft loss rate (Fig. 4) [98]. It is postulated that in addition to the DSA titer, DSA characteristics can affect the allograft outcome. In a patient in whom the C1q binding DSA was converted to negative, but CDC crossmatch remained positive at the time of transplantation, a favorable outcome was observed without evidence of antibody-mediated injury after transplantation [74]. In the future, additional studies on allograft outcomes according to the characteristics of DSA (C1q binding, C3d binding, or IgG subclass) are necessary.

Although HLAi KT has a higher ABMR incidence and lower allograft survival rate than HLAc KT, HLAi KT has advantages over continuing dialysis while waiting for deceased donor KT. Montgomery et al. [62] reported that the HLAi KT group showed more than twice the survival benefit when compared with the dialysis-only group and the dialysis-or-deceased donor KT group in a single-center study. Similarly, Orandi et al. [98] reanalyzed this through the national cohort and reported that HLAi KT demonstrated a better long-term survival rate when compared with dialysis only and dialysis-or-deceased donor KT groups. Although HLAi KT costs approximately $30,000 more than HLAc KT in terms of economics [99], compared to continuing dialysis, HLAi KT increases the quality of life and patient survival and reduces the need for dialysis, making it more cost-effective than continuing dialysis [100].

Our center’s experiences and outcomes

At our center, a total of 137 HLAi KTs were performed from 2010 to 2020. Based on immunologic stratification,
<table>
<thead>
<tr>
<th>Study</th>
<th>Year of publication</th>
<th>No. of patients</th>
<th>Desensitization method</th>
<th>Acute rejection (%)</th>
<th>Graft survival (%)</th>
<th>Patient survival (%)</th>
<th>Follow-up (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sonnenday et al.¹</td>
<td>2002</td>
<td>18 (X+)</td>
<td>PP + LD IVIG</td>
<td>27.8</td>
<td>94.4</td>
<td>100</td>
<td>17</td>
</tr>
<tr>
<td>Thielke et al.²</td>
<td>2009</td>
<td>57 (X+)</td>
<td>PP + LD IVIG with/without rituximab</td>
<td>43.0</td>
<td>93.0</td>
<td>95.0</td>
<td>12</td>
</tr>
<tr>
<td>Vo et al.³</td>
<td>2010</td>
<td>76 (X+)</td>
<td>HD IVIG + rituximab</td>
<td>37.0</td>
<td>84.0</td>
<td>95.0</td>
<td>24</td>
</tr>
<tr>
<td>Montgomery et al. [11]</td>
<td>2011</td>
<td>211 (X+)</td>
<td>PP + LD IVIG</td>
<td>-</td>
<td>-</td>
<td>90.6</td>
<td>12</td>
</tr>
<tr>
<td>Bentall et al.⁴</td>
<td>2013</td>
<td>102 (X+)</td>
<td>PP + LD IVIG + splenectomy (n = 16)</td>
<td>37</td>
<td>70.7</td>
<td>83.5</td>
<td>60</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>PP + LD IVIG (n = 48)</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>HD IVIG (n = 21)</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>None (n = 17)</td>
<td></td>
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</tr>
<tr>
<td>Orandi et al.⁵</td>
<td>2014</td>
<td>304 (PCC)</td>
<td>-</td>
<td>-</td>
<td>60.1 (PCC)</td>
<td>80.9 (PCC)</td>
<td>60</td>
</tr>
<tr>
<td></td>
<td></td>
<td>536 (PFNC)</td>
<td></td>
<td></td>
<td>71.2 (PFNC)</td>
<td>87.1 (PFNC)</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>185 (PLNF)</td>
<td></td>
<td></td>
<td>79.8 (PLNF)</td>
<td>90.4 (PLNF)</td>
<td></td>
</tr>
<tr>
<td>Okada et al.⁶</td>
<td>2018</td>
<td>36 (X–D+)</td>
<td>Rituximab (2 doses) (X–D+)</td>
<td>19.4 (X–D+)</td>
<td>97.2 (X–D+)</td>
<td>100 (X–D+)</td>
<td>48</td>
</tr>
<tr>
<td></td>
<td></td>
<td>15 (X+D+)</td>
<td>PP + LD IVIG + rituximab (X+D+)</td>
<td>60.0 (X+D+)</td>
<td>86.7 (X+D+)</td>
<td>93.3 (X+D+)</td>
<td></td>
</tr>
<tr>
<td>Kwon et al.⁷</td>
<td>2019</td>
<td>176 (ABOc/X+)</td>
<td>PP + LD IVIG + rituximab</td>
<td>11.7 (ABOc)</td>
<td>95.5 (ABOc)</td>
<td>98.6 (ABOc)</td>
<td>60</td>
</tr>
<tr>
<td></td>
<td></td>
<td>87 (ABOi/X+)</td>
<td></td>
<td>25.5 (ABOi)</td>
<td>89.9 (ABOi)</td>
<td>80.9 (ABOi)</td>
<td></td>
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<tr>
<td>Our center</td>
<td></td>
<td>41 (PCC)</td>
<td>PP + LD IVIG + rituximab</td>
<td>41.5 (PCC)</td>
<td>80.5 (PCC)</td>
<td>92.7 (PCC)</td>
<td>45</td>
</tr>
<tr>
<td></td>
<td></td>
<td>46 (PFNC)</td>
<td>(with/without bortezomib)</td>
<td>32.6 (PFNC)</td>
<td>84.8 (PFNC)</td>
<td>89.1 (PFNC)</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>50 (PLNF)</td>
<td></td>
<td>20.0 (PLNF)</td>
<td>92.0 (PLNF)</td>
<td>94.0 (PLNF)</td>
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</tbody>
</table>

41 patients (29.9%) were PCC, 46 (33.6%) were PFNC, and 50 (36.5%) were PLNF. Among these patients, 41 patients (29.9%) had concomitant ABO incompatibility. Desensitization treatment was performed with rituximab and plasmapheresis with low-dose IVIG according to our center protocol (Fig. 3A). In five patients, the bortezomib-based protocol was performed (Fig. 3B). Antithymocyte globulin was used in 62.0% (85 of 137) and basiliximab in 38.0% (52 of 137) as induction therapy before transplantation. In the posttransplant allograft outcome, de novo DSAs occurred in 10.2% (14 of 137) of patients, and preexisting DSA rebound occurred in 21.9% (30 of 137) of patients. On analyzing biopsy-proven rejection, the acute rejection rate was 30.7% (42 of 137) and the chronic rejection rate was 11.7% (16 of 137). In sub-analysis, the acute T cell-mediated rejection (TCMR) rate was 14.6% (20 of 137), acute ABMR rate was 20.4% (28 of 137), chronic active TCMR rate was 0.7% (1 of 137), and the chronic active ABMR rate was 10.9% (15 of 137). The median follow-up duration was 44.8 months, death censored graft loss rate was 9.5% (13 of 137), overall graft loss rate was 13.9% (19 of 137), and the patient death rate was 8.0% (11 of 137). Following analysis according to the immunological risk group, the overall graft loss rate was 19.5% (8 of 41) in the PCC group, 15.2% (7 of 46) in the PFNC group, and 8.0% (4 of 50) in the PLNF group. It should be considered that the median follow-up duration was 44.8 months, but the overall graft survival of HLAi KT in crossmatch-positive patients at our center was marginally improved compared to previous studies (Table 3).

**Conclusion**

Highly sensitized recipients are less likely to have deceased donor KT opportunities than non-sensitized recipients. Moreover, in these patients, living donor KT after desensitization treatment reportedly presents a better patient survival rate than that observed with continuing dialysis while waiting for deceased donor KT. Therefore, if a potential donor is available, it is necessary to actively perform HLAi KT. Furthermore, owing to great advances in SAB assays and desensitization treatment in the field of transplantation, it is expected that patient prognosis can be improved through appropriate immunologic risk stratification and desensitization treatment. Moreover, many researches are ongoing in the field of transplant immunity and new agents of desensitization treatment. Based on these findings, in the future, we anticipate that safe KT will be performed even in highly sensitized recipients, thereby actively improving their prognosis.

**Conflicts of interest**

All authors have no conflicts of interest to declare.

**Authors’ contributions**

Investigation, Data curation: EJK, BHC

Writing—original draft: YP, CWY

Writing—review & editing: YP, CWY

All authors read and approved the final manuscript.

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Association between copeptin levels and treatment responses to hypertonic saline infusion in patients with symptomatic hyponatremia: a prospective cohort study

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Background: Copeptin is secreted in equimolar amounts as arginine vasopressin, main hormone regulating body fluid homeostasis. A recent study reported a copeptin-based classification of osmoregulatory defects in syndromes of inappropriate antidiuresis that may aid in prediction of therapeutic success. We investigated usefulness of copeptin for differentiating etiologies of hyponatremia and predicting efficacy and safety of hypertonic saline treatment in hyponatremic patients.

Methods: We performed a multicenter, prospective cohort study of 100 inpatients with symptomatic hyponatremia (corrected serum sodium [sNa] ≤ 125 mmol/L) treated with hypertonic saline. Copeptin levels were measured at baseline and 24 hours after treatment initiation, and patients were classified as being below or above median of copeptin at baseline or at 24 hours, respectively. Correlations between target, under correction, and overcorrection rates of sNa within 24 hours/24-48 hours and copeptin levels at baseline/24 hours were analyzed.

Results: Mean sNa and median copeptin levels were 117.9 and 16.9 pmol/L, respectively. Ratio of copeptin-to-urine sodium allowed for an improved differentiation among some (insufficient effective circulatory volume), but not all hyponatremia etiologic subgroups. Patients with below-median copeptin levels at baseline achieved a higher target correction rate in 6/24 hours (odds ratio [OR], 2.97; p = 0.02/OR, 6.21; p = 0.006). Patients with below-median copeptin levels 24 hours after treatment showed a higher overcorrection rate in next 24 hours (OR, 18.00, p = 0.02).

Conclusion: There is a limited diagnostic utility of copeptin for differential diagnosis of hyponatremia. However, copeptin might be useful for predicting responses to hypertonic saline treatment in hyponatremic patients.

Keywords: Copeptins, Diagnosis, Hypertonic saline solution, Hyponatremia, Treatment outcome
Introduction

Hyponatremia is the most common electrolyte abnormality encountered in clinical practice. It is associated with increased mortality and morbidity rates that arise from the abnormality itself and from treatment errors [1,2]. Hypertonic saline infusion is generally accepted as the treatment of choice for severe symptomatic hyponatremia [2,3]. However, overcorrection of chronic hyponatremia may lead to osmotic demyelination syndrome (ODS), causing permanent neurological disability, while an under correction may be insufficient to prevent the life-threatening manifestations of cerebral edema [4–6].

In most cases, hyponatremia occurs due to the inappropriate activation of arginine vasopressin (AVP) [7,8]. Therefore, AVP can be used for the diagnosis and prediction of treatment response [9]. However, due to its short half-life (24 minutes) and high platelet affinity, it is difficult to precisely measure AVP levels. Therefore, AVP levels are not commonly used in clinical practice for hyponatremia diagnosis [10]. Copeptin has recently been reported to be highly correlated with AVP in response to hypoosmolar or stressful conditions [11]. Copeptin is a stable, nonfunctional, 39-amino acid glycopeptide. It forms the C-terminal of pre-proAVP, which is a precursor peptide composed of a signal peptide, AVP, and neurophysin II [12]. Unlike AVP, copeptin is highly stable in terms of storage at room temperature and can be easily detected by sandwich immunoassay. Furthermore, its level correlates well with AVP levels [11,13]. Therefore, copeptin is a promising alternative marker of AVP.

Several studies have investigated the role of copeptin in a variety of conditions, including its role in: (1) the diagnosis of central diabetes insipidus caused by a primary AVP-synthesis defect [14,15]; (2) early detection and exclusion of acute myocardial infarction [16,17]; and (3) the prognosis of heart failure, sepsis, chronic renal failure, liver cirrhosis, and polycystic kidney disease [18–21]. Furthermore, in terms of pathophysiology, several reports have shown its capability to differentiate the underlying cause of hyponatremia, using copeptin/urine Na (UNa) ratios or copeptin itself to distinguish primary AVP release (syndrome of inappropriate antidiuresis [SIAD]) and AVP release secondary to hemodynamic stimuli, including heart failure or Na depletion [10,22–24]. However, copeptin levels widely overlap in patients with hyponatremia [9] and vary among patients with SIAD [8]. Physiological increases in copeptin following hypertonic saline-induced osmotic stimulation have been observed in a healthy population [8]. However, the response of copeptin to hypertonic saline infusion varied substantially in patients with SIAD according to impaired osmoregulation or nonosmotic inhibitory pathway [8]. Defining SIAD subtypes according to copeptin responses to osmotic stimulation by hypertonic saline infusion may serve as the starting point for assessing individual treatment responses in SIAD [8]. However, only a few studies have used copeptin to predict responses to treatment with hypertonic saline in hyponatremic patients using clinical indices such as target, under correction, and overcorrection rates. Therefore, this study aimed to evaluate copeptin levels as a marker for responses to hypertonic saline treatment in hyponatremic patients.

Methods

Study population

A multicenter, prospective, randomized clinical trial was designed to evaluate the efficacy and safety of rapid intermittent correction compared with slow continuous correction with hypertonic saline in patients with symptomatic hyponatremia (SALSA trial) (Clinicaltrials.gov: NCT02887469) [25]. The detailed study protocol is described elsewhere [26]. In brief, the study participants with symptomatic hyponatremia were recruited from August 24, 2016 to August 21, 2019. Inclusion criteria for the original study included: age > 18 years and symptomatic hyponatremia (glucose-corrected serum Na [sNa] ≤ 125 mmol/L). Table 1 summarizes the inclusion and exclusion criteria used in the SALSA study.

Of the 178 participants from the SALSA study, 62 (34.8%) who had available data for copeptin at baseline and 24 hours after initiation of hypertonic saline treatment were included in the present analyses. We further prospectively recruited 38 patients with symptomatic hyponatremia who were treated with hypertonic saline between May 2018 and July 2019, with the same inclusion and exclusion criteria as the SALSA study (Fig. 1). Finally, using a total of 100 patients with symptomatic hyponatremia who were treated with hypertonic saline, the usefulness of copeptin as a diagnostic and responsive marker for hypertonic saline was evaluated at the Hallym University Dongtan Sacred Heart Hospital and the Seoul National University Bundang Hospital. All clinical
investigations were conducted in accordance with the 2008 Declaration of Helsinki principles and good clinical practice guidelines. This study was approved by the Institutional Review Boards of the Hallym University Dongtan Sacred Heart Hospital (No. 2018-04-009) and the Seoul National University Bundang Hospital (No. H-1508-310-115). Written informed consent was obtained from all patients.

Table 1. Inclusion and exclusion criteria of SALSA study

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Age over 18 years</td>
<td>• Primary polydipsia (urine osmolality ≤ 100 mOsm/kg)</td>
</tr>
<tr>
<td>• Glucose-corrected serum Na ≤ 125 mmol/L</td>
<td>• Arterial hypotension (systolic blood pressure &lt; 90 mmHg and mean arterial pressure &lt; 70 mmHg)</td>
</tr>
<tr>
<td>• Symptoms</td>
<td>• Liver disease (transaminase levels &gt; 3 times the upper limit of normal, known decompensated liver cirrhosis with ascites or diuretic use, hepatic encephalopathy, and varices)</td>
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<tr>
<td></td>
<td>• Uncontrolled diabetes mellitus (glycated hemoglobin&gt; 9%)</td>
</tr>
<tr>
<td></td>
<td>• Had a history of cardiac surgery, acute myocardial infarction, sustained ventricular tachycardia, ventricular fibrillation, acute coronary syndrome, cerebral trauma, and increased intracranial pressure within 3 months prior to randomization</td>
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<td>• Pregnant or breast feeding</td>
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</tbody>
</table>

SALSA, a randomized clinical trial to evaluate the efficacy and safety of rapid intermittent correction compared with slow continuous correction with hypertonic saline in patients with symptomatic hyponatremia.

Figure 1. Study population algorithm.

ITT, intention to treat; PP, per protocol; SALSA, a randomized clinical trial to evaluate the efficacy and safety of rapid intermittent correction compared with slow continuous correction with hypertonic saline in patients with symptomatic hyponatremia.

Data collection and definitions

Anthropometric markers (including height and weight) and resting systolic and diastolic blood pressure were measured at baseline. Based on the International Classification of Disease (10th revision) codes, comorbidities such as hypertension, diabetes mellitus, congestive heart failure, adrenal insufficiency, hypothyroidism, and cancer were assessed.
by screening for the I10–I15; E10–14; I11.0, I13.0, I13.2, I50; E27.1–27.4; E03; and C codes, respectively. The presence of all comorbidities was determined by a self-reported history or medical record review, and the presence of hypertension, diabetes mellitus, and hypothyroidism was confirmed on the basis of a history of antihypertensive medications, antihyperglycemic agents, and levothyroxine use, respectively. Hypothyroidism was defined as a thyroid-stimulating hormone concentration above the reference range (0.4–4.0 mIU/L) and free thyroxine concentration below the reference range. Adrenal insufficiency was defined as a basal cortisol level below 3 µg/dL or plasma cortisol level below 18 µg/dL 30 to 60 minutes after 250-µg cosyntropin administration. The amounts of hypertonic saline administered were recorded for 48 hours. Concentrations of sNa were measured via an indirect ion-selective electrode method using the AU5800 (Beckman Coulter, Brea, CA, USA) at the Hallym University Dongtan Sacred Heart Hospital and Seoul National University Bundang Hospital, and the Dimension Vista 1500 (Siemens Healthineers, Erlangen, Germany) at Seoul National University Bundang Hospital.

Biochemistry measurement and analysis

Blood samples for the determination of copeptin were collected at baseline and 24 to 48 hours after the initiation of hypertonic saline. After centrifugation at 2,000 × g, the samples were frozen at -70°C until assayed. Serum copeptin concentrations were determined in a single batch using a commercial automated immunofluorescence assay (B.R.A.H.M.S KRYPTOR Copeptin proAVP; Thermo Scientific Biomarkers, Hennigsdorf, Germany).

Study outcomes

To determine the underlying cause of hyponatremia, a structured diagnostic approach was implemented [1]. This approach was based on the patient’s history, physical examination, and laboratory test results. All patients were classified into five categories: (1) decreased extracellular fluid (ECF) volume due to renal Na loss (e.g., diuretics, especially thiazides); (2) decreased ECF volume due to non-renal Na loss (e.g., gastrointestinal Na loss or third spacing: vomiting, diarrhea, or malnutrition); (3) increased ECF volume (e.g., heart failure, liver cirrhosis, and nephrotic syndrome); (4) normal ECF volume with adrenal insufficiency; and (5) normal ECF volume fulfilling the essential criteria for SIAD [1,27].

The overcorrection rate, a surrogate marker of ODS, was defined as follows: an increase in the sNa level above 12 mmol/L within the first 24 hours or above 18 mmol/L within the first 24 to 48 hours based on previously published criteria [28] and recent guidelines [1,7]. Target correction rates were defined as sNa levels of 5 to 9 mmol/L within 24 hours and 10 to 17 mmol/L within 24 to 48 hours or ≥130 mmol/L. Under correction rates were defined as sNa levels of less than 5 mmol/L within 24 hours and less than 10 mmol/L within 24 to 48 hours.

Hypertonic saline infusion protocol

Participants from the SALSA trial underwent either rapid intermittent correction or slow continuous correction with hypertonic saline after randomization, as previously reported [26]. Participants from the prospective cohort underwent either rapid intermittent correction and/or slow continuous correction with no formalized protocol, according to the physician’s discretion.

Statistical analysis

The baseline characteristics and laboratory data are expressed as means ± standard deviations for normally distributed variables, medians (interquartile range) for non-normally distributed variables, and frequencies and percentages for categorical variables. The chi-square and Fisher exact tests were used to analyze categorical variables. The intergroup differences in the continuous variables were analyzed using the analysis of variance, Kruskal-Wallis tests, and Bonferroni post hoc tests to account for multiple testing. To compare two disorders among the five groups, a Mann-Whitney test with Bonferroni post hoc analysis was used; P < 0.005 was considered statistically significant. To present the diagnostic utility of copeptin, we used the area under the receiver operator characteristic curve (AUROC). Logistic regression analysis was performed to evaluate the risk of under correction, target correction, and overcorrection. The odds ratios (ORs) and 95% confidence intervals (CIs) for the risk of outcomes were calculated after stepwise adjustment for multiple confounders. Statistical significance was set at p < 0.05. All analyses were performed using IBM
Results

Study population

Table 2 shows baseline patient characteristics and biochemical data. The mean age and sNa level were 73 years and 117.9 mmol/L, respectively. The causes of hyponatremia were renal loss due to thiazide use, decreased ECF due to non-renal Na loss, increased ECF, adrenal insufficiency only, and SIAD in 30%, 9%, 11%, 11%, and 39% of the patients, respectively. The infusion modes of hypertonic saline were bolus therapy, continuous infusion, and mixed type in 45%, 54%, and 1% of the patients, respectively.

Copeptin levels and the copeptin-to-urine Na ratio according to the cause of hyponatremia

The overall median copeptin level and copeptin-to-UNa ratio (×100) at baseline were 16.9 pmol/L (7.6–43.8 pmol/L) and 28.0 pmol/mol (11.6–88.3 pmol/mol), respectively. The median copeptin and copeptin-to-UNa ratios are expressed as standard box plots according to the cause of hyponatremia (Fig. 2). Although there were no differences in the copeptin levels among the five groups, the copeptin-to-UNa ratio differed significantly according to the cause of hyponatremia (p = 0.001). The copeptin-to-UNa ratios in disorders with low effective arterial blood volume, secondary copeptin secretion (increased ECF or decreased ECF secondary to non-renal Na loss) tended to be higher than those with other causes of hyponatremia. The copeptin-to-UNa ratio exhibited a diagnostic utility identifying low effective arterial volume with an AUROC value of 0.78 (95% CI, 0.65–0.91, p < 0.001) (Fig. 3). The copeptin-to-UNa ratio in the group with decreased ECF due to non-renal Na loss was significantly higher than that in the groups of thiazide use (p < 0.001), adrenal insufficiency (p < 0.001), and SIAD (p < 0.001); however, there were no differences in the copeptin levels or the copeptin-to-UNa ratios among the three groups. Furthermore, there were no differences in copeptin levels or copeptin-to-UNa ratios between groups with decreased ECF due to non-renal Na loss and increased ECF (Table 3; Supplementary Table 1, available online).

Table 2. Baseline characteristics at initiation of study

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total (n = 100)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic</td>
<td></td>
</tr>
<tr>
<td>Male sex</td>
<td>48 (48.0)</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>73.0 ± 12.1</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>57.8 ± 10.9</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>22.9 ± 4.9</td>
</tr>
<tr>
<td>Comorbidity</td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>29 (29.0)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>64 (64.0)</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>6 (6.0)</td>
</tr>
<tr>
<td>Liver cirrhosis</td>
<td>2 (2.0)</td>
</tr>
<tr>
<td>Nephrotic syndrome</td>
<td>6 (6.0)</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>6 (6.0)</td>
</tr>
<tr>
<td>Malignancy</td>
<td>23 (23.0)</td>
</tr>
<tr>
<td>Hyponatremia cause</td>
<td></td>
</tr>
<tr>
<td>Thiazide use</td>
<td>30 (30.0)</td>
</tr>
<tr>
<td>Decreased ECF due to non-renal sodium loss</td>
<td>9 (9.0)</td>
</tr>
<tr>
<td>Increased ECF</td>
<td>11 (11.0)</td>
</tr>
<tr>
<td>Adrenal insufficiency</td>
<td>11 (11.0)</td>
</tr>
<tr>
<td>Syndrome of inappropriate antidiuresis</td>
<td>39 (39.0)</td>
</tr>
<tr>
<td>Infusion mode of hypertonic saline (bolus/continuous/mixed)</td>
<td>45/54/1</td>
</tr>
<tr>
<td>Laboratory value</td>
<td></td>
</tr>
<tr>
<td>Na (mmol/L)</td>
<td>117.9 ± 5.3</td>
</tr>
<tr>
<td>Serum osmolality (mOsm/kg)</td>
<td>250.7 ± 18.9</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>1.04 ± 1.06</td>
</tr>
<tr>
<td>White blood cell (10⁹/L)</td>
<td>8.4 ± 4.3</td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>11.7 ± 1.9</td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>4.0 ± 0.6</td>
</tr>
<tr>
<td>Ca (mg/dL)</td>
<td>8.7 ± 0.7</td>
</tr>
<tr>
<td>P (mg/dL)</td>
<td>3.2 ± 1.2</td>
</tr>
<tr>
<td>K (mmol/L)</td>
<td>3.9 ± 0.7</td>
</tr>
<tr>
<td>Total CO₂ (mmol/L)</td>
<td>23.3 ± 5.7</td>
</tr>
<tr>
<td>Uric acid (mg/dL)</td>
<td>4.0 ± 2.7</td>
</tr>
<tr>
<td>Total cholesterol (mg/dL)</td>
<td>155.0 ± 50.4</td>
</tr>
<tr>
<td>Total bilirubin (mg/dL)</td>
<td>0.9 ± 0.4</td>
</tr>
<tr>
<td>AST (IU/L)</td>
<td>31.1 ± 17.3</td>
</tr>
<tr>
<td>ALT (IU/L)</td>
<td>17.2 ± 8.9</td>
</tr>
<tr>
<td>C-reactive protein (mg/L)</td>
<td>25.8 ± 34.4</td>
</tr>
<tr>
<td>Urine osmolality (mOsm/kg)</td>
<td>418.0 ± 156.3</td>
</tr>
<tr>
<td>Urine Na (mmol/L)</td>
<td>73.5 ± 47.5</td>
</tr>
<tr>
<td>Urine K (mmol/L)</td>
<td>34.0 ± 24.0</td>
</tr>
</tbody>
</table>

Data are expressed as number (%), mean ± standard deviation, or number only.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; ECF, extracellular fluid.
Factors associated with serum copeptin levels at baseline

Table 4 shows the clinical and biochemical determinants of hyponatremic patients with copeptin levels above and below the median. Univariable analysis revealed that patients with copeptin levels above the median were characterized by lower sNa and serum potassium levels and a higher urine potassium level. Multivariable logistic regression analysis revealed that lower sNa levels (OR, 0.82; 95% CI, 0.73–0.93) and higher serum creatinine (OR, 2.91, 95% CI, 1.22–6.95) and urine potassium (OR, 1.05; 95% CI, 1.02–1.09) levels were independently associated with copeptin levels above the median.

Predicting responses to hypertonic saline

Supplementary Table 2 (available online) shows the cumulative amounts of hypertonic saline by time frame according to the infusion methods. The cumulative amounts of hypertonic saline were 173.6 mL within 6 hours, 337.7 mL within 24 hours, and 521.4 mL within 48 hours.

Table 5, Fig. 4, and Fig. 5 show the frequency and adjusted ORs for associations between copeptin at baseline and 24 hours after hypertonic saline treatment and the outcomes. Under correction, target correction, and overcorrection within 6 hours after treatment occurred in 38, 47, and five patients, respectively. Evaluation of the relationship between copeptin levels at baseline and target correction rate using multivariable logistic regression, even after adjustment for covariates such as infusion methods (rapid intermittent correction or slow continuous correction) and amounts of

Figure 2. Box plot for copeptin levels (A) and copeptin-to-urine Na × 100 (B) according to etiologies of hyponatremia. ECF, extracellular fluid; SIAD, syndrome of inappropriate antidiuresis. *P < 0.005, compared with decreased ECF due to non-renal Na loss (Kruskal-Wallis test and Bonferroni post hoc test).

Figure 3. Area under receiver operating characteristics curve for insufficient effective arterial blood volume (secondary copeptin release).
hypertonic saline, revealed that baseline copeptin levels below the median had an increased probability of reaching target correction within 6 hours (OR, 2.97; 95% CI, 1.16–7.64; p = 0.02). In terms of under correction and overcorrection within 6 hours, no differences were observed according to the copeptin levels (Fig. 4A). Under correction, target correction, and overcorrection occurred within 24 hours in 8, 44, and 22 patients, respectively. On multivariable logistic regression, even after adjustment for covariates including infusion methods and amounts of hypertonic saline, baseline copeptin levels below the median had an increased probability of reaching target correction within 24 hours (OR, 6.21; 95% CI, 1.67–23.09; p = 0.006). In terms of under correction and overcorrection within 24 hours, no differences were observed based on the copeptin levels (Fig. 4B). Overall, the median copeptin levels at 24 hours and 48 hours after treatment were 7.9 pmol/L (4.7–20.6 pmol/L) and 7.5 pmol/L (4.3–18.4 pmol/L), respectively. Under correction, target correction, and overcorrection occurred within 24 to 48 hours in 28, 54, and 12 patients, respectively. Multivariable logistic

Table 3. Baseline characteristics and biochemical data according to cause of hyponatremia

<table>
<thead>
<tr>
<th>Diagnostic category</th>
<th>Thiazide use (n = 30)</th>
<th>Decreased ECF due to non-renal Na loss (n = 9)</th>
<th>Increased ECF (n = 11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>74.5 ± 9.9</td>
<td>67.4 ± 19.3</td>
<td>79.4 ± 4.3</td>
</tr>
<tr>
<td>Male sex</td>
<td>9 (30.0)</td>
<td>5 (55.6)</td>
<td>4 (36.4)</td>
</tr>
<tr>
<td>Laboratory value</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum Na (mmol/L)</td>
<td>117.0 ± 5.0</td>
<td>116.2 ± 5.4</td>
<td>116.4 ± 7.1</td>
</tr>
<tr>
<td>Baseline copeptin (pmol/L)</td>
<td>14.7 ± 4.7</td>
<td>55.9 ± 1.6</td>
<td>20.2 ± 6.4</td>
</tr>
<tr>
<td>[Copeptin/urine Na] ratio × 100 (pmol/mol)</td>
<td>24.6 ± 12.9</td>
<td>228.4 ± 55.0</td>
<td>20.4 ± 5.8</td>
</tr>
<tr>
<td>Serum osmolality (mOsm/kg)</td>
<td>30.4 ± 12.9</td>
<td>30.9 ± 12.0</td>
<td>35.4 ± 12.9</td>
</tr>
<tr>
<td>Serum K (mmol/L)</td>
<td>3.8 ± 0.6</td>
<td>3.9 ± 0.7</td>
<td>4.5 ± 0.9</td>
</tr>
<tr>
<td>Serum uric acid (mg/dL)</td>
<td>3.7 ± 1.9</td>
<td>3.9 ± 0.7</td>
<td>4.5 ± 0.9</td>
</tr>
<tr>
<td>Serum creatinine (mg/dL)</td>
<td>0.96 ± 0.84</td>
<td>0.92 ± 0.34</td>
<td>1.40 ± 0.7</td>
</tr>
<tr>
<td>Urine Na (mmol/L)</td>
<td>20.4 ± 5.8</td>
<td>33.4 ± 15.4</td>
<td>35.4 ± 12.9</td>
</tr>
<tr>
<td>Urine K (mmol/L)</td>
<td>3.7 ± 1.9</td>
<td>3.7 ± 1.9</td>
<td>4.6 ± 12.9</td>
</tr>
<tr>
<td>Urine osmolality (mOsm/kg)</td>
<td>436 ± 172</td>
<td>366 ± 172</td>
<td>374 ± 100</td>
</tr>
</tbody>
</table>

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

Table 4. Factors associated with serum copeptin (above/below the median) at baseline as a categorical variable in patients with hyponatremia

<table>
<thead>
<tr>
<th>Parameter</th>
<th>OR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.00 (0.97–1.04)</td>
<td>0.88</td>
</tr>
<tr>
<td>Male sex</td>
<td>1.00 (0.45–2.21)</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.84 (0.36–1.92)</td>
<td>0.67</td>
</tr>
<tr>
<td>Diabetics vs. non-diabetics</td>
<td>1.50 (0.62–3.62)</td>
<td>0.37</td>
</tr>
<tr>
<td>Cancer</td>
<td>0.89 (0.35–2.81)</td>
<td>0.81</td>
</tr>
<tr>
<td>Cause of hyponatremia</td>
<td>1.76</td>
<td></td>
</tr>
<tr>
<td>Body mass index</td>
<td>1.02 (0.94–1.11)</td>
<td>0.68</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>0.99 (0.97–1.01)</td>
<td>0.27</td>
</tr>
<tr>
<td>Serum Na</td>
<td>0.85 (0.78–0.94)</td>
<td>0.001*</td>
</tr>
<tr>
<td>Serum K</td>
<td>0.49 (0.26–0.95)</td>
<td>0.03*</td>
</tr>
<tr>
<td>Serum osmolality</td>
<td>1.02 (1.00–1.05)</td>
<td>0.64</td>
</tr>
<tr>
<td>Serum creatinine</td>
<td>1.97 (1.00–3.86)</td>
<td>0.05</td>
</tr>
<tr>
<td>Serum uric acid</td>
<td>1.20 (1.00–1.44)</td>
<td>0.05</td>
</tr>
<tr>
<td>Serum C-reactive protein</td>
<td>1.00 (0.99–1.02)</td>
<td>0.64</td>
</tr>
<tr>
<td>Urine osmolality</td>
<td>1.00 (1.00–1.00)</td>
<td>0.74</td>
</tr>
<tr>
<td>Urine Na</td>
<td>0.99 (0.99–1.00)</td>
<td>0.16</td>
</tr>
<tr>
<td>Urine K</td>
<td>1.04 (1.01–1.06)</td>
<td>0.002*</td>
</tr>
</tbody>
</table>

CI, confidence interval; OR, odds ratio.
*p < 0.05.
regression analysis revealed associations between copeptin levels at 24 hours after treatment and outcomes within 24 to 48 hours. Patients with copeptin levels below the median at 24 hours after treatment had an increased risk of overcorrection within 24 to 48 hours (OR, 18.00; 95% CI, 1.59–203.45; p = 0.02) (Fig. 5). None of the patients developed ODS during the study period.

### Discussion

In this prospective cohort study, copeptin and copeptin-to-UNa ratios showed limited diagnostic utility in the differential diagnosis of hyponatremia. Hyponatremic patients with below-median copeptin levels at baseline achieved a higher target correction rate within -6/24 hours, while those with below-median copeptin levels 24 hours after treatment experienced a lower target correction rate within 24–48 hours. This suggests that copeptin levels can be used to predict the efficacy of treatment for hyponatremia.

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**Table 5. Adjusted ORs for association between copeptin below the median at baseline and outcomes**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Number (low, high)</th>
<th>Univariable</th>
<th>Multivariablea</th>
<th>Multivariableb</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>OR (95% CI)</td>
<td>p-value</td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td>Copeptin at baseline</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Under correction within 6 hr</td>
<td>(17/49, 21/49)</td>
<td>0.71 (0.31–1.60)</td>
<td>0.41</td>
<td>0.70 (0.31–1.60)</td>
</tr>
<tr>
<td>Target correction within 6 hr</td>
<td>(30/49, 17/49)</td>
<td>2.97 (1.31–6.76)</td>
<td>0.009*</td>
<td>3.12 (1.35–7.22)</td>
</tr>
<tr>
<td>Overcorrection within 6 hr</td>
<td>(1/49, 4/49)</td>
<td>0.23 (0.03–2.18)</td>
<td>0.20</td>
<td>2.23 (0.02–2.24)</td>
</tr>
<tr>
<td>Under correction within 24 hr</td>
<td>(2/49, 6/49)</td>
<td>0.31 (0.06–1.59)</td>
<td>0.16</td>
<td>0.31 (0.06–1.64)</td>
</tr>
<tr>
<td>Target correction within 24 hr</td>
<td>(26/49, 18/49)</td>
<td>1.95 (0.87–4.37)</td>
<td>0.11</td>
<td>2.01 (0.88–4.57)</td>
</tr>
<tr>
<td>Overcorrection within 24 hr</td>
<td>(11/49, 11/49)</td>
<td>1.00 (0.39–2.58)</td>
<td>&gt;0.99</td>
<td>0.92 (0.34–2.51)</td>
</tr>
<tr>
<td>Copeptin at 24 hr after treatment</td>
<td>(9/47, 19/50)</td>
<td>0.39 (0.15–0.97)</td>
<td>0.04*</td>
<td>0.38 (0.15–0.97)</td>
</tr>
<tr>
<td>Target correction within 24–48 hr</td>
<td>(27/47, 27/50)</td>
<td>1.15 (0.52–2.57)</td>
<td>0.73</td>
<td>1.16 (0.52–2.59)</td>
</tr>
<tr>
<td>Overcorrection within 24–48 hr</td>
<td>(10/47, 2/50)</td>
<td>6.49 (1.34–31.42)</td>
<td>0.02p</td>
<td>6.49 (1.34–31.42)</td>
</tr>
</tbody>
</table>

CI, confidence interval; OR, odds ratio.

*Analysed with age and sex; **analyzed with age, sex, body mass index, systolic blood pressure, diabetes mellitus, liver cirrhosis, cancer, serum sodium/creatinine/uric acid/C-reactive protein/serum osmolality/urine osmolality/urine sodium at baseline, cause of hyponatremia, hypertonic saline volume, and infusion mode of hypertonic saline (bolus/continuous/mixed).

*p < 0.05.

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**Figure 4.** Outcomes within 6 hours (A) and 24 hours (B) stratified by copeptin level at baseline (below/above median).
rienced a higher overcorrection rate within the next 24 hours.

In this study, the median copeptin level was 16.9 pmol/L, which is similar to the level reported in previous studies when classified according to the cause of hyponatremia [24,29]. As shown in Table 4, determinants of copeptin levels were sNa and serum creatinine, in accordance with previous studies [29,30]. High copeptin levels were associated with low sNa and high serum creatinine levels.

We categorized the causes of hyponatremia into five groups and evaluated the diagnostic validity of copeptin for differentiating between the underlying etiologies of hyponatremia. In agreement with a previous study, we observed that while the copeptin level by itself did not have any diagnostic utility, the copeptin-to-UNa ratio allowed for improved differentiation among some subgroups (distinguishing conditions of a secondary AVP surge from a primary AVP release), but not all hyponatremia etiologic subgroups [29]. The copeptin-to-UNa ratio was highest in patients with decreased ECF volume due to non-renal Na loss compared to other etiologies. These observations are similar to those of Nigro et al. [22]. Although copeptin in addition to volume status improved the identification of hypovolemic hyponatremia, copeptin did not seem to have a higher diagnostic value compared with UNa. The copeptin-to-UNa ratio was higher in groups with a low effective arterial blood volume (decreased ECF volume due to non-renal Na loss and the increased ECF group), in other words, secondary AVP release. These two groups had higher serum copeptin levels and lower UNa levels, which resulted in a higher ratio. In agreement with previous reports, copeptin levels widely overlapped among the different etiologies of hyponatremia, and also showed large variability within a single category. One of the possible explanations for this observation is that hyponatremia is not only caused by inappropriate AVP secretion, but also by other factors including comorbidities [17,21], medications, dehydration [23], or stress [31]. Additionally, the correlation between the changes in copeptin levels over the course of 24 hours and the etiologies of hyponatremia were not statistically significant (data not shown).

We also evaluated the efficacy of copeptin as a predictive marker of treatment response. Patients with a baseline serum copeptin level below the median achieved target correction of sNa within 6 hours of treatment. Copeptin and AVP respond to either a decreased ECF volume or increased osmolality to maintain fluid homeostasis [10]. When baseline copeptin levels are low, it could be considered that there is less chance of having previous hyperosmolar or hypovolemic stimuli; sNa may respond better to a hypertonic saline infusion. Conversely, when baseline copeptin levels are high, achieving target correction by hypertonic saline treatment may be more difficult.

Meanwhile, patients with copeptin levels below the median at 24 hours after treatment showed a higher frequency of overcorrection within 24 to 48 hours after treatment. Plasma copeptin is reported to increase rapidly as osmolality changes in response to hypertonic saline infusion in healthy subjects [32]; however, a low copeptin level 24 hours after treatment may indicate a somewhat decreased antidiuretic response during hypertonic saline infusion. A low copeptin level, and thus a low AVP level, at 24 hours after treatment indicates that a greater excretion of free water can occur [33], and the effect of increasing sNa for the same amount of hypertonic saline can be augmented.

It is still unclear why some patients present with low copeptin levels, while others present with high copeptin levels despite receiving the same hypertonic saline treatment, given that most hyponatremic states are characterized by an inappropriate antidiuresis. We present two possible explanations for this finding. First, the atrial natriuretic protein (ANP) may play a role in this complicated response. Previous studies have demonstrated an immediate release of ANP in re-
sponse to a hypertonic saline infusion, regardless of the etiology of hyponatremia [34,35]. Seeing that ANP inhibits not only the secretion of AVP, but also the antidiuretic response itself [36], this may lead to a decrease in AVP levels due to the negative feedback of ANP on AVP. This could explain the low copeptin levels in some of the patients included in our study. Recently, Nigro et al. [37] reported an association between midregional proANP and the differential diagnosis of hyponatremia; the midregional proANP levels were prominently higher in the hypervolemic hyponatremia group at baseline. It may not respond normally to hypertonic saline in conditions with chronic hypervolemic hyponatremia, such as heart failure or liver cirrhosis. If low copeptin levels are observed 24 hours after treatment, it is necessary to re-evaluate the change in volume status or other comorbidities before continuing with the hypertonic saline infusion.

The second possible explanation for the low copeptin level at 24 hours after treatment is the pathological heterogeneity of SIAD. In our study, 39% of the patients were diagnosed with SIAD. Fenske et al. [8] suggested a copeptin-based classification of SIAD subtypes, and stated that there were five subtypes according to the changes in copeptin levels during a hypertonic saline treatment. One-fourth of the SIAD patients presented with elevated copeptin levels, while the remaining patients were in the normal or below normal range despite hypertonic saline infusion [8]. Due to the varying degree of osmoregulatory defects, it is necessary to pay attention to the correction rate of sNa during hypertonic saline treatment in SIAD, especially when the copeptin levels after 24 hours of treatment are low. We divided our population into five groups (designated A–E) according to copeptin levels measured at baseline and at 24 hours as in a previous study [8]. We then analyzed the association between A and E grouping and outcomes within 24 hours. Among all patients, 2.2%, 9.7%, 40.9%, 1.1%, and 46.2% of patients were in groups A to E. However, this classification was not statistically significant in predicting outcomes (target, under-, and overcorrection rates of sNa) within 24 hours (data not shown). It is presumed that the number of patients was too small to prove the relevance of these classifications and outcomes.

In hyponatremic patients, serum copeptin at baseline predicted a target correction within 6 hours of hypertonic saline treatment, thereby serving as an efficacy index. Furthermore, copeptin at 24 hours after treatment predicted an overcorrection rate within 24 to 48 hours posttreatment, thus serving as a safety index. The clinical application of our findings lies in the suggestion that for patients with low copeptin levels, a bolus therapy of hypertonic saline is more useful than a continuous infusion because bolus therapy limits the risk of overcorrection, which is commonly associated with continuous infusion [1,38].

In acute illness, the secretion of AVP and copeptin may be driven by nonosmotic stimuli [31]. In this study, patients with anemia or acute inflammation/infection were also included. Therefore, we performed sensitivity analysis for the association between copeptin and outcomes, excluding patients with anemia (hemoglobin ≤ 10 g/dL, n = 16) or acute inflammation (C-reactive protein ≥ 50 mg/L, n = 23). In patients with hemoglobin levels above 10 g/dL (n = 84), similar results were obtained. However, in patients with C-reactive protein levels below 50 mg/dL (n = 77), the association of copeptin at baseline with the target correction within 24 hours, and the association of copeptin at 24 hours after treatment with overcorrection within 24 to 48 hours, was statistically significant (Supplementary Table 3, available online).

This study has several limitations. First, the sample size of 100 patients with hyponatremia is somewhat small. Second, while we evaluated the correction rate or the magnitude of sNa in the treatment of hyponatremia, no patient developed ODS, which is the true outcome of interest despite overcorrection; however, several studies have reported that overcorrection may be one of the main causes of ODS [5,39,40]. Overcorrection may be a good laboratory outcome and may be resolved by lowering the infused amount in clinical practice [28]. Third, copeptin is not commercially available at present, similar to other biomarker studies. We acknowledge that it is important to improve the prognosis by repeatedly measuring sNa to achieve the target correction rate in the treatment of hyponatremia. We hypothesized that copeptin might be useful as an additional factor to sNa itself in treating hyponatremic patients by suggesting the methods of hypertonic saline administration. Fourth, 38 participants from the prospective cohort did not receive hypertonic saline with the formalized protocol as bolus therapy or continuous infusion. However, there was no difference in distribution between bolus and continuous infusion in all patients, and we tried to reduce potential confounding by adjusting hypertonic saline volume for 48 hours in multivariable analysis. Fifth, we did not include healthy controls. Finally, we did not routinely measure serum or urine osmolality after
hypertonic saline infusion. Thus, we could not examine the association between copeptin levels and osmolality to predict treatment response.

Nonetheless, this is the first study to demonstrate the usefulness of copeptin in predicting the efficacy and safety of hypertonic saline treatment in patients with hyponatremia. We suggest that measuring copeptin in addition to sNa itself may help physicians achieve proper correction of hyponatremia. Further studies involving a large number of patients and a formalized infusion protocol for hypertonic saline are required.

Conflicts of interest

All authors have no conflicts of interest to declare.

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References


Urinary exosomal microRNA profiling in type 2 diabetes patients taking dipeptidyl peptidase-4 inhibitor compared with sulfonylurea

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Background: Dipeptidyl peptidase-4 (DPP-4) inhibitor has been reported to have kidney-protective benefits. To elucidate how antidiabetic agents prevent diabetic kidney disease progression, it is important to investigate their effect on the kidney environment in type 2 diabetes mellitus (DM) patients. Herein, we investigated the expression pattern of urinary exosome-derived microRNA (miRNA) in patients taking a combination of DPP-4 inhibitor and metformin (DPP-4 inhibitor group) and compared them with patients taking a combination of sulfonylurea and metformin (sulfonylurea group).

Methods: This was a prospective study involving 57 patients with type 2 DM (DPP-4 inhibitor group, n = 34; sulfonylurea group, n = 23) and healthy volunteers (n = 7). We measured urinary exosomal miRNA using the NanoString nCounter miRNA array (NanoString Technologies) across the three groups (n = 4 per each group) and validated findings using real-time polymerase chain reaction.

Results: Twenty-one differentially expressed candidate miRNAs were identified, and six (let-7c-5p, miR-23a-3p, miR-26a-3p, miR-30d, miR-205, and miR-200a) were selected for validation. Validation showed no significant difference in miRNA expression between the DPP-4 inhibitor and sulfonylurea groups. Only miR-23a-3p was significantly overexpressed in the diabetes group compared with the control group (DPP-4 inhibitor vs. control, p = 0.01; sulfonylurea vs. control, p = 0.007). This trend was consistent even after adjusting for age, sex, and body mass index.

Conclusion: There was no significant difference in urine exosome miRNA expression between diabetic participants taking DPP-4 inhibitor and those taking sulfonylurea. The miR-23a levels were higher in diabetic participants than in nondiabetic controls.

Keywords: Biomarkers, Diabetic nephropathies, Exosomes, MicroRNAs, Diabetes mellitus, Type 2
Introduction

Type 2 diabetes mellitus (DM) has reached endemic levels and is a major public health concern [1]. Chronic exposure to hyperglycemia due to long-standing DM and poor glycemic control damages the microvasculature eventually leading to a number of complications including kidney disease, retinopathy, and peripheral neuropathy. Therefore, strict control of blood glucose is essential to prevent microvascular complications in type 2 DM as well as type 1 DM [2,3]. There are currently several antidiabetic drugs on the market for maintaining proper glycemic targets and reducing complications.

Metformin monotherapy has been the preferred first-line treatment for type 2 DM [4]. In cases where metformin monotherapy is inadequate for glycemic control, and the patient does not have atherosclerotic cardiovascular disease or chronic kidney disease, a combination of metformin with an antihyperglycemic drug from any one of the following six antidiabetic drugs classes is recommended; sulfonylurea, thiazolidinedione, dipeptidyl peptidase-4 (DPP-4) inhibitor, sodium-glucose cotransporter 2 inhibitor, glucagon-like peptide-1 receptor agonist, or basal insulin. The choice of combination therapy is based on drug-specific effects and patient factors [4]. Sulfonylurea and DPP-4 inhibitors are currently the most widely prescribed second-line oral antidiabetic agents [5]. DPP-4 inhibitor provides renoprotection in addition to lowering blood glucose levels by ameliorating kidney fibrosis, reducing renal oxidative stress, and attenuating filtration barrier injury [6–10]. While DPP-4 inhibitor represents a major milestone in DM management, there are limited clinical data to support the claim that these drugs are renoprotective [11–13].

MicroRNAs (miRNAs) are small, noncoding RNAs involved in negative posttranscriptional regulation. miRNA are critical for normal animal development and are involved in various biological processes [14,15]. Previous studies reported that miRNA plays a pivotal role in DM development by affecting pancreatic β-cell function and insulin resistance [16]. MiRNA is thought to influence diabetic complications and can thus serve as potential biomarkers and therapeutic targets [17]. DPP-4 inhibitor has been reported to regulate miRNAs by suppressing the transforming growth factor-β signaling pathway, which induces miR-29 and miR-let-7; these two miRNAs comprise positive feedback loops of anti-endothelial mesenchymal transition [6,18,19]. Another study reported that treatment with linagliptin, a DPP-4 inhibitor, restored miR-29c levels while suppressing profibrotic miRNA induction such as miR-199-3p [20].

While the majority of miRNAs are located within the cell microenvironment, some miRNAs known as circulating miRNAs or extracellular miRNAs are found in the extracellular environment [21]. Extracellular miRNAs are bound to proteins or wrapped with small membranous particles such as exosomes, microvesicles, and apoptotic bodies to shield them from degradation [21]. Exosome-mediated miRNA transfer, mediates cell-cell communications, and has been associated with several human diseases including kidney diseases [22–24].

In this study, we evaluated DPP-4 inhibitor effects on the kidney microenvironment and their kidney-protective effect in type 2 DM patients. We hypothesized that DPP-4 inhibition will change the kidney microenvironment, and this will affect miRNA expression of urinary exosome. Considering the urinary exosome as a reflection of the renal microenvironment [25], we investigated and compared the expression pattern of urinary exosome-derived miRNAs in patients taking a DPP-4 inhibitor with patients taking sulfonylurea as second-line antihyperglycemic treatments.

Methods

Study subjects

This was a prospective observational study of patients who received outpatient treatment at the endocrinology department of Soonchunhyang University Cheonan Hospital in Cheonan, Republic of Korea. The study complied with the Declaration of Helsinki and the study protocol was approved by the Institutional Review Board of Soonchunhyang University Cheonan Hospital (No. 2017-11-031). All patients provided written informed consent before enrollment.

We recruited type 2 DM patients who were on a combination of sulfonylurea (glimepiride or gliclazide) or DPP-4 inhibitor (gemigliptin) and metformin for at least 3 months and had not taken other diabetic medications. Inclusion criteria included being 20 to 60 years old, glycated hemoglobin level between 6% and 10%, and eGFR of >60 mL/min/1.73 m². Exclusion criteria included patients who had pancreas, heart, liver, or blood diseases, had a history of cancer, suf-
ferred from an infection or inflammatory disease, had been treated for an acute diabetic complication recently, or who had a history of hospitalization within the last 3 months. Nondiabetic patients who did not have DM, hypertension, and cardiovascular disease were also enrolled as controls for comparison. We categorized patients who took metformin and sulfonylurea as the sulfonylurea group and patients that took metformin and DPP-4 inhibitor as the DPP-4 inhibitor group. The nondiabetic participants were the control group.

**Isolation of exosomal microRNA from urine**

Fasting urine samples (10 mL) were collected in sterile containers and centrifuged at 10,000 × g for 10 minutes to remove large particles (apoptotic bodies, microparticles), cell debris, organelles, and protein aggregates. Extracellular vesicles were then precipitated from 15 mL of urine using miRCURYTM Exosome Isolation Kits (Exiqon A/S, Vedbaek, Denmark), according to the manufacturer’s protocol. RNA was extracted from the exosomes using the miRNeasy Mini Kit (Qiagen, Hilden, Germany). Exosome suspensions (200 μL) were mixed with QIAzol lysis buffer (1 mL; Qiagen), and the mixtures were processed according to the manufacturer’s guidelines. RNA was eluted in RNase-free water (20 μL; Qiagen). Noncoding RNAs were isolated from exosomes using the miRNeasy Micro Kit (Qiagen, Valencia, CA, USA).

**miRNA profiling using NanoString technology**

To profile miRNA expression from urinary exosomes, the NanoString nCounter system assay was performed using the NanoString platform and nCounter Human v3 miRNA Expression Assay Kits (NanoString Technologies, Seattle, WA, USA), according to the manufacturer’s instructions. miRNA profiling was performed on four samples each from the sulfonylurea, DPP-4 inhibitor, and control groups, starting from 3 μL of isolated RNA (~150 ng). Samples were processed using the automated nCounter Prep Station; following hybridization, they were purified and immobilized on a sample cartridge for quantification and data collection using the nCounter Digital Analyzer.

**Comparing miRNA expression levels between groups**

To compare miRNA expression between the groups, we used the open-source statistical platform NanoStringDiff [26]. Briefly, this method assumes a negative binomial-based model to fit the discrete nature of the nCounter data and corrects for platform variation, sample content variation, and background noise. Data normalization was incorporated into the model framework using data normalization parameters, which were estimated from positive controls, negative controls, and housekeeping genes embedded in the nCounter system. Additionally, false discovery rate adjusted p-values were based on a significance level of p < 0.05 for every comparison per gene.

**Quantitative real-time polymerase chain reaction**

miRNAs were isolated from urinary exosomes. To synthesize complementary DNA (cDNA), we used the TaqMan Advanced miRNA CDNA Synthesis Kit (Applied Biosystems, Franklin Lakes, NJ, USA). We followed the guidelines for preparing cDNA templates, using 2 μL of exosomal RNA sample, all mature miRNAs in the sample were reverse transcribed to cDNA. To evaluate miRNA expression levels, we used TaqMan Advanced miRNA assays (Applied Biosystems) with synthesized cDNA. Gene expression levels were quantified using the StepOneTM real-time (RT) polymerase chain reaction (PCR) System (Applied Biosystems). The same amount of miRNA was used for validation [27]. Comparative RT-PCR including the no-template controls was performed using specific primers for let-7c-5p, miR-23a-3p, miR-26a-3p, miR-30d, miR-205, and miR-200a, with reagents from TaqMan reagents (Applied Biosystems). The PCR was carried out with the following conditions: 95°C for 20 seconds (polymerase activation step), denaturation at 95°C for 1 second, and anneal/extend at 60°C for 20 seconds (40 cycles). PCR results were calculated using the comparative threshold method.

**Statistical analysis**

Statistical tests and data representation were performed using R version 4.0.0 (The R Foundation for Statistical Computing, Vienna, Austria). Categorical variables are expressed as count (percentage). Normally distributed continuous variables are expressed as mean ± standard deviation and non-normally distributed continuous variables are expressed as medians with interquartile ranges. Groups were compared with Student two-tailed unpaired t test or one-
way analysis of variance, followed by post hoc test using a pairwise t test with Bonferroni correction. Data are represented as mean values with 95% confidence intervals in error bar plot. Multiple linear regression models were used to compare miRNA expression between groups after adjusting for confounders. A p-value of <0.05 was considered statistically significant.

Results

Patient characteristics

A total of 64 participants were enrolled in this study; 34 participants in the DPP-4 inhibitor group, 23 participants in the sulfonylurea group, and seven participants in the control group. The mean age of diabetic participants was 53.4 ± 11.6 years, with a mean body mass index (BMI) of 26.1 ± 3.3 kg/m²; 36 diabetic patients (63.2%) were men. The mean age of the nondiabetic participants was 42.3 ± 11.5 years, with a mean BMI of 21.5 ± 1.7 kg/m², and four nondiabetic patients (57.1%) were men. Baseline characteristics of the study participants are presented in Table 1. There was no significant difference in baseline clinical parameters between the DPP-4 inhibitor group and the sulfonylurea group. In the DPP-4 inhibitor and sulfonylurea groups, 14 patients (41.2%) and 11 patients (47.8%) took angiotensin converting enzyme inhibitors or angiotensin receptor blocker, respectively, and this difference was not significant. Four representatives from each group (DPP-4, sulfonylurea, control) were selected to undergo NanoString analysis by matching age, gender, and BMI. Their baseline characteristics are presented in Supplementary Table 1 (available online). There were no significant

Table 1. Baseline characteristics of study subjects

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Nondiabetic control</th>
<th>Type 2 DM</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>7</td>
<td>34</td>
<td>23</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>42.3 ± 11.5</td>
<td>53.2 ± 11.6</td>
<td>53.7 ± 11.9</td>
</tr>
<tr>
<td>Male sex</td>
<td>4 (57.1)</td>
<td>24 (70.6)</td>
<td>12 (52.2)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>167.3 ± 7.8</td>
<td>166.5 ± 7.2</td>
<td>162.5 ± 10.6</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>60.0 ± 5.8</td>
<td>72.9 ± 10.3</td>
<td>69.7 ± 16.2</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>21.5 ± 1.7</td>
<td>26.3 ± 2.8</td>
<td>25.8 ± 3.9</td>
</tr>
<tr>
<td>ACEi/ARB use</td>
<td>0 (0)</td>
<td>14 (41.2)</td>
<td>11 (47.8)</td>
</tr>
<tr>
<td>WBC (×10³/μL)</td>
<td>5.57 ± 1.18</td>
<td>7.64 ± 2.15</td>
<td>7.37 ± 2.75</td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>13.8 ± 2.0</td>
<td>14.8 ± 1.8</td>
<td>14.3 ± 1.6</td>
</tr>
<tr>
<td>Total protein (g/dL)</td>
<td>7.25 ± 0.30</td>
<td>7.45 ± 0.42</td>
<td>7.44 ± 0.36</td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>4.65 ± 0.33</td>
<td>4.70 ± 0.23</td>
<td>4.68 ± 0.22</td>
</tr>
<tr>
<td>Glucose (mg/dL)</td>
<td>97.3 ± 6.4</td>
<td>140.3 ± 38.1</td>
<td>137.9 ± 50.5</td>
</tr>
<tr>
<td>AST (IU/L)</td>
<td>18.0 (15.5–20.5)</td>
<td>22.0 (18.0–33.5)</td>
<td>23.0 (20.5–26.8)</td>
</tr>
<tr>
<td>ALT (IU/L)</td>
<td>16.0 (10.5–19.0)</td>
<td>29.5 (20.2–48.5)</td>
<td>29.5 (18.2–38.8)</td>
</tr>
<tr>
<td>Urea nitrogen (mg/dL)</td>
<td>11.8 ± 2.4</td>
<td>14.4 ± 5.0</td>
<td>13.0 ± 4.3</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>0.82 ± 0.11</td>
<td>0.84 ± 0.18</td>
<td>0.77 ± 0.19</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>6.76 ± 0.94</td>
<td>7.21 ± 1.34</td>
<td>7.21 ± 1.34</td>
</tr>
<tr>
<td>eGFR (mL/min/1.73 m²)</td>
<td>104.7 ± 15.1</td>
<td>95.1 ± 15.3</td>
<td>97.9 ± 16.7</td>
</tr>
<tr>
<td>Total cholesterol (mg/dL)</td>
<td>185.6 ± 31.8</td>
<td>149.4 ± 36.2</td>
<td>165.7 ± 49.0</td>
</tr>
<tr>
<td>HDL cholesterol (mg/dL)</td>
<td>61.1 ± 11.3</td>
<td>50.4 ± 11.1</td>
<td>47.3 ± 15.1</td>
</tr>
<tr>
<td>LDL cholesterol (mg/dL)</td>
<td>120.1 ± 28.0</td>
<td>89.2 ± 29.3</td>
<td>99.5 ± 39.4</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>75.0 (73.0–85.0)</td>
<td>135.0 (83.0–228.0)</td>
<td>141.0 (96.0–251.0)</td>
</tr>
<tr>
<td>UACR (mg/gCr)</td>
<td>6.66 (3.83–19.57)</td>
<td>6.51 (4.29–14.86)</td>
<td>0.91</td>
</tr>
</tbody>
</table>

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

Patients with type 2 DM were categorized according to their antidiabetic medication.

ACEi, angiotensin converting enzyme inhibitors; ALT, alanine aminotransferase; ARB, angiotensin receptor blocker; AST, aspartate aminotransferase; BMI, body mass index; DM, diabetes mellitus; DPP-4, dipeptidyl peptidase-4; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; LDL, high-density lipoprotein; NA, not available; UACR, urine albumin-to-creatinine ratio; WBC, white blood cell.
differences in baseline characteristics between all patients and the four representative patients included in the NanoString analysis.

**Exosomal miRNA expression profiles**

In miRNA profiling analyses with NanoString technology, there were 21 differentially expressed candidate miRNAs between the DPP-4 inhibitor group and the sulfonylurea group (Fig. 1A). Of these, four miRNAs were upregulated in the DPP-4 inhibitor group and 17 miRNAs were upregulated in the sulfonylurea group (Fig. 1B). The expression patterns of these 21 miRNAs are presented as a heatmap (Fig. 1C). Altogether, 90 miRNAs were differentially expressed between the sulfonylurea group and the control group (58 miRNAs upregulated in the sulfonylurea group and 32 miRNAs upregulated in the control group), and 84 miRNAs differentially expressed between the DPP-4 inhibitor group and the control group (72 miRNAs upregulated in the DPP-4 inhibitor group and 12 miRNAs upregulated in the control group) (Supplementary Fig. 1, available online).

**Validation of candidate urinary exosomal miRNAs expression**

From the 21 differentially expressed urinary exosomal miRNAs between the DPP-4 inhibitor group and the sulfonylurea group, six miRNAs (let-7c-5p, miR-23a-3p, miR-26a-3p, miR-30d, miR-205, and miR-200a) were selected for validation. These six miRNAs were selected through literature review, and it was confirmed that the miRNAs were associated with DM. Unlike with the NanoString analysis results, we failed to reproduce differences between miRNA expression in the DPP-4 inhibitor group and the sulfonylurea group in all the six miRNAs. Only miR-23a-3p was significantly overexpressed in the urinary exosome of the DM groups compared with the nondiabetic control group (p for DPP-4 inhibitor group vs. control group = 0.01, p for sulfonylurea group vs. control group = 0.007) (Fig. 2; Supplementary Fig. 3, available online). Even after adjusting for age, sex, and BMI, miR-23a-3p expression was significantly higher in the DM groups than in the control group (p for DPP-4 inhibitor group vs. control group = 0.01, p for sulfonylurea group vs. control group = 0.02). There was no significant difference between the control groups and the two DM groups (DPP-4 inhibitor group and sulfonylurea group) in let-7c-5p, miR-26a-3p, miR-30d, miR-205, and miR-200a expression (Fig. 2, Supplementary Fig. 3). There was no clear correlation between the urinary exosomal miRNAs and kidney function and albuminuria (Supplementary Table 2, available online).

**Discussion**

In this study, NanoString analysis showed 21 differentially expressed urinary exosomal miRNAs between the DPP-4 inhibitor group and the sulfonylurea group. However, we failed to reproduce differences in miRNA expression with RT-PCR validation. Based on our RT-PCR results, miR-23a-3p was significantly higher in the urinary exosome of the diabetic participants than in the nondiabetic controls.

There was no difference in urinary exosomal miRNA expression between the DPP-4 inhibitor group and the sulfonylurea group in this study. This is likely because there was no difference between the two groups, but non-drug-related reasons may have obscured any actual difference. Heterogeneity in participant baseline characteristics could have made it challenging to find the true difference. In particular, the duration of drug use and duration of DM status were variable between the study participants. Furthermore, the homogeneity between the two diabetic groups could have masked differences resulting from the two antidiabetic drugs. The participants across the two diabetic groups had similar overall characteristics in that both groups comprised type 2 DM patients who received outpatient care without other problems.

Urinary exosome-derived miRNAs are protected from endogenous RNase activity, they are remarkably stable, and they are not easily confounded by circulating miRNAs that pass through the glomerular filtration barrier [28,29]. This makes miRNA profiling useful in DM cases and suggests that urinary exosome-derived miRNAs might be better diagnostic markers than free miRNAs. Although there are many studies that reported a role for exosomal miRNAs in DM [17,30], no research study has reported expression patterns of exosomal miRNAs with regard to diabetic medications. Our work presents insights and approaches for new research on diabetic medication. If the shortcomings of our research are addressed in future research, we can further evaluate how diabetic medications affect the kidney environment.

In our study, miR-23a-3p was significantly overexpressed...
Figure 1. Expression patterns of urinary exosomal miRNAs from nondiabetic controls and type 2 diabetic participants who were grouped according to their medication. (A) Venn diagrams of differentially expressed miRNAs between the sulfonylurea (SU) group, the DPP-4 inhibitor (DPP4i) group, and the control (CTRL) group. (B) Log fold change (FC) values of differentially expressed miRNA in the DPP4i group compared with the SU group. (C) Heatmap representing hierarchical clustering of differentially expressed miRNAs in the DPP4i group and the SU group.

DPP-4, dipeptidyl peptidase-4; miRNA, microRNA.
in the urinary exosome of the DM groups compared with the nondiabetic control group. Xu et al. [31] reported that miR-23a was upregulated in renal tissue of diabetic patients and high glucose-induced HK cells. This result was consistent with our findings, especially considering that most exosomes in urine might originate from the kidney cells. Their study also showed that knockdown of miR-23a suppressed high glucose-induced epithelia-mesenchymal transition.

Figure 2. Expression of candidate urinary exosomal miRNAs between the control (CTRL), DPP-4 inhibitor (DPP4i), and sulfonylurea (SU) groups. The comparative threshold values of quantitative real-time polymerase chain reaction of urinary exosomal miRNAs including let-7c-5p (A), miR-23a-3p (B), miR-26a-3p (C), miR-30d (D), miR-205 (E), and miR-200a (F) are presented as arithmetic means and 95% confidence intervals in an error bar plot. DPP-4, dipeptidyl peptidase-4; miRNA, microRNA. *p < 0.05, **p < 0.01.
and renal fibrosis. Our research only revealed that miR-23a levels were elevated in the urinary exosome of diabetic participants, so further research to verify the association between miR-23a in the urinary exosome and diabetic kidney disease severity is needed.

Our study has a number of limitations. First, the changes in miRNA levels over time were not measured because of the cross-sectional design of this study. If the changes had been analyzed, the effects of the drugs on exosomal miRNA would have been more conspicuous, which would have increased our statistical power. Second, as previously mentioned, the duration of diabetic medication varied among study subjects. Third, the association of miR-23a levels in urinary exosome with the degree of kidney damage was not examined because most of the participants included in this study had a normal range of albuminuria and renal function.

In conclusion, there was no significant difference in urine exosome miRNA expression between diabetic participants taking a DPP-4 inhibitor and those taking sulfonylurea. The miR-23a was elevated in diabetic participants compared with nondiabetic controls. Further research on the effects of diabetic medication on exosomal miRNA expression is required.

Conflicts of interest

All authors have no conflicts of interest to declare.

Funding

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Authors’ contributions

Conceptualization: HWG, SWC, DYK, NJC
Data curation: SWC, DYK, HWG, SP, EL
Formal analysis, Visualization: TWH, HKK, NJC
Funding acquisition: HWG
Investigation: TWH, HKK, MRL
Methodology: MRL, SHK, HWG, NJC
Project administration: HWG
Writing-Original Draft: NJC, HWG
Writing-Review & Editing: All authors
All authors read and approved the final manuscript.

References


Effect of pravastatin on erythrocyte membrane fatty acid contents in patients with chronic kidney disease

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Background: Statin treatment has decreased the risk of cardiovascular events in patients with chronic kidney disease (CKD). Erythrocyte membrane oleic acid level is higher in patients with acute coronary syndrome. This study aimed to evaluate the effect of pravastatin on the erythrocyte membrane fatty acid (FA) contents in patients with CKD.

Methods: Sixty-two patients were enrolled from January 2017 to March 2019 (NCT02992548). Pravastatin was initially administered at a dose of 20 mg for 24 weeks. The pravastatin dose was increased to 40 mg after 12 weeks if it was necessary to control dyslipidemia. The primary outcome was change in erythrocyte membrane FA, including oleic acid, after pravastatin treatment for 24 weeks.

Results: Forty-five patients finished this study, and there was no adverse effect related to pravastatin. Compared with baseline, total cholesterol and low-density lipoprotein cholesterol levels were significantly decreased after pravastatin treatment. Compared with baseline, saturated FA, oleic acid, and arachidonic acid levels were significantly increased and polyunsaturated FA and linoleic acid (LA) levels were significantly decreased after pravastatin treatment. There was also a decrease in eicosapentaenoic acid after pravastatin treatment in CKD patients with estimated glomerular filtration rate < 60 mL/min/1.73 m².

Conclusion: Administration of pravastatin in patients with CKD leads to a decrease in FA known to be protective against the risk of CVD. Omega-3 FA or LA supplementation might be necessary to recover changes in erythrocyte membrane FA contents when pravastatin is used for treating dyslipidemia in patients with CKD.

Keywords: Chronic kidney disease, Omega-3 fatty acid, Pravastatin

Introduction

The mortality rate in patients with chronic kidney disease (CKD) increases with a decrement of kidney function and presence of cardiovascular disease (CVD), and this is a major cause of morbidity in patients with CKD. According to the United States Renal Data System, patients with CKD experienced higher mortality rates of 111.2 per 1,000 patient-years than the general population, at 45.2 per 1,000 in 2014. In particular, the mortality rate is higher in patients with CKD
having diabetes mellitus (DM) than in those with DM alone [1]. This is because there are nontraditional risk factors such as insulin resistance, malnutrition, mineral bone disorders, and traditional risk factors inducing cardiovascular complications such as dyslipidemia, smoking, and obesity in CKD [2]. Some patients with CKD die of CVD before need for dialysis [3].

Treatment with the statins class of drugs has decreased the risk of CVD in patients with CKD. The Kidney Disease: Improving Global Outcomes guideline recommend the use of statin drugs in predialysis patients [4]. The effect of statins is attributed to a decrease in low-density lipoprotein (LDL)-cholesterol, sometimes accompanied by an increase in high-density lipoprotein (HDL)-cholesterol and a decrease in triglycerides. Recent clinical trials have shown that drugs, such as fibrate or nicotinic acid, that increase HDL-cholesterol or reduce triglycerides are not recommended in patients with CKD owing to safety or toxicity concerns [4,5]. In particular, if statins are used effectively, there are no additional benefits of those drugs to the incidence of CVD or mortality [6,7]. This suggests that treatment with statins is sufficient to achieve the same effects as use of nicotinic acid or fibrate.

Omega-3 fatty acid (FA) is known to reduce the incidence of CVD, especially myocardial infarction or arrhythmia, in such drug-naive patients [8,9]. This FA is associated with anti-inflammatory, anti-thrombotic, and antioxidant effects. As statins also have anti-inflammatory and antioxidant effects [10,11], it is postulated that the cardioprotective effects of omega-3 FA can be achieved by statin treatment alone. However, there are no reports on the effect of statins on erythrocyte membrane FA contents in patients with CKD. Erythrocyte membrane FA contents is not affected by temporary dietary changes and reflect the dietary FA contents within 3 months [12]. The omega-3 index, which represents the sum of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) contents in the erythrocyte membrane, is a risk factor of death from CVD [13]. This study aimed to evaluate the effect of pravastatin on erythrocyte membrane FA contents in patients with CKD.

**Methods**

**Study design and patients**

We performed a single-arm prospective clinical trial at two centers between January 2017 and March 2019 (NCT 02992548). Sixty-two patients who were treated for CKD not requiring dialysis were included. The exclusion criteria were history of statins, fish oil, or omega-FA supplementation within 3 months; history of fish, gelatin, and/or omega-3 FA allergies; history of hospital admission caused by CVD, infection, or acute kidney injury within 3 months; dyslipidemia caused by nephrotic syndrome; use of contrast within 2 weeks; albumin level < 3.0 g/dL; and malignancy and/or liver cirrhosis. After exclusion of patients, 45 patients completed this study.

Pravastatin was prescribed for patients with LDL-cholesterol of >100 mg/dL and with coronary artery disease or equivalent risk factors (peripheral artery disease, abdominal aneurysm, carotid artery disease, or DM); patients with LDL-cholesterol of >130 mg/dL and with two or more cardiovascular risk factors; and patients with LDL-cholesterol of >160 mg/dL. Pravastatin was administered initially at dose of 20 mg for 24 weeks. The pravastatin dose was increased to 40 mg after 12 weeks if it was necessary to control dyslipidemia. Subjects were divided into ≥60 or <60 estimated glomerular filtration rate (eGFR, mL/min/1.73 m²).

The primary outcome of this study was change in erythrocyte membrane FA, including oleic acid, after pravastatin treatment for 24 weeks. We measured total cholesterol, triglycerides, LDL-cholesterol, HDL-cholesterol, and adiponectin levels as secondary outcomes at baseline and at 24 weeks. Informed consent was obtained from all enrolled patients. The study was approved by the Dong-A University and Inje University Hospital Institutional Review Boards (No. 15-038). This study was conducted according to the Helsinki Declaration.

**Biochemical and hematologic evaluation**

Blood samples were obtained, processed, refrigerated, and stored at −70°C until analysis. Serum hemoglobin, glucose, blood urea nitrogen, creatinine (sCr), albumin, cystatin C, C-reactive protein (CRP), total cholesterol, triglycerides, LDL-cholesterol, and HDL-cholesterol levels were analyzed. Adiponectin level was measured using enzyme-linked immunoassay (BioVendor Laboratory Medicine, Modrice, Czech Republic).

**Gas chromatography**

Erythrocyte membrane FA contents were measured us-
ing gas chromatography at baseline and at 24 weeks using methods reported previously [14,15]. The omega-3 index is a measure of EPA and DHA in erythrocyte membranes [13]. Erythrocyte membrane FA contents are expressed as a weight percentage of total FA.

Statistics

We calculated that a sample size of 31 patients per group was needed to achieve at least 80% power to detect an effective mean difference in erythrocyte membrane oleic acid content of 2.5 ± 2.0 weight % at a two-sided significance level of 0.05 and assuming a dropout rate of 20% [14]. Sixty-two participants were divided into two groups of 31 participants based on eGFR and analyzed.

The data are presented as means ± standard deviations or frequencies. The characteristics were analyzed using the Mann-Whitney U test or Wilcoxon exact rank sum test for nonparametric data and the chi-square test for categorical variables. All analyses were performed using PASW Statistics version 18.0 (IBM Corp., Armonk, NY, USA). A p-value of <0.05 was considered statistically significant.

Results

Baseline characteristics

Forty-five patients completed this study. As shown in Table 1, the average age of the patients was 59.2 ± 12.4 years, 42.2% were male patients, and 48.9% had DM. The mean systolic and diastolic blood pressure readings were 132.6 ± 24.7 and 72.6 ± 13.1 mmHg, respectively. Baseline sCr was 1.5 ± 0.7 mg/dL, and eGFR was 54.2 ± 27.3 mL/min/1.73 m². All patients were treated with an initial dose of 20 mg pravastatin for 24 weeks. The pravastatin dose was increased to 40 mg after 12 weeks in five patients.

Changes in biochemical data

Compared with baseline, total cholesterol, LDL-cholesterol, and CRP levels were significantly decreased after pravastatin treatment (Table 1). There were no significant changes in triglycerides, HDL-cholesterol, sCr, amount of proteinuria, and adiponectin levels.

Changes in erythrocyte membrane fatty acid content

As shown in Table 2 and Fig. 1, the erythrocyte membrane contents of saturated FA (SFA), stearic acid, lignoceric acid, oleic acid, and arachidonic acid (AA) were significantly increased after pravastatin treatment compared with baseline (p = 0.04, p = 0.006, p = 0.02, p = 0.006, and p < 0.001, respectively). The erythrocyte membrane contents of polyunsaturated FA (PUFA) and linoleic acid (LA) were significantly decreased after pravastatin treatment compared with baseline (p = 0.001, p = 0.001, respectively). The erythrocyte membrane contents of EPA and the omega-3 index tended to decrease after pravastatin treatment, although these changes were not statistically significant (p = 0.07, p = 0.09, respectively).

Changes in biochemical and erythrocyte membrane fatty acid contents according to kidney function

Participants were divided into two groups of ≥60 and <60 mL/min/1.73 m² eGFR level. The total cholesterol and LDL-cholesterol levels decreased after pravastatin use regardless of kidney function. The erythrocyte membrane FA contents at baseline showed no significant difference between the two groups (Table 3). In patients with eGFR of <60 mL/min/1.73 m², the erythrocyte membrane contents of SFA, monounsaturated FA, and oleic acid were significantly increased after 24 weeks compared with baseline (p = 0.04, p = 0.04, and p = 0.006, respectively, Table 3). Compared with baseline, the erythrocyte membrane contents of PUFA, LA, and EPA were significantly decreased after pravastatin treatment in patients with eGFR of <60 mL/min/1.73 m² (p < 0.001, p = 0.008, and p = 0.04, respectively, Fig. 2). Erythrocyte membrane content of AA was significantly increased after pravastatin treatment in both groups (p = 0.009 in patients with eGFR of ≥60 mL/min/1.73 m² and p = 0.01 in those with eGFR of <60 mL/min/1.73 m²). The erythrocyte membrane omega-3 index was decreased in both groups after 24 weeks compared with baseline, although this was not statistically significant (p = 0.72 in patients with eGFR of ≥60 mL/min/1.73 m² and p = 0.07 in those with eGFR of <60 mL/min/1.73 m²).

Adverse effects and dropout

There were no adverse effects related to pravastatin treatment. Six patients refused final sampling, three patients dropped out, and blood samples of four patients were lost.
Table 1. Clinical blood biochemical analyses of the subjects

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Baselin</th>
<th>At 24 weeks</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>45</td>
<td>45</td>
<td></td>
</tr>
<tr>
<td>Age (yr)</td>
<td>59.2 ± 12.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male sex</td>
<td>19 (42.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>22 (48.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>132.6 ± 24.7</td>
<td>124.4 ± 21.3</td>
<td>0.04*</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>72.6 ± 13.1</td>
<td>68.2 ± 14.1</td>
<td>0.11</td>
</tr>
<tr>
<td>Calcium (mg/dL)</td>
<td>9.3 ± 0.5</td>
<td>9.1 ± 0.5</td>
<td>0.05</td>
</tr>
<tr>
<td>Phosphorus (mg/dL)</td>
<td>3.8 ± 0.5</td>
<td>3.8 ± 0.6</td>
<td>0.83</td>
</tr>
<tr>
<td>Glucose (mg/dL)</td>
<td>123.8 ± 33.2</td>
<td>120.3 ± 29.6</td>
<td>0.63</td>
</tr>
<tr>
<td>BUN (mg/dL)</td>
<td>24.2 ± 12.5</td>
<td>24.5 ± 13.8</td>
<td>0.78</td>
</tr>
<tr>
<td>Creatinine (mg/L)</td>
<td>1.5 ± 0.7</td>
<td>1.6 ± 0.9</td>
<td>0.20</td>
</tr>
<tr>
<td>GFR (mL/min/1.73 m²)</td>
<td>54.2 ± 27.3</td>
<td>54.1 ± 30.2</td>
<td>0.38</td>
</tr>
<tr>
<td>Cystatin C (mg/dL)</td>
<td>1.8 ± 0.7</td>
<td>1.8 ± 0.8</td>
<td>0.52</td>
</tr>
<tr>
<td>Uric acid (mg/dL)</td>
<td>6.7 ± 1.8</td>
<td>6.6 ± 1.7</td>
<td>0.38</td>
</tr>
<tr>
<td>Total cholesterol (mg/dL)</td>
<td>223.1 ± 50.8</td>
<td>168.4 ± 32.5</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>4.2 ± 0.3</td>
<td>4.3 ± 0.3</td>
<td>0.11</td>
</tr>
<tr>
<td>AST (U/L)</td>
<td>27.5 ± 11.0</td>
<td>25.7 ± 8.7</td>
<td>0.33</td>
</tr>
<tr>
<td>ALT (U/L)</td>
<td>28.4 ± 40.0</td>
<td>22.5 ± 12.0</td>
<td>0.65</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>185.7 ± 111.8</td>
<td>159.2 ± 85.5</td>
<td>0.40</td>
</tr>
<tr>
<td>HDL-cholesterol (mg/dL)</td>
<td>50.0 ± 18.2</td>
<td>46.8 ± 15.4</td>
<td>0.26</td>
</tr>
<tr>
<td>LDL-cholesterol (mg/dL)</td>
<td>149.1 ± 35.3</td>
<td>100.1 ± 25.4</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>CRP (mg/dL)</td>
<td>0.4 ± 0.4</td>
<td>0.2 ± 0.2</td>
<td>0.04*</td>
</tr>
<tr>
<td>Urine protein (g/g)</td>
<td>1.3 ± 2.0</td>
<td>1.6 ± 3.5</td>
<td>0.39</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>6.5 ± 1.0</td>
<td>6.7 ± 1.2</td>
<td>0.24</td>
</tr>
<tr>
<td>Adiponectin (µg/mL)</td>
<td>8.8 ± 4.3</td>
<td>8.9 ± 4.9</td>
<td>0.57</td>
</tr>
</tbody>
</table>

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

Alt, alanine aminotransaminase; AST, aspartate aminotransferase; BP, blood pressure; BUN, blood urea nitrogen; CRP, C-reactive protein; DM, diabetes mellitus; GFR, glomerular filtrate rate; HbA1c, glycosylated hemoglobin; HDL-cholesterol, high-density lipoprotein cholesterol; LDL-cholesterol, low-density lipoprotein cholesterol.

The nonparametric Wilcoxon exact rank sum test was used to compare baseline data with 24-weeks data; *p < 0.05 (mean values are significantly different from baseline).

Four patients were withdrawn from analysis because of acute kidney injury not related to pravastatin. No hepatic dysfunction was found during the course of the study.

Discussion

In this single-arm prospective study, 24 weeks-administration of pravastatin reduced total cholesterol and LDL-cholesterol in patients with CKD. In contrast, erythrocyte membrane level of oleic acid was increased by pravastatin treatment. Erythrocyte membrane level of oleic acid is significantly higher in patients with acute coronary syndrome and undergoing dialysis than in control subjects [16,17]. Therefore, increased oleic acid level after pravastatin use reflects harmful cardiovascular outcome. Statins are approved as a standard therapy for patients with dyslipidemia because of their potent effects of controlling lipid levels and preventing cardiovascular events. In this study, the percentage reduction in average LDL-cholesterol level was 32.9%, and it is expected that lowered LDL-cholesterol level resulted in fewer cardiovascular complications. However, there were unexpected changes in oleic acid level in patients with CKD using pravastatin. In addition, it might be necessary to investigate the clinical outcomes and mechanisms responsible for the change in oleic acid level.

The important pleiotropic effect of statins is anti-inflammatory. Pravastatin therapy produced an anti-inflammatory effect...
by decreasing CRP in patients with CKD in this study. However, erythrocyte membrane level of AA was increased by pravastatin treatment, which can induce inflammatory mediators and is associated with inflammation. For erythrocyte membrane FA contents, anti-inflammatory strategies are necessary for augmenting the anti-inflammatory effect of pravastatin. The distribution degree of omega-3 FA, such as EPA and DHA, and the omega-3 index are well-known major risk factors of CVD [13,18]. Omega-3 FA supplementation, which produces an anti-inflammatory effect, can lower the risk of inflammation caused by increased AA.

Decreased erythrocyte membrane LA level is related to DM prevalence [19]. Previous studies have reported a relationship between use of statins and increased risk of DM [20,21]. Therefore, supplementation of LA is important to reduce possible risk of DM, especially in patients with CKD. In a previous study, erythrocyte membrane EPA and DHA levels were significantly increased in patients with diabetic nephropathy after omega-3 FA use [22]. A study reporting a decrease in erythrocyte membrane oleic acid level after omega-3 FA suggests that the cardioprotective effect of omega-3 FA in dialysis patients is related to modulation of erythrocyte membrane FA contents [14]. These studies suggest that additional supplementation with PUFA can be helpful to correct changes that occur in erythrocyte membrane FA contents, including oleic acid and LA, after pravastatin use. Our study provides additional information to attend to erythrocyte membrane FA during statin use in patients with CKD. Additional studies are necessary to support the possible risks of using statins in patients with CKD.

Some studies suggest that combination therapy with statins and omega-3 FA did not show an additional decrease in cardiovascular events compared with therapy with statins alone [6,7,23]. Whether administration of omega-3 FA in addition to statins is effective in preventing CVD remains controversial; however, triglyceride lowering treatment is effective in preventing CVD [9]. Additional administration of omega-3 FA might help patients with hypertriglyceridemia because of its potent effect on triglyceride levels [24]. In addition, the beneficial effects of statins on the lipid profile and their effects on the erythrocyte membrane FA contents are not known. This is the first study assessing changes in erythrocyte membrane FA contents after statin treatment in patients with CKD. Based on our data, there was a decrease in EPA level and an increase in oleic acid level after pravastatin treatment, especially in patients with eGFR of <60 mL/min/1.73 m². Therefore, we recommend that the changes in erythrocyte membrane FA contents after pravastatin treatment can be recovered by co-supplementation with omega-3 FA, especially in patients with eGFR of <60 mL/min/1.73 m². We assume that these nonsignificant changes in patients with eGFR of >60 mL/min/1.73 m² are related with high dropout rate and relatively higher EPA level compared to patients with eGFR of <60 mL/min/1.73 m².

The first treatment in patients with dyslipidemia is lifestyle modification, including dietary education. Dietary guidelines, including the American College of Cardiology/American Heart Association Cholesterol Guideline [25] and the Dietary Reference Intake for Koreans [26], emphasize the quality and quantity of dietary fat. The guidelines recommend restricting SFA intake to <7% and trans-FA intake to <1% of total energy intake. The importance of dietary fat is emphasized in patients with CKD. In patients with DM,
Table 3. Clinical blood biochemical analyses of the subjects according to kidney function

<table>
<thead>
<tr>
<th>Variable</th>
<th>≥60 (n = 17)</th>
<th>&lt;60 (n = 28)</th>
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<td>Baseline At 24 weeks</td>
<td>Baseline At 24 weeks</td>
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<tr>
<td></td>
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<td></td>
</tr>
<tr>
<td><strong>Biochemical data</strong></td>
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<td></td>
</tr>
<tr>
<td>Age (yr)</td>
<td>56.0 ± 12.5</td>
<td>61.1 ± 12.2</td>
</tr>
<tr>
<td>Male sex</td>
<td>9 (52.9)</td>
<td>10 (35.7)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>7 (41.2)</td>
<td>15 (53.6)</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>125.5 ± 20.8</td>
<td>120.4 ± 9.1</td>
</tr>
<tr>
<td></td>
<td>136.9 ± 26.1</td>
<td>126.7 ± 22.5</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>71.0 ± 9.7</td>
<td>71.9 ± 13.5</td>
</tr>
<tr>
<td></td>
<td>73.6 ± 14.9</td>
<td>91.0 ± 5.0</td>
</tr>
<tr>
<td>Calcium (mg/dL)</td>
<td>9.3 ± 0.5</td>
<td>9.2 ± 0.5</td>
</tr>
<tr>
<td></td>
<td>9.3 ± 0.5</td>
<td>9.1 ± 0.5</td>
</tr>
<tr>
<td>Phosphorus (mg/dL)</td>
<td>3.7 ± 0.6</td>
<td>3.7 ± 0.5</td>
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<td></td>
<td>3.9 ± 0.5</td>
<td>3.8 ± 0.6</td>
</tr>
<tr>
<td>Glucose (mg/dL)</td>
<td>122.9 ± 34.9</td>
<td>113.3 ± 17.3</td>
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<td>124.4 ± 32.8</td>
<td>124.4 ± 34.4</td>
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<td>Creatinine (mg/dL)</td>
<td>14.8 ± 3.5</td>
<td>15.3 ± 5.6</td>
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<tr>
<td></td>
<td>29.9 ± 12.5*</td>
<td>29.8 ± 14.4</td>
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<tr>
<td>eGFR (mL/min/1.73 m²)</td>
<td>82.9 ± 18.3</td>
<td>84.5 ± 22.9</td>
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<td></td>
<td>36.8 ± 13.5*</td>
<td>35.7 ± 15.6</td>
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<tr>
<td>Cystatin C (mg/dL)</td>
<td>1.3 ± 0.5</td>
<td>1.0 ± 0.2</td>
</tr>
<tr>
<td></td>
<td>2.0 ± 0.7*</td>
<td>2.1 ± 0.7</td>
</tr>
<tr>
<td>Uric acid (mg/dL)</td>
<td>6.0 ± 1.3</td>
<td>6.4 ± 1.7</td>
</tr>
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<td></td>
<td>7.0 ± 2.0</td>
<td>6.7 ± 1.8</td>
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<tr>
<td>Total cholesterol (mg/dL)</td>
<td>226.2 ± 8.4</td>
<td>182.8 ± 34.3</td>
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<td>221.3 ± 38.8</td>
<td>161.6 ± 29.9*</td>
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<td>Albumin (g/dL)</td>
<td>4.2 ± 0.4</td>
<td>4.3 ± 0.3</td>
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<td>4.2 ± 0.3</td>
<td>4.3 ± 0.4</td>
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<tr>
<td>AST (U/L)</td>
<td>30.0 ± 10.5</td>
<td>30.1 ± 10.2</td>
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<tr>
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<td>25.8 ± 11.1</td>
<td>22.9 ± 6.4</td>
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<tr>
<td>ALT (U/L)</td>
<td>28.9 ± 0.3</td>
<td>28.9 ± 13.6</td>
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<td></td>
<td>28.1 ± 48.6</td>
<td>18.5 ± 9.1</td>
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<tr>
<td>Triglycerides (mg/dL)</td>
<td>192.1 ± 139.4</td>
<td>149.4 ± 89.9</td>
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<tr>
<td></td>
<td>181.7 ± 93.1</td>
<td>165.8 ± 83.8</td>
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<td>HDL-cholesterol (mg/dL)</td>
<td>54.8 ± 19.9</td>
<td>53.4 ± 12.1</td>
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<td>47.0 ± 16.8</td>
<td>43.2 ± 19.1</td>
</tr>
<tr>
<td>LDL-cholesterol (mg/dL)</td>
<td>154.4 ± 45.8</td>
<td>110.9 ± 29.0*</td>
</tr>
<tr>
<td></td>
<td>145.8 ± 27.2</td>
<td>92.8 ± 20.3*</td>
</tr>
<tr>
<td>CRP (mg/dL)</td>
<td>0.4 ± 0.6</td>
<td>0.1 ± 0.1</td>
</tr>
<tr>
<td></td>
<td>0.3 ± 0.3</td>
<td>0.2 ± 0.2</td>
</tr>
<tr>
<td>Urine protein (g/g)</td>
<td>0.8 ± 1.7</td>
<td>1.3 ± 4.3</td>
</tr>
<tr>
<td></td>
<td>1.6 ± 2.1</td>
<td>1.7 ± 3.1</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>6.2 ± 1.0</td>
<td>6.3 ± 1.0</td>
</tr>
<tr>
<td></td>
<td>6.7 ± 1.0</td>
<td>7.1 ± 1.3</td>
</tr>
<tr>
<td>Adiponectin (μg/mL)</td>
<td>8.2 ± 4.9</td>
<td>8.1 ± 5.0</td>
</tr>
<tr>
<td></td>
<td>9.1 ± 3.9</td>
<td>9.4 ± 4.9</td>
</tr>
<tr>
<td><strong>Erythrocyte membrane fatty acid (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Saturated</td>
<td>40.7 ± 2.0</td>
<td>40.8 ± 1.6</td>
</tr>
<tr>
<td>Myristic</td>
<td>0.4 ± 0.1</td>
<td>0.3 ± 0.1</td>
</tr>
<tr>
<td>Palmitic</td>
<td>23.4 ± 1.8</td>
<td>23.1 ± 1.4</td>
</tr>
<tr>
<td>Stearic</td>
<td>16.4 ± 1.1</td>
<td>16.9 ± 1.4</td>
</tr>
<tr>
<td>Lignoceric</td>
<td>0.5 ± 0.2</td>
<td>0.4 ± 0.1</td>
</tr>
<tr>
<td>Monounsaturated</td>
<td>15.8 ± 1.2</td>
<td>15.8 ± 1.1</td>
</tr>
<tr>
<td>Palmitoleic</td>
<td>0.6 ± 0.3</td>
<td>0.5 ± 0.2</td>
</tr>
<tr>
<td>Trans-oleic</td>
<td>0.3 ± 0.1</td>
<td>0.3 ± 0.1</td>
</tr>
<tr>
<td>Oleic</td>
<td>14.7 ± 1.1</td>
<td>14.8 ± 1.0</td>
</tr>
<tr>
<td>Polysaturated</td>
<td>42.7 ± 2.7</td>
<td>42.6 ± 1.9</td>
</tr>
<tr>
<td>Omega-6</td>
<td>28.3 ± 2.8</td>
<td>28.3 ± 2.9</td>
</tr>
<tr>
<td>Linoleic</td>
<td>12.0 ± 2.6</td>
<td>11.0 ± 2.2</td>
</tr>
<tr>
<td>AA</td>
<td>12.6 ± 2.1</td>
<td>13.4 ± 1.9*</td>
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<tr>
<td>Omega-3</td>
<td>14.3 ± 2.9</td>
<td>14.2 ± 2.7</td>
</tr>
<tr>
<td>Alpha-linolenic</td>
<td>0.3 ± 0.3</td>
<td>0.2 ± 0.1*</td>
</tr>
<tr>
<td>EPA</td>
<td>2.4 ± 1.1</td>
<td>2.3 ± 1.0</td>
</tr>
<tr>
<td>DHA</td>
<td>8.9 ± 1.6</td>
<td>8.8 ± 1.3</td>
</tr>
<tr>
<td>Omega-3 index</td>
<td>11.3 ± 2.4</td>
<td>11.1 ± 2.2</td>
</tr>
</tbody>
</table>

(Continued to the next page)
intake of greater SFA and lesser PUFA including LA is associated with progression of nephropathy [27,28]. A Mediterranean diet rich in foods containing omega-3 FA has reduced the incidence of CKD [29,30]. Changes in erythrocyte membrane FA, an indicator of FA status in the previous 3 months, have been linked to CKD. Changes in the contents of erythrocyte membrane FA are related to the poor prognosis of CKD or CVD. The mechanism of statin-induced erythrocyte membrane FA modulation is unknown. The erythrocyte membrane contains cholesterol, and changes in transmembrane cationic transport systems with statin use have resulted in alterations in erythrocyte membrane cholesterol content [31,32]. Coenzyme Q10 acts in the transmembrane electron transport system in the mitochondria and prevents lipid peroxidation during oxidative damage [33]. FA could increase bioavailability by increasing coenzyme Q10 absorption, and lack of FA could damage the enzyme activity in mitochondria [34]. Statins inhibit the production of coenzyme Q10 and could affect the structure of FA [35]. Negative pleiotropic effects of statins should be corrected by modification of erythrocyte membrane FA contents.

The current study has some limitations. First, clinical outcomes such as CVD development or mortality rate were not evaluated because of the short study period. Second, there was a relatively small sample size, high dropout rate in patients with eGFR of >60 mL/min/1.73 m², and no control group. To overcome these limitations, additional clinical studies with large sample sizes are required.

In conclusion, supplementations for PUFA, such as omega-3 FA or LA, might be necessary to recover erythrocyte membrane FA changes when pravastatin is used to treat dyslipidemia in patients with CKD. Further studies on reducing cardiovascular events using combined PUFA and pravastatin treatment are necessary.

**Conflicts of interest**

All authors have no conflicts of interest to declare.
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Authors’ contributions

Conceptualization, Funding acquisition: WSA
Data curation, Methodology: SML, YHK, WSA
Formal analysis, Visualization: SML, WSA
Investigation: SML, YKS, SEK, YHK, YP, WSA
Project administration: SML, YKS, SEK, YHK, WSA
Writing–original draft: SML, WSA
Writing–review & editing: All authors
All authors read and approved the final manuscript.

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References

Mortality predictors in critically ill patients with acute kidney injury requiring continuous renal replacement therapy

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Background: Because of high cost of continuous renal replacement therapy (CRRT) and the high mortality rate among severe acute kidney injury patients, careful identification of patients who will benefit from CRRT is warranted. This study determined factors associated with mortality among critically ill patients requiring CRRT.

Methods: This was a retrospective observational study of 414 patients admitted to the intensive care unit of four hospitals in South Korea who received CRRT from June 2017 to September 2018. Patients were divided according to degree of fluid overload (FO) and disease severity. The Cox proportional hazards model was used to explore the effect of relevant variables on mortality.

Results: In-hospital mortality rate was 57.2%. Ninety-day mortality rate was 58.5%. Lower creatinine and blood pH were significant predictors of mortality. A one-unit increase in the Sequential Organ Failure Assessment (SOFA) score was associated with increased risk of and 90-day mortality (hazard ratio [HR], 1.07; p < 0.001). The risk of 90-day mortality in FO patients was 57.2% (p < 0.001) higher than in those without FO. High SOFA score was associated with increased risk for 90-day mortality (HR, 1.79; p = 0.03 and HR, 3.05; p = 0.001) in patients without FO and with FO ≤ 10%, respectively. The highest mortality rates were in patients with FO > 10%, independent of disease severity.

Conclusion: FO increases the risk of mortality independent of other factors, including severity of acute illness. Prevention of FO should be a priority, especially when managing the critically ill.

Keywords: Acute kidney injury, Continuous renal replacement therapy, Critical illness, Mortality
Acute kidney injury (AKI) is a common complication among critically ill patients worldwide and is associated with substantial morbidity and mortality rates of 50% to 90% [1]. Approximately 5% to 10% of AKI patients require acute renal replacement therapy (RRT) during intensive care unit (ICU) admission [2–4]. AKI patients requiring RRT are reported to have very high mortality rates, as much as 50% to 80% [5]. Risk factors for mortality include advanced age, sepsis, disease severity and number of failing organs, need for mechanical ventilation, presence of circulatory shock, and oliguria [6]. Several studies have also established the relationship between fluid overload (FO) and mortality [7–10]. Continuous RRT (CRRT) is the preferred renal replacement modality in the management of critically ill patients with hemodynamic instability and AKI [5]. The Kidney Disease: Improving Global Outcome (KDIGO) Clinical Practice Guideline for AKI suggests that CRRT be used for hemodynamically unstable patients and patients with acute brain injury or other causes of increased intracranial pressure [11]. Many studies show that CRRT offers superior hemodynamic stability, metabolic clearance, and volume control. Other advantages of CRRT include enhanced clearance of inflammatory mediators and better preservation of cerebral perfusion among patients with acute brain injury or fulminant hepatic failure [12].

The limited availability in some areas and the high cost of CRRT, in addition to the high mortality rate among critically ill patients with severe AKI, warrant careful selection of patients who will benefit from it. Identifying patients who are most likely to have positive outcomes with CRRT is challenging. More studies are needed to identify such patients to guide therapeutic decisions, optimize limited resources, and provide realistic prognostic information to patients and their families. This study aims to determine mortality rates and identify factors associated with mortality among critically ill patients in the ICU with AKI who received CRRT.

**Methods**

**Research design**

This is multicenter observational study comprising all AKI patients who were admitted and received CRRT in the ICUs of Seoul National University Bundang Hospital, Seoul National University Hospital, Seoul National University Boramae Medical Center, and Ehwa Womans University Mokdong Hospital, from June 2017 to September 2018. This study was approved by the Institutional Review Boards of Seoul National University Bundang Hospital (No. 1801-44-106), Seoul National University Hospital (No. 1801-036-913), Seoul National University Boramae Medical Center (No. 10-2018-05), and Ehwa Womans University Mokdong Hospital (No. 2018-01-071). This study was performed in accordance with the Declaration of Helsinki. Informed consent was waived because the study is retrospective and noninterventional in nature.

**Inclusion and exclusion criteria**

All patients with AKI who received CRRT in the ICUs of Seoul National University Bundang Hospital, Seoul National University Hospital, Seoul National University Boramae Medical Center, and Ehwa Womans University Mokdong Hospital from June 2017 to September 2018 were eligible. Patients already on chronic dialysis before the study period were excluded.

**Data collection**

Records of ICU patients with AKI who received CRRT over the study period were retrieved. Baseline demographics such as age and sex, preexisting comorbid conditions, and etiology of AKI were collected. Although AKI is often multifactorial, we classified patients into one of four etiologic groups: (1) septic, (2) cardiogenic, (3) postoperative, and (4) others. Use of mechanical ventilation and vasopressor(s), urine output 24 hours prior to CRRT, length of stay in the ICU and in the hospital, and time on CRRT were also noted. Disease severity was assessed using the Sequential Organ Failure Assessment (SOFA) score. Laboratory findings were also recorded.

**Definitions**

The AKI diagnostic criteria utilized in this study were in accordance with the 2012 KDIGO Clinical Practice Guideline for AKI: increase in serum creatinine (SCr) ≥ 0.3 mg/dL within 48 hours, increase in SCr ≥ 1.5 times the baseline, or...
urine volume < 0.5 mL/kg/hour for 6 hours [11]. The degree of FO was expressed as percent FO, which was calculated as follows: [(weight at start of CRRT - baseline body weight)/ baseline body weight] × 100.

**Groups**

Patients were grouped according to presence and degree of FO: group 1, no FO; group 2, FO ≤ 10%; and group 3, FO > 10%. Patients were also classified according to SOFA score: A, low SOFA score (<10) and B, high SOFA score (≥10), using the median SOFA score.

**Outcomes**

The primary outcomes were in-hospital mortality and 90-day mortality. We analyzed 90-day mortality to reduce bias related to short-term prognosis brought about by the acute illness.

**Statistical analysis**

Categorical data are expressed as the number of cases and percentages. Continuous data are expressed as the mean ± standard deviation (SD). Statistical comparisons were made between survivors and non-survivors using the independent t-test and the chi-square test, as appropriate. The Cox proportional hazards model was used to explore the effect of variables on mortality. The adjusted model included age, sex, hypertension, diabetes mellitus (DM), malignancy, and sepsis. Mortality data were analyzed using Kaplan-Meier survival curves. Statistical significance was defined as a p-value of <0.05. All statistical analyses were performed using IBM SPSS version 20 (IBM Corp., Armonk, NY, USA).

**Results**

**Baseline characteristics**

We identified 414 critically ill patients with AKI who received CRRT. When patients were divided into survivor and non-survivor groups, there was no difference in the age or sex distribution (p = 0.50 and p = 0.90, respectively). The mean age was 65.8 ± 15.3 years in the survivor group and 66.8 ± 14.4 years in the non-survivor group. A majority of the patients in both groups (67.8% and 68.4%, respectively) were male. The two most common comorbidities among all patients were hypertension and DM. The non-survivors had a higher mean SOFA score (10.3 ± 3.8 vs. 8.9 ± 3.2, p < 0.001), lower mean arterial pressure (77.8 ± 15.8 mmHg vs. 83.2 ± 17.6 mmHg, p = 0.001), and required at least one vasopressor (78.1% vs. 62.1%, p < 0.001). A majority of the patients in both groups required mechanical ventilation (56.5% among survivors vs. 74.3% among non-survivors, p < 0.001). Sepsis was the most common cause of AKI in either group. The mean SCr was lower in the non-survivor group (2.9 ± 1.7 mg/dL vs. 4.3 ± 3.1 mg/dL in the survivor group, p < 0.001). Analysis showed that a lower SCr and blood pH and a higher SOFA score were independently associated with increased risk for in-hospital and 90-day mortality. A 1-SD increase in SCr and blood pH was associated with a decreased risk of in-hospital mortality (SCr: HR, 0.87; 95% CI, 0.81–0.93; p < 0.001 / blood pH: HR, 0.15; 95% CI, 0.06–0.36; p < 0.001) and 90-day mortality (SCr: HR, 0.84; 95% CI, 0.79–0.90, p < 0.001 / blood pH: HR, 0.17; 95% CI, 0.07–0.42; p < 0.001). On the other hand, a 1-unit increase in SOFA score was significantly associated with increased risk of in-hospital mortality (HR, 1.06; 95% CI, 1.02–1.09; p < 0.001) and 90-day mortality (HR, 1.07; 95% CI, 1.04–1.10; p < 0.001). More importantly, after adjustment for demographic factors and the other variables, SCr, blood pH, and SOFA score each remained significantly associated with in-
Table 1. Baseline characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total</th>
<th>Survivor</th>
<th>Non-survivor</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No. of patients</strong></td>
<td>414</td>
<td>177</td>
<td>237</td>
<td></td>
</tr>
<tr>
<td><strong>Demographic</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (yr)</td>
<td>66.4 ± 14.8</td>
<td>65.8 ± 15.3</td>
<td>66.8 ± 14.4</td>
<td>0.50</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>282 (68.1)</td>
<td>120 (67.8)</td>
<td>162 (68.4)</td>
<td>0.90</td>
</tr>
<tr>
<td>Female</td>
<td>132 (31.9)</td>
<td>57 (32.2)</td>
<td>75 (31.6)</td>
<td></td>
</tr>
<tr>
<td><strong>Comorbid disease</strong></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>202 (48.8)</td>
<td>99 (55.9)</td>
<td>103 (43.5)</td>
<td>0.01</td>
</tr>
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<td>Diabetes mellitus</td>
<td>162 (39.1)</td>
<td>88 (49.7)</td>
<td>74 (31.2)</td>
<td>&lt;0.001</td>
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<tr>
<td>Malignancy</td>
<td>100 (24.2)</td>
<td>28 (15.8)</td>
<td>72 (30.4)</td>
<td>0.001</td>
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<tr>
<td>Liver disease</td>
<td>63 (15.2)</td>
<td>23 (13.0)</td>
<td>40 (16.9)</td>
<td>0.28</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>52 (12.6)</td>
<td>31 (17.5)</td>
<td>21 (8.9)</td>
<td>0.009</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>28 (6.8)</td>
<td>16 (9.0)</td>
<td>12 (5.1)</td>
<td>0.11</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>21 (5.1)</td>
<td>10 (5.6)</td>
<td>11 (4.6)</td>
<td>0.64</td>
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<tr>
<td>COPD</td>
<td>21 (5.1)</td>
<td>8 (4.5)</td>
<td>13 (5.5)</td>
<td>0.66</td>
</tr>
<tr>
<td>Cerebrovascular accident</td>
<td>14 (3.4)</td>
<td>5 (2.8)</td>
<td>9 (3.8)</td>
<td>0.59</td>
</tr>
<tr>
<td>Peptic ulcer disease</td>
<td>5 (1.2)</td>
<td>1 (0.6)</td>
<td>4 (1.7)</td>
<td>0.30</td>
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<tr>
<td>MAP (mmHg)</td>
<td>80.0 ± 16.8</td>
<td>83.2 ± 17.6</td>
<td>77.8 ± 15.8</td>
<td>0.001</td>
</tr>
<tr>
<td><strong>Illness severity</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SOFA score&lt;sup&gt;a&lt;/sup&gt;</td>
<td>9.7 ± 3.6</td>
<td>8.9 ± 3.2</td>
<td>10.3 ± 3.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Vasopressor use</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>None</td>
<td>119 (28.7)</td>
<td>67 (37.9)</td>
<td>52 (21.9)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>182 (44.0)</td>
<td>79 (44.6)</td>
<td>103 (43.5)</td>
<td></td>
</tr>
<tr>
<td>≥2</td>
<td>113 (27.3)</td>
<td>31 (17.5)</td>
<td>82 (34.6)</td>
<td></td>
</tr>
<tr>
<td>Use of mechanical ventilation</td>
<td>276 (66.7)</td>
<td>100 (56.5)</td>
<td>176 (74.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>AKI etiology&lt;sup&gt;b&lt;/sup&gt;</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Postoperative</td>
<td>21 (5.1)</td>
<td>10 (5.6)</td>
<td>11 (4.6)</td>
<td>0.71</td>
</tr>
<tr>
<td>Septic</td>
<td>285 (68.8)</td>
<td>111 (62.7)</td>
<td>174 (73.4)</td>
<td>0.004</td>
</tr>
<tr>
<td>Cardiogenic</td>
<td>24 (5.8)</td>
<td>9 (5.1)</td>
<td>15 (6.3)</td>
<td>0.47</td>
</tr>
<tr>
<td>Others</td>
<td>65 (15.7)</td>
<td>34 (19.2)</td>
<td>31 (13.1)</td>
<td>0.11</td>
</tr>
<tr>
<td>Serum creatinine (mg/dL)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>3.5 ± 2.5</td>
<td>4.3 ± 3.1</td>
<td>2.9 ± 1.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Blood pH&lt;sup&gt;d&lt;/sup&gt;</td>
<td>7.31 ± 0.13</td>
<td>7.33 ± 0.13</td>
<td>7.29 ± 0.13</td>
<td>0.006</td>
</tr>
<tr>
<td>UO 24 hours prior to CRRT (L)&lt;sup&gt;e&lt;/sup&gt;</td>
<td>0.4 ± 0.6</td>
<td>0.4 ± 0.5</td>
<td>0.5 ± 0.6</td>
<td>0.07</td>
</tr>
<tr>
<td>Intensive care unit stay (day)</td>
<td>9.5 ± 14.8</td>
<td>10.8 ± 17.2</td>
<td>8.5 ± 12.7</td>
<td>0.11</td>
</tr>
<tr>
<td>Hospital stay (day)</td>
<td>21.2 ± 39.3</td>
<td>35.8 ± 54.1</td>
<td>10.2 ± 15.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CRRT duration (day)</td>
<td>5.1 ± 5.6</td>
<td>4.6 ± 4.4</td>
<td>5.4 ± 6.3</td>
<td>0.16</td>
</tr>
<tr>
<td>Fluid overload</td>
<td>182 (44.0)</td>
<td>61 (34.5)</td>
<td>121 (51.1)</td>
<td>0.001</td>
</tr>
<tr>
<td>Degree of fluid overload</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>≤10%</td>
<td>115 (27.8)</td>
<td>49 (27.7)</td>
<td>66 (27.8)</td>
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<tr>
<td>&gt;10%</td>
<td>67 (16.2)</td>
<td>12 (6.8)</td>
<td>55 (23.2)</td>
<td></td>
</tr>
</tbody>
</table>

Data are presented as number only, mean ± standard deviation for continuous variables, or number (%) for categorical variables.

AKI, acute kidney injury; COPD, chronic obstructive pulmonary disease; CRRT, continuous renal replacement therapy; MAP, mean arterial pressure; SOFA, Sequential Organ Failure Assessment; UO, urine output.

<sup>a</sup>Incomplete data. The missing data rate is 0.2% for the SOFA score, 4.6% for AKI etiology, 0.5% for serum creatinine, 1.0% for blood pH, and 12.8% for the UO 24 hours prior to CRRT.
hospital mortality (SCr: HR, 0.87; 95% CI, 0.81–0.93, p < 0.001 / blood pH: HR, 0.11; 95% CI, 0.04–0.28; p < 0.001 / SOFA score: HR, 1.05; 95% CI, 1.01–1.08; p = 0.008). By multivariate Cox regression analysis, SCr (HR, 0.86; 95% CI, 0.80–0.93; p < 0.001), blood pH (HR, 0.16; 95% CI, 0.06–0.43; p < 0.001), and SOFA score (HR, 1.06; 95% CI, 1.02–1.09; p = 0.001) were associated with 90-day mortality, independent of age, sex, comorbidities, and sepsis (Table 2).

FO was likewise significantly associated with an increased risk of in-hospital (HR, 1.54; 95% CI, 1.19–1.98; p = 0.001) and 90-day mortality (HR, 1.57; 95% CI, 1.22–2.02; p < 0.001). Patients with FO were 1.39 times (95% CI, 1.07–1.81; p = 0.02) more likely to die within 90 days following CRRT initiation after adjustment for age, sex, SCr, blood pH, SOFA score, DM, hypertension, malignancy, and sepsis (Table 2).

Subgroup analyses

We also classified the patients according to degree of FO. One hundred fifteen patients (27.8%) had FO of ≤10%, while 67 patients (16.2%) had more severe FO of >10%. Two hundred thirty-one patients (55.8%) did not present with FO on CRRT initiation. Our results showed that mortality rates increased as the degree of FO increased. The highest mortality rates were recorded in patients with FO > 10% (in-hospital mortality: 82.1% vs. 57.4% in FO ≤ 10%, p < 0.001; 90-day mortality: 85.1% vs. 59.1% in FO ≤ 10%, p < 0.001).

We further subdivided the patients into the following six groups to examine whether the increased mortality risk observed in patients with FO was adversely affected by SOFA score: group 1A, no FO and low SOFA score; group 1B, no FO and high SOFA score; group 2A, FO ≤ 10% and low SOFA score; group 2B, FO ≤ 10% and high SOFA score; group 3A, FO > 10% and low SOFA score; and group 3B, FO > 10% and high SOFA score (Table 3, 4).

In patients without FO (group 1), higher mortality was observed in the high SOFA subgroup (in-hospital: group 1B, 58.3% vs. group 1A, 43.1%; 90-day: group 1B, 58.3% vs. group 1A, 43.9%). Hazard ratios were 1.85 (95% CI, 1.10–3.12; p = 0.02) for in-hospital mortality (Table 3) and 1.79 (95% CI, 1.06–3.02; p = 0.03) for 90-day mortality in group 1B (Table 4).

Among patients with FO ≤ 10%, a high SOFA score (group 2B) was also associated with increased hazard ratios for both in-hospital mortality (2.92; 95% CI, 1.53–5.59; p = 0.001) and 90-day mortality (3.05; 95% CI, 1.59–5.88; p = 0.001).
Among patients with a low SOFA score, it is noteworthy that the mortality risk of patients with FO ≤ 10% (group 2A) was not statistically different from that of patients without FO (group 1A) (in-hospital: HR, 1.06; 95% CI, 0.56–2.01; p = 0.87 / 90-day: HR, 1.10; 95% CI, 0.58–2.09; p = 0.77).

Patients with FO > 10% had the highest risk of in-hospital mortality (group 3A: HR, 5.81; 95% CI, 2.07–16.35; p = 0.001 / group 3B: HR, 6.23; 95% CI, 2.56–15.17; p < 0.001) and 90-day mortality (group 3A: HR, 10.22; 95% CI, 2.92–35.75; p < 0.001 / group 3B: HR, 6.02; 95% CI, 2.47–14.67; p < 0.001) among the entire study population (Table 3, 4, respectively). The Kaplan-Meier survival curves also showed that survival was lowest in group 3 (Fig. 1, 2).

**Discussion**

We studied a multicenter population of 414 ICU patients with AKI who subsequently underwent CRRT. This study showed that the mortality rate was high among critically ill patients who received CRRT (in-hospital, 57.2% and 90-day, 58.5%). Our result is comparable to mortality rates in previously published data [3,13–15] but better than those reported by Prasad et al. [16] (64%), Kao et al. [17] (66.5%), and Gonzalez et al. [18] (68.4%). Some studies have even reported in-hospital mortality as high as 70%–80% [19,20].

Several articles have previously cited male sex, older age, and sepsis as risk factors for severe AKI requiring RRT [3,8]. Similar to previous studies, a majority of the patients in this study were male (282, 68.1%) [17,21]. The mean age was 66.4 ± 14.8 years, and most of the patients were ≥65 years (250, 60.4%). The most common etiology of AKI was sepsis, as was the case in the studies conducted by Kao et al. [17], Gonzalez et al. [18], and Soni et al. [19].

The association between advanced age and mortality among AKI patients has been extensively studied [17–19].

In a study by Allegretti et al. [14] of 725 AKI patients who received CRRT, age over 60 years was an independent risk factor of in-hospital mortality (odds ratio [OR], 1.9; 95% CI, 1.3–2.7; p = 0.001) and mortality following hospital discharge (HR, 1.9; 95% CI, 1.2–3.0). Another study by Conroy et al. [22] reported that patients 75 years and older had higher hospital mortality (54.2% vs. 44%, p = 0.02) and 1-year mortality (63.6% vs. 50.6%, p = 0.005) than younger patients. Although poor outcomes have been observed in elderly AKI patients, this has not been consistent across all studies [23]. A retrospective study done in Germany of 424 patients found that the course and prognosis of AKI do not differ greatly in the elderly population [24]. Our study also did not identify age as a predictor of mortality in patients with CRRT-requiring AKI.

A lower Scr and blood pH and a higher SOFA score were independently associated with an increased risk of death. Several studies have identified high Scr as an independent factor for better outcomes [20,25]. Soubrier et al. [26], in a study of 197 patients treated with CRRT, found that Scr > 3.4 mg/dL predicted a favorable outcome. In our study, the non-survivors had a lower mean Scr at CRRT initiation.
A 1-SD increase was associated with a decreased risk of in-hospital and 90-day mortality (HR, 0.87 and 0.84, respectively; p < 0.001). Possible explanations for this occurrence are decreased protein production and reduced muscle mass among the more critically ill patients. SOFA represents a severity parameter and is widely accepted as a prognostic factor for critically ill patients. In a study of 240 patients with AKI who received CRRT, Kee et al. [27] found that blood pH < 7.35 (OR, 4.33; 95% CI, 2.41–7.77; p < 0.001) and a 1-SD increase in SOFA score (OR, 1.99; 95% CI, 1.49–2.69; p < 0.001) were significantly associated with mortality within 7 days of CRRT initiation. Another single-center, retrospective cohort study of 562 patients also reported that acidemia and a higher SOFA score at the time of CRRT initiation were independently associated with a higher short-term mortality rate (death in-hospital or within one week of discharge) [28].

FO is known to be associated with mortality in critically ill patients with AKI [4,25,29]. Similar to other studies, and not surprisingly, FO was associated with increased mortality in our study. Although most studies have defined FO as more than a 10% increase in body weight relative to baseline, we included patients with less than 10% increase in body weight

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**Figure 1.** Kaplan-Meier curves of in-hospital survival among the six groups.

FO, fluid overload; SOFA, Sequential Organ Failure Assessment.
from baseline in our analysis since a study by Bagshaw et al. [30] found that a lower threshold of fluid accumulation (>5%) was associated with hospital mortality (OR, 2.31). This negative effect of FO ≤ 10% on survival was more clearly seen in patients presenting with more severe illness (group 2B). Patients with a lesser degree of FO (<10%) should be given more attention since they are also at an increased risk for adverse outcomes. Timely recognition and subsequent management of FO in its earlier stages could positively impact patients’ hospital course and long-term prognosis.

Moreover, our results showed that a higher degree of FO was associated with higher risk of mortality. We observed a relationship between increasing degree of FO, increasing SOFA score, and mortality. In a study of 341 AKI patients who underwent CRRT, Kim et al. [31] observed that the adverse effect of FO on survival was more evident in patients with sepsis or more severe illness. In contrast, our results revealed that the increased risk of mortality associated with FO was also observed in patients with a low SOFA score. Patients with FO > 10% and low SOFA score (group 3A) were 5.8 times more likely to die in-hospital than patients with no FO and low SOFA score (group 1A). This risk increased to 6.3 when patients had high SOFA score and FO > 10% (group 3B). This highlights the importance of proper fluid manage-
ment among critically ill patients with AKI regardless of disease severity.

This study showed that mortality following CRRT initiation for AKI was high. Our study demonstrated that SCr, blood pH, SOFA score, and FO are significant independent risk factors for in-hospital and 90-day mortality after adjustment for age, sex, sepsis, and comorbidities. In patients without FO and with FO ≤ 10%, a lower SOFA score corresponded to a lower risk of in-hospital and 90-day mortality. Patients with FO > 10% had worse outcomes regardless of SOFA score.

In conclusion, the presence of FO signifies an increased risk of mortality independent of other factors, including severity of acute illness. Prevention of FO should be a priority, especially when managing the critically ill. Measures to ensure this include correctly identifying patients who are fluid-responsive, choosing the appropriate type and quantity of fluids to be given, and frequent clinical assessment of fluid status. Benefits and risks should always be weighed prior to starting or deciding to continue fluid therapy. A judicious fluid therapy is indispensable in the management of critically ill patients.

Although the predictors we identified in this study were identified separately in previous studies, our findings reaffirm the clinical importance of these factors in the management and prognosis of critically ill patients with AKI. This study has several strengths. It is a multicenter study and also included a larger number of patients compared to previous studies. Our findings can be extended to other ICU patients. This is an observational study. Interventions were not standardized. The decision to start CRRT, choice of CRRT modality, and CRRT prescription were made by the attending nephrologist. Our results can only predict the associations between factors and outcomes but do not determine causal relationship.

Conflicts of interest

All authors have no conflicts of interest to declare.

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Authors’ contributions

Conceptualization, Methodology: All authors
Data curation: KPML, JCJ, SK
Writing—original draft: KPML
Writing—review & editing: JCJ, SK
All authors read and approved the final manuscript.

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References


Background: Minimal change disease (MCD) is one of the most common causes of nephrotic syndrome worldwide. Hyperuricemia increases the end-stage renal disease (ESRD) risk in glomerulonephritis. In this study, we aimed to determine the effect of high serum uric acid levels on the progression to ESRD in MCD.

Methods: A total of 800 patients diagnosed with MCD by kidney biopsy were retrospectively analyzed. We determined the relationship of hyperuricemia with the progression to ESRD in MCD using the Cox proportional hazard model and Kaplan-Meier survival analysis. The primary outcome was defined as the initiation of dialysis or kidney transplantation.

Results: A total of 42 patients (5.3%) progressed to ESRD during the follow-up period. In the restricted cubic spline curve, serum uric acid levels exhibited a positive correlation with ESRD progression in patients with MCD. In the fully adjusted model, the risk of MCD progression increased by 29% for every 1 mg/dL increase in the baseline serum uric acid level (hazard ratio [HR], 1.29; 95% confidence interval [CI], 1.09–1.54; p = 0.004). Falling into the high uric acid group (serum uric acid level > 7 mg/dL in men and > 6 mg/dL in women) was also a risk factor for progression of MCD to ESRD (HR, 3.40; 95% CI, 1.59–7.31; p < 0.001).

Conclusion: Our study shows that hyperuricemia is an independent risk factor for the progression to ESRD in patients with MCD.

Keywords: Chronic kidney disease, End-stage renal disease, Hyperuricemia, Minimal change disease

Introduction

Minimal change disease (MCD) is a kidney disease in which large amounts of protein are excreted via urine, and it is one of the most common causes of nephrotic syndrome worldwide [1]. The prognosis is relatively good, and the disease usually responds to corticosteroid treatment with disappearance of the ultrastructural alteration [2]. Therefore, chronic
Kidney disease or end-stage renal disease (ESRD) is not typically seen in adult MCD. As a result, little is known about the risk factors for ESRD progression in MCD [3]. However, acute kidney injury (AKI) occurs in 10% to 25% of adult patients diagnosed with MCD [4-6]. These patients tend to be older males with hypertension and have more severe proteinuria, hypoalbuminemia, and arteriosclerosis on kidney biopsy than patients who do not develop AKI [6,7]. Unfortunately, AKI is not a self-limiting event. Increasing evidence has demonstrated the bidirectional link between AKI and chronic kidney disease (CKD) [8].

Serum uric acid is the final enzymatic product of purine metabolism [9]. Hyperuricemia has been associated with AKI, CKD, hypertension, dyslipidemia, diabetes mellitus (DM), stroke, cardiovascular events, and hepatitis B virus-associated glomerulonephritis [10-15]. We recently reported that hyperuricemia was also a risk factor for progression of immunoglobulin A nephropathy and lupus nephritis in women [16,17]. However, little is known about the effect of uric acid on progression to ESRD in patients with MCD. Therefore, we investigated the effect of high serum uric acid levels on progression to ESRD in MCD.

Methods

Data source and study population

Of the 21,697 patients who underwent kidney biopsies from January 1979 until October 2018 at 19 Korean university hospitals (Kyungpook National University Hospital, Kyung Hee University Hospital at Gandong, Kangdong Sacred Heart Hospital, Gangnam Severance Hospital, Korea University Guro Hospital, Korea University Anam Hospital, Eulji University Hospital, Seoul National University Boramae Medical Center, Seoul National University Bundang Hospital, Seoul National University Hospital, Severance Hospital, Pusan National University Yangsan Hospital, The Catholic University of Korea, Eunpyeong St. Mary’s Hospital, Ewha Womans University Mokdong Hospital, National Health Insurance Service Ilsan Hospital, Chonnam National University Hospital, Chonbuk National University Hospital, and Hallym University Sacred Heart Hospital), 1,949 patients were diagnosed with MCD. We excluded 159 patients aged <18 years, 130 patients in whom the status of disease progression was unknown, and 860 patients whose serum uric acid levels were not measured. Finally, data from 800 patients were retrospectively analyzed in this study. Fig. 1 shows the flowchart for selecting cases for this study.

Study endpoint, definitions, and measurements

The primary endpoint of the study was MCD progression, defined as the initiation of dialysis or kidney transplantation. In our study, we defined the ‘hyperuricemia group’ as individuals with a serum uric acid level > 7 mg/dL in men and > 6 mg/dL in women [18]. The estimated glomerular filtration rate (eGFR) was calculated using the original Modification of Diet in Renal Disease equation for adults [19].

Statistical analyses

All continuous variables were tested for normality using the Shapiro-Wilk test. Normally distributed data are expressed as mean ± standard deviation, and skewed data are expressed as the median and interquartile range (25th percentile–75th percentile). To compare the clinical characteristics and differences between the control group and hyperuri-
cemia group, the Student t-test was used for the normally distributed variables and the Mann-Whitney U test was used to analyze the skewed data. The categorical variables were expressed as numbers and percentages, and the chi-squared test was used to compare the groups. Kaplan-Meier survival curves with log-rank tests and a univariate Cox proportional hazards model were used to examine the effect of the serum uric acid level on MCD progression. A multivariate Cox proportional hazards regression model was applied to adjust the variables that may affect MCD progression. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated to estimate the risk of MCD progression. We examined the assumption of the proportional hazard in the Cox model using cox.zph() in R. We stratified DM to satisfy the assumption of the proportional hazard in the fully adjusted model. We used restricted cubic spline curve to illustrate the nonlinear association between the serum uric acid level and MCD progression. We used four knots for the restricted cubic spline curve. The data were analyzed and plotted using R, version 4.0.2 (R Foundation for Statistical Computing, Vienna, Austria). All statistical tests were two-tailed, and a p-value of <0.05 was considered statistically significant.

Ethical approval and informed consent

This study complied with the tenets of the Declaration of Helsinki. Because the database used in this study did not include personal identifiers and the study was retrospective and observational in its design, the need for informed consent was waived. The study was approved by the Institutional Review Board of Chonnam National University Hospital (CNUH-EXP-2020-312).

Results

Baseline characteristics of the study population

The baseline characteristics of the participants are presented in Table 1. The mean patient age was 43.1 ± 18.3 years, and 475 participants (59.4%) were male. In total, 82 participants (10.3%) had DM, and the mean serum creatinine was 1.1 ± 0.8 mg/dL at baseline. Participants in the high uric acid group had significantly higher serum creatinine (1.4 mg/dL vs. 0.9 mg/dL, p < 0.001), higher blood urea nitrogen (26.4 mg/dL vs. 16.3 mg/dL, p < 0.001), lower serum protein (5.1

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total</th>
<th>High uric acid group</th>
<th>Control group</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>800</td>
<td>285</td>
<td>515</td>
<td></td>
</tr>
<tr>
<td>Uric acid (mg/dL)</td>
<td>6.27 ± 1.93</td>
<td>8.26 ± 1.45</td>
<td>5.17 ± 1.11</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>43.1 ± 18.3</td>
<td>44.6 ± 18.7</td>
<td>42.2 ± 18.1</td>
<td>0.07</td>
</tr>
<tr>
<td>Male sex</td>
<td>475 (59.4)</td>
<td>181 (63.5)</td>
<td>294 (57.1)</td>
<td>0.09</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>82 (10.3)</td>
<td>34 (11.9)</td>
<td>48 (9.3)</td>
<td>0.31</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>256 (32.0)</td>
<td>109 (38.2)</td>
<td>147 (28.7)</td>
<td>0.007</td>
</tr>
<tr>
<td>Smoking (%)</td>
<td>192 (24.0)</td>
<td>73 (25.6)</td>
<td>119 (23.1)</td>
<td>0.40</td>
</tr>
<tr>
<td>MDRD eGFR (mL/min/1.73 m²)</td>
<td>85.4 (55.6–106.3)</td>
<td>67.4 (43.5–87.6)</td>
<td>96.7 (76.6–116.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BUN (mg/dL)</td>
<td>19.9 ± 14.4</td>
<td>26.4 ± 1.85</td>
<td>16.3 ± 9.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>14.0 ± 2.0</td>
<td>14.0 ± 2.1</td>
<td>14.0 ± 2.0</td>
<td>0.85</td>
</tr>
<tr>
<td>Glucose (mg/dL)</td>
<td>105.9 ± 34.4</td>
<td>107.2 ± 35.5</td>
<td>105.3 ± 33.8</td>
<td>0.46</td>
</tr>
<tr>
<td>Protein (g/dL)</td>
<td>5.3 ± 1.4</td>
<td>5.1 ± 1.4</td>
<td>5.4 ± 1.4</td>
<td>0.001</td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>2.8 ± 1.2</td>
<td>2.6 ± 1.1</td>
<td>2.9 ± 1.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cholesterol (mg/dL)</td>
<td>309.2 ± 143.5</td>
<td>318.7 ± 144.2</td>
<td>304.1 ± 142.9</td>
<td>0.18</td>
</tr>
<tr>
<td>UPCR (g/gCr)</td>
<td>6.6 (1.0–10.2)</td>
<td>7.2 (1.2–10.8)</td>
<td>6.2 (0.9–9.6)</td>
<td>0.04</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>24.7 ± 3.9</td>
<td>25.5 ± 3.7</td>
<td>24.3 ± 4.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>123.3 ± 16.8</td>
<td>125.9 ± 18.5</td>
<td>121.9 ± 15.7</td>
<td>0.003</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>77.5 ± 12.1</td>
<td>79.0 ± 14.0</td>
<td>76.8 ± 10.9</td>
<td>0.03</td>
</tr>
<tr>
<td>Follow-up (yr)</td>
<td>5.8 ± 4.1</td>
<td>5.3 ± 4.3</td>
<td>6.1 ± 4.0</td>
<td>0.004</td>
</tr>
</tbody>
</table>

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

MDRD, modification of diet in renal disease; eGFR, estimated glomerular filtration rate; BUN, blood urea nitrogen; DBP, diastolic blood pressure; UPCR, urine protein-to-creatinine ratio; SBP, systolic blood pressure.
g/dL vs. 5.4 g/dL, p = 0.001), lower serum albumin (2.6 g/dL vs. 2.9 g/dL, p < 0.001), higher urine protein-to-creatinine ratio (7.2 g/g Cr vs. 6.2 g/g Cr, p = 0.04), higher prevalence of hypertension (38.2% vs. 28.7%, p = 0.007), higher body mass index (25.5 kg/m² vs. 24.3 kg/m², p < 0.001), and higher systolic blood pressure (126 mmHg vs. 122 mmHg, p = 0.003) than those in the control group. The distribution of serum uric acid levels differed significantly according to sex (Fig. 2).

Independent risk factors for progression of minimal change disease to end-stage renal disease

A total of 42 patients (5.3%) have progressed to ESRD during the follow-up period. The unadjusted analysis is presented in Supplementary Table 1 (available online). We have also created a Cox regression model using restricted cubic spline curve to assess the association between serum uric acid level and HR of MCD progression (Fig. 3). The serum uric acid level exhibited a positive correlation with MCD progression.

Adjusted Cox proportional hazard models were used to determine whether serum uric acid levels and falling into the high uric acid group were independent risk factors for MCD progression. In the fully adjusted model, the risk of MCD progression increased by 29% for every 1 mg/dL increase in the baseline serum uric acid level (HR, 1.29; 95% CI, 1.09–1.54; p = 0.004). Falling into the high uric acid group was also a risk factor for progression of MCD to ESRD (HR, 3.40; 95% CI, 1.59–7.31; p < 0.001) (Table 2).

Kaplan-Meier survival curves showed statistically significant differences between the high uric acid group and the low uric acid group in relation to MCD progression to ESRD (p < 0.001) (Fig. 4).

Sensitivity analysis

Since the number of renal events was small and may lead to an over-fitting problem, we performed a propensity score-adjusted analysis by combining the covariates. The propensity score-matching results showed that falling into the high uric acid group (HR, 2.37; 95% CI, 1.20–4.68; p = 0.01) and high serum uric acid (HR, 1.17; 95% CI, 1.01–1.35; p = 0.004) were risk factors for progression of MCD to ESRD (Table 3). To exclude the possibility of an initial free-ESRD

### Table 2. Hazard ratio for progression of minimal change disease by uric acid with Cox proportion hazard models

<table>
<thead>
<tr>
<th>Model</th>
<th>High uric acid group HR (95% CI)</th>
<th>p-value</th>
<th>Serum uric acid HR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crude</td>
<td>3.88 (2.04–7.37)</td>
<td>&lt;0.001</td>
<td>1.26 (1.10–1.44)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Model 1</td>
<td>3.66 (1.92–6.97)</td>
<td>&lt;0.001</td>
<td>1.26 (1.10–1.44)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Model 2</td>
<td>3.79 (1.96–7.29)</td>
<td>&lt;0.001</td>
<td>1.27 (1.11–1.46)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Model 3</td>
<td>3.40 (1.59–7.31)</td>
<td>&lt;0.001</td>
<td>1.29 (1.09–1.54)</td>
<td>0.004</td>
</tr>
</tbody>
</table>

Crude: unadjusted analysis; model 1: adjusted for age and sex; model 2: model 1 + diabetes mellitus, hypertension; model 3: model 2 + albumin, body mass index, creatine, hemoglobin, smoking.

![Figure 2](http://www.krcp-ksn.org)  
**Figure 2.** The difference in distributions of the serum uric acid levels according to sex. The median serum uric acid level was 5.5 mg/dL in females and 6.8 mg/dL in males.

![Figure 3](http://www.krcp-ksn.org)  
**Figure 3.** Restricted cubic spline curve of the hazard ratio of serum uric acid for end-stage renal disease survival probability. The serum uric acid level exhibited a positive correlation with minimal change in disease progression.
probability gap in Kaplan-Meier curves affecting the final free-ESRD probability, we analyzed Cox proportional hazard models, except renal events in the first year. This sensitivity analysis is presented in Table 3.

**Discussion**

Our study showed that hyperuricemia is an independent risk factor for the progression of MCD. A recent study reported that serum uric acid levels at the time of biopsy predicted steroid-resistant nephrotic syndrome (SRNS) in children [20]. SRNS children with hyperuricemia had a significantly higher rate of glomerulosclerosis, tubular atrophy, diffuse interstitial fibrosis, and ESRD at last follow-up compared with those without hyperuricemia. Renal survival analysis of children showed that the hyperuricemia group compared with the non-hyperuricemia group had a higher rate of SRNS progression. However, the association between MCD and hyperuricemia in adults was previously unknown. Therefore, this study has important implications.

Various biologic mechanisms could explain the relationship between serum uric acid and kidney disease progression. The main histologic feature of MCD is foot process effacement. Asakawa et al. [21] revealed that hyperuricemia is related to podocyte injury and albuminuria. Hyperuricemic rats showed significant albuminuria, and the podocyte injury marker, desmin, was upregulated in the glomeruli. Urinary 8-hydroxy-2’-deoxyguanosine levels were significantly increased and correlated with albuminuria and podocytopathy.

The progression of MCD is related to a combination of ischemic injury, tubular injury, and diminished capillary fil-

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**Figure 4.** Kaplan-Meier free-ESRD probability curve with the log-rank test between the hyperuricemia group and MCD progression. MCD progression occurred more frequently in the high uric acid (HUA) group than in the low uric acid (LUA) group. ESRD, end-stage renal disease; MCD, minimal change disease.

**Table 3.** Sensitivity analysis using a propensity score-adjusted analysis model and Cox hazard model excluding renal events in the first year

<table>
<thead>
<tr>
<th>Model</th>
<th>High uric acid group</th>
<th>Serum uric acid</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>p-value</td>
</tr>
<tr>
<td>Propensity score-adjusted analysis model</td>
<td>2.37 (1.20–4.68)</td>
<td>0.01</td>
</tr>
<tr>
<td>Cox hazard model excluding renal events in the first year</td>
<td>3.59 (1.14–11.30)</td>
<td>0.03</td>
</tr>
</tbody>
</table>

CI, confidence interval; HR, hazard ratio.
In idiopathic nephrotic syndrome including MCD, the current hypothesis suggests that immune cells release a putative factor, which alters podocyte function resulting in nephrotic proteinuria [29,30]. CD4+ cells, CD8+ cells, and macrophages have been shown to be prominent components of interstitial inflammation in chronic proteinuric renal disease [31]. Most CD8+ cells have suppressor or cytotoxic functions and induce renal injury [32]. Webb et al. [33] revealed that uric acid directly activated primary human T cells. Uric acid may help dendritic cells recognize apoptotic cells, and it activates CD8+ cells in the immune system [34]. Consequently, hyperuricemia may cause the progression of MCD by several different biologic mechanisms.

Our study has several strengths. First, to the best of our knowledge, this study is the first one to reveal the association between hyperuricemia and MCD progression in adults. Second, this study has a large sample size and a long-term follow-up regarding disease outcomes. Our study also has some limitations. First, as this was an observational study, we could not establish the causality between hyperuricemia and MCD progression. However, observational studies are powerful tools that enable assessment of epidemiologic relationships, and we capitalized on the complementary analytic methods to examine the relationship between serum uric acid and MCD progression [35]. Second, due to the lack of data describing patient use of uric acid-lowering medications and corticosteroids, we could not evaluate the effects of medications on disease progression. Third, as we mentioned above, MCD progression has previously been shown to be related to arteriosclerosis or tubular atrophy in kidney biopsies. However, we could not evaluate their relationship in this study due to lack of detailed findings from the kidney biopsy.

In conclusion, our study showed that hyperuricemia was associated with the progression of MCD. We suggest that screening for hyperuricemia in MCD patients would help identify high-risk groups for disease progression. It could help to manage the MCD patients in a timely manner.

Conflicts of interest

All authors have no conflicts of interest to declare.

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Authors’ contributions

Conceptualization: EHB, TRO, SHS
Data curation: TRO, SHS, CSK, SHP
Formal analysis: TRO, SHS
Investigation: HSC, CSK, DRR, SGK, SHP, SKM, SWK, EHB
Funding acquisition: EHB
Writing–original draft: SHS, TRO
Writing–review & editing: SHS, EHB, SKM, SWK

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Nephrol 2017;18:326.


Preexisting comorbidities are associated with the mortality rate as well as the predialysis adverse events in incident dialysis patients

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Background: Optimal estimated glomerular filtration rate (eGFR) to start maintenance dialysis is controversial. Observational studies have reported that initiation of dialysis at high eGFRs is associated with worse postdialysis survival.

Methods: We retrospectively investigated 1,038 incident dialysis patients who started maintenance dialysis during 2010-2015. Patients were assessed for comorbidities and adverse events during the transitional period of dialysis initiation. Patients were classified as planned dialysis (PD) vs. unplanned dialysis (UD) according to indications for dialysis initiation.

Results: UD group comprised 352 patients (33.9%). Mean eGFR at dialysis initiation was higher in UD patients than PD patients (7.9 ± 5.1 vs. 5.9 ± 3.4 mL/min/1.73 m², p < 0.001). Mean Davies comorbidity index in the UD group was higher (vs. PD group, 1.3 ± 1.0 vs. 0.9 ± 1.0, p < 0.001). Patients with more comorbidities experienced more ischemic heart disease (hazard ratio [HR], 4.36; 95% confidence interval [CI], 1.71–11.14) in the medium-risk group and HR of 8.84 (95% CI, 3.06–25.55) in the high-risk group (vs. low-risk group, p < 0.001)) during the predialysis period. High-risk group had increased postdialysis mortality (HR, 2.48; 95% CI, 1.46–4.20; p = 0.001). Adjusted HR of mortality was higher in the medium-risk group of UD patients (HR, 1.72; 95% CI, 1.16–2.56; p = 0.007).

Conclusion: Patients with more comorbidities were at increased risk of predialysis ischemic heart disease and postdialysis mortality. UD patients in the medium-risk population had increased risk of postdialysis mortality. Dialysis start should be individualized by considering comorbidities.

Keywords: Comorbidity, Dialysis, Glomerular filtration rate, Mortality

Introduction

The number of end-stage renal disease (ESRD) patients requiring dialysis treatment has been continuously and rapidly increasing over the past few decades [1–4]. Nevertheless, the optimal estimated glomerular filtration rate (eGFR) to start renal replacement therapy (RRT) is still controversial. In the 1990s, nephrologists believed that early initiation of dialysis
could improve patient survival. Several observational cohort and case-control studies suggested that starting dialysis early may improve patients’ survival, quality of life, capacity for employment, and decrease complications [5,6]. Recently, several observational studies have shown that initiation of dialysis at high eGFR is associated with worse postdialysis patient survival [7–12]. The Initiating Dialysis Early and Late (IDEAL) study, the only randomized trial to investigate the appropriate eGFR to initiate dialysis, evaluated the impact of dialysis initiation on outcomes at two different levels of kidney function. This study showed that initiation of dialysis at higher eGFR was not associated with an improvement in patient survival or clinical outcomes [13]. In that study, the decision to start dialysis was originally guided by eGFR based on serum creatinine, but the clinical profile of the patient such as uremic symptoms, signs of protein-energy wasting, or fluid overload also affected the decision to initiate dialysis. The focus of previous studies when planning the timing of dialysis initiation has primarily been on eGFR; in this study, we focused on predialysis comorbidity status in addition to eGFR. We advocate that dialysis initiation should be based on both eGFR and the comorbidities of the patient, and argue that previous studies did not capture the comorbidity profile nor capture dialysis indications accurately because most previous studies were based on administrative or claim data. Here, we investigated predialysis comorbidities and indications for dialysis initiation based on manual medical record review.

Unplanned dialysis is associated with increased patient morbidity and mortality and added health care costs [14,15]. Given the high prevalence of unplanned dialysis and its association with poor patient outcomes, it is important to identify risk factors for unplanned dialysis initiation. Therefore, we also investigated to what extent predialysis comorbidities affect dialysis initiation timing in terms of eGFR and urgency.

**Methods**

We performed a retrospective cohort study at Ajou University Medical Center (AJMC) in Suwon, Korea. We enrolled patients 18 years of age or older at initiation of dialysis with progressive chronic kidney disease (CKD). The study was approved by the Institutional Review Board (IRB) of Ajou University School of Medicine in Suwon, Korea (No. AJIRB-MED-MDB-15-514). Informed consent was waived due to the retrospective nature of the study. The study design followed the tenets of the Declaration of Helsinki for biomedical research.

**Study populations**

We retrieved a list of patients receiving their first medical order for dialysis at AJMC from the AUMC clinical data warehouse system. We reviewed medical charts of all enrolled patients. A total of 2,746 patients received conventional hemodialysis for the first time at AJMC between January 2010 and December 2015. Of these, 1,362 patients were excluded because they were predominantly hemodialysis patients. Other excluded patients included 374 who received hemodialysis for the management of acute kidney injury, 46 who switched to hemodialysis from peritoneal dialysis, 38 who returned to hemodialysis following renal allograft failure, one for whom there was insufficient data in their electrical medical record, and three who refused hemodialysis (hemodialysis prescribed but not performed). Therefore, of the original 2,746 patients, 922 patients started maintenance hemodialysis for management of ESRD between January 2010 and December 2015. Of these 922 patients, 26 were preemptive kidney transplantation cases that underwent brief hemodialysis immediately before kidney transplantation. We enrolled 14 alleged CKD stage IV patients who received continuous RRT (CRRT) as the initial dialysis modality. These patients were patients who were continuing to be treated for progressive CKD in the outpatient clinic of the nephrology department. Because we retrieved the patient list based from the data warehouse based on medical orders, we excluded other CRRT cases such as patients with acute kidney injury who needed temporary RRT or ESRD patients who needed CRRT due to unstable vital signs. Peritoneal dialysis patients were included. Over the 6-year study period, 102 patients started peritoneal dialysis for the management of ESRD. In total, the medical records of 1,038 incident dialysis patients who started maintenance dialysis between January 2010 and December 2015 were reviewed. The process for constructing the retrospective cohort is summarized in Fig. 1.
Data collection

Demographic, laboratory, and clinical information was collected. The presence of comorbid illnesses was assessed at the time of enrollment by complete review of inpatient and outpatient records (containing information about medical and surgical consultations and previous hospital admissions). eGFR was calculated using the Modification of Diet in Renal Disease study equation [16]. Enrollment time was defined as the first time of eGFR below 20 mL/min/1.73 m² referencing the criteria of other studies of patients with advanced CKD [17–19]. We reviewed predialysis adverse outcomes, such as ischemic heart disease (nonfatal myocardial infarction, new-onset angina requiring percutaneous intervention), cerebrovascular events (nonfatal stroke, transient ischemic attack), and infection requiring hospitalization from time of enrollment to dialysis initiation. Early referral and late referral were defined according to whether the patient’s first encounter with a nephrologist was more than or less than 3 months prior to dialysis initiation [20]. Body mass index (BMI) was categorized according to the World Health Organization classification for Asian populations [21]. Mortality data were obtained from the time of dialysis initiation until December 2017. When classifying the main indications for dialysis initiation, uremic symptoms were defined as following: anorexia, nausea, decreased appetite, general aches, peripheral neuropathy, pruritus, anemia despite proper medication, and other symptoms [22].

Comorbidity index

Comorbidities were defined as follows: diabetes mellitus, hypertension, ischemic heart disease (stable angina, unstable angina, and myocardial infarction), heart failure, peripheral arterial occlusive disease, cerebrovascular disease, liver cirrhosis (compensated, decompensated), chronic obstructive pulmonary disease, malignancy, acquired immune deficiency syndrome, neuromuscular disease, and systemic collagen disorder. Davies [23] comorbidity indices were calculated for each patient based on their comorbidities at enrollment. The Davies score is based on the presence or absence of seven comorbid conditions and produces three risk groups. Age is not included in this index. Patients without comorbid conditions are classified as low-risk. Patients with one or two comorbid diseases are regarded as medium-risk patients. Patients with three or more comorbid conditions are classi-
fied as high-risk patients.

Definitions of planned and unplanned dialysis

Patients were assigned to the planned dialysis group or unplanned dialysis group [14,24,25]. The unplanned dialysis group included patients who started maintenance dialysis due to a life-threatening situation regardless of a permanent access device in place. A life-threatening situation was defined as one of the following: uremic encephalopathy, uremic pericarditis, pulmonary edema on chest X-ray with consistent clinical symptoms of dyspnea, and a change in electrocardiogram rhythm with serum potassium more than 7.0 mEq/L despite proper medical treatment. The planned dialysis group was defined as the remaining cases that did not undergo unplanned dialysis.

Statistical analysis

Continuous variables are summarized as means (± standard deviation) for normally distributed data; categorical variables are presented as frequencies (percentages). The significance of differences in continuous variables between groups was assessed using the Student t test, the Mann-Whitney test, or one-way analysis of covariance (for nonnormally distributed data), while the significance of differences in categorical data among groups was evaluated using chi-square tests.

Logistic regression models were used to identify univariate and multivariable risk factors for unplanned dialysis. Comorbidity indices and predialysis adverse events between the planned dialysis group and the unplanned dialysis group were compared using Cox regression analysis. Kaplan-Meier plots were used to visualize the associations between comorbidities and predialysis adverse outcomes. We used the Cox proportional hazards model to assess factors associated with the endpoint of death from any cause. To further investigate temporal changes in the hazard ratio (HR) of different subpopulations, we applied time-varying hazard regression based on fractional polynomials [26].

All reported p-values are two-tailed, with a p-value of 0.05 indicating statistical significance. Analyses were performed using Stata software, version 15.0 (Stata Corp., College Station, TX, USA).

Results

Baseline characteristics

Between Jan 2010 and Dec 2015, a total of 1,038 patients were enrolled for final analysis (Fig. 1). Table 1 shows the baseline characteristics of the patients. Four hundred 61 patients (44.4%) were female. Mean age at dialysis initiation was 58.6 ± 14.8 years old. Mean eGFR at the enrollment time was 14.1 ± 5.9 mL/min/1.73 m², and mean eGFR at dialysis initiation was 6.6 ± 4.2 mL/min/1.73 m². The proportion of early referrals was 84.2%. Common comorbidities at enrollment were hypertension (87.7%), diabetes mellitus (53.7%), previous cerebrovascular disease (12.4%), heart failure (8.9%), previous angina s/p (status post) stent insertion (7.7%), and previous myocardial infarction (5.5%). In the unplanned dialysis group, the prevalence of diabetes mellitus was higher, the duration of diabetes mellitus was longer, and insulin use was higher than in the planned dialysis group. In the unplanned dialysis group, cardiovascular disease, such as myocardial infarction and angina, heart failure, and peripheral arterial occlusive disease were more prevalent. History of chronic obstructive pulmonary disease, malignancy, neuromuscular disease, or systemic collagen disease did not differ between the two groups.

Unplanned vs. planned dialysis

There were 352 patients (33.9%) in the unplanned dialysis group and these patients were older than those in the planned dialysis group (p < 0.001). Mean eGFR at dialysis initiation in the unplanned dialysis group was higher than that in the planned dialysis group (8.0 ± 5.1 mL/min/1.73 m² vs. 5.9 ± 3.4 mL/min/1.73 m²; p < 0.001). Table 2 shows in detail the main indications for dialysis and what symptoms were prevalent at the start of dialysis. In the planned dialysis group, the main indication for dialysis initiation was uremic symptoms (41.8%) while in the unplanned dialysis group, the main indication for dialysis initiation was volume overload (67.0%). The unplanned dialysis group had higher comorbidity scores than the planned dialysis group (Table 3). Logistic regression analysis showed that age at enrollment time (odds ratio [OR], 1.03; 95% confidence interval [95% CI], 1.02–1.04; p < 0.001), diabetes mellitus (OR, 1.94; 95% CI, 1.44–2.61; p < 0.001), heart failure (OR, 2.81; 95%
CI, 1.71–4.62; p < 0.001), peripheral arterial occlusive disease (OR, 2.22; 95% CI, 1.12–4.37; p = 0.02), and late referral (OR, 0.63; 95% CI, 0.45–0.88) were independent risk factors for unplanned dialysis (Supplementary Table 1, available online). When divided into comorbidity risk index groups, the OR for unplanned dialysis was 2.43 times higher in the medium-risk group (95% CI, 1.79–3.31; p < 0.001) and 3.27 times higher in the high-risk group (95% CI, 2.03–5.26; p < 0.001) than in the low-risk group. In addition, eGFR at dialysis initiation was higher in the unplanned dialysis group than in the planned dialysis group for all comorbidity risk index groups (Table 3).

Subgroup analysis of planned and unplanned dialysis according to RRT modality is shown in Supplementary Table 2.

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

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total</th>
<th>Planned dialysis</th>
<th>Unplanned dialysis</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>At the time of enrollment</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient</td>
<td>1,038 (100)</td>
<td>686 (66.1)</td>
<td>352 (33.9)</td>
<td>-</td>
</tr>
<tr>
<td>Male sex</td>
<td>577 (55.6)</td>
<td>383 (55.7)</td>
<td>195 (55.4)</td>
<td>0.93</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>58.6 ± 14.8</td>
<td>56.1 ± 14.6</td>
<td>63.8 ± 13.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>DM</td>
<td>557 (53.7)</td>
<td>325 (47.4)</td>
<td>235 (66.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>DM duration (yr)</td>
<td>8.8 ± 10.5</td>
<td>7.3 ± 9.8</td>
<td>11.7 ± 11.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Use of insulin</td>
<td>251 (24.2)</td>
<td>143 (20.8)</td>
<td>108 (30.7)</td>
<td>0.006</td>
</tr>
<tr>
<td>HTN</td>
<td>910 (87.7)</td>
<td>600 (87.5)</td>
<td>310 (88.1)</td>
<td>0.78</td>
</tr>
<tr>
<td>HTN duration (yr)</td>
<td>9.0 ± 9.7</td>
<td>8.1 ± 7.6</td>
<td>10.6 ± 8.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>eGFR at enrollment time (mL/min/1.73 m²)</td>
<td>14.1 ± 5.9</td>
<td>13.9 ± 6.0</td>
<td>14.4 ± 5.8</td>
<td>0.26</td>
</tr>
<tr>
<td>Early referral</td>
<td>874 (84.2)</td>
<td>587 (85.6)</td>
<td>287 (81.5)</td>
<td>0.09</td>
</tr>
<tr>
<td><strong>Comorbidities at enrollment time</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cancer</td>
<td>93 (9.0)</td>
<td>58 (8.5)</td>
<td>35 (10.0)</td>
<td>0.47</td>
</tr>
<tr>
<td>Liver cirrhosis</td>
<td>41 (4.0)</td>
<td>27 (3.9)</td>
<td>14 (4.9)</td>
<td>0.61</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>129 (12.4)</td>
<td>78 (11.4)</td>
<td>51 (14.5)</td>
<td>0.18</td>
</tr>
<tr>
<td>COPD</td>
<td>11 (1.1)</td>
<td>5 (0.7)</td>
<td>6 (1.7)</td>
<td>0.15</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>57 (5.5)</td>
<td>29 (4.2)</td>
<td>28 (8.0)</td>
<td>0.01</td>
</tr>
<tr>
<td>Angina</td>
<td>80 (7.7)</td>
<td>41 (6.0)</td>
<td>39 (11.1)</td>
<td>0.01</td>
</tr>
<tr>
<td>Heart failure</td>
<td>92 (8.9)</td>
<td>35 (5.1)</td>
<td>57 (16.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PAOD</td>
<td>41 (4.0)</td>
<td>16 (2.3)</td>
<td>25 (7.1)</td>
<td>0.001</td>
</tr>
<tr>
<td>Neuromuscular disease</td>
<td>1 (0.1)</td>
<td>1 (0.2)</td>
<td>0 (0)</td>
<td>0.47</td>
</tr>
<tr>
<td>Systemic collagen disease</td>
<td>22 (2.1)</td>
<td>16 (2.3)</td>
<td>6 (1.7)</td>
<td>0.51</td>
</tr>
<tr>
<td>Davies comorbidity index</td>
<td>1.0 ± 1.0</td>
<td>0.9 ± 1.0</td>
<td>1.3 ± 1.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>At dialysis initiation time</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Follow-up (day)</td>
<td>434.1 ± 557.2</td>
<td>462.7 ± 581.9</td>
<td>378.4 ± 501.8</td>
<td>0.02</td>
</tr>
<tr>
<td>Modality, HD:PD</td>
<td>936:102</td>
<td>590:96</td>
<td>346:6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Temporary catheter insertion</td>
<td>764 (81.6)</td>
<td>445 (75.4)</td>
<td>319 (92.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>eGFR at dialysis initiation (mL/min/1.73 m²)</td>
<td>6.6 ± 4.2</td>
<td>5.9 ± 3.4</td>
<td>8.0 ± 5.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>23.1 ± 3.6</td>
<td>23.0 ± 3.5</td>
<td>23.3 ± 4.0</td>
<td>0.32</td>
</tr>
<tr>
<td><strong>Predialysis adverse outcome</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>53 (5.1)</td>
<td>27 (3.9)</td>
<td>26 (7.4)</td>
<td>0.02</td>
</tr>
<tr>
<td>Cerebrovascular event</td>
<td>33 (3.2)</td>
<td>15 (2.2)</td>
<td>18 (5.1)</td>
<td>0.01</td>
</tr>
<tr>
<td>Infection requiring hospitalization</td>
<td>112 (10.8)</td>
<td>65 (9.5)</td>
<td>47 (13.6)</td>
<td>0.06</td>
</tr>
</tbody>
</table>

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

COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; HD, hemodialysis; HTN, hypertension; PAOD, peripheral arterial occlusive disease; PD, peritoneal dialysis.

*Unplanned dialysis group was defined as starting maintenance dialysis in a life-threatening situation regardless of a permanent access device in place.

Follow-up: from time of enrollment to dialysis initiation. Temporary catheter insertion was analyzed only in hemodialysis patients.
Table 2. Main indications and prevalent symptoms at dialysis initiation

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total</th>
<th>Planned dialysis</th>
<th>Unplanned dialysis</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Main indication for dialysis initiation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Azotemia without specific symptom</td>
<td>228 (22.0)</td>
<td>228 (33.2)</td>
<td>0 (0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Uremic symptom(^b)</td>
<td>291 (28.0)</td>
<td>287 (41.8)</td>
<td>4 (1.1)</td>
<td></td>
</tr>
<tr>
<td>Volume overload</td>
<td>351 (33.8)</td>
<td>115 (16.8)</td>
<td>236 (67.1)</td>
<td></td>
</tr>
<tr>
<td>Electrolyte imbalance</td>
<td>89 (8.6)</td>
<td>18 (2.6)</td>
<td>71 (20.2)</td>
<td></td>
</tr>
<tr>
<td>Uremic encephalopathy</td>
<td>30 (2.9)</td>
<td>2 (0.3)</td>
<td>28 (8.0)</td>
<td></td>
</tr>
<tr>
<td>Uremic pericarditis</td>
<td>7 (0.7)</td>
<td>0 (0)</td>
<td>7 (2.0)</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>42 (4.1)</td>
<td>36 (5.3)</td>
<td>6 (1.7)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>1,038 (100)</td>
<td>686 (100)</td>
<td>352 (100)</td>
<td></td>
</tr>
</tbody>
</table>

Prevalent symptoms at dialysis initiation

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total</th>
<th>Planned dialysis</th>
<th>Unplanned dialysis</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loss of consciousness</td>
<td>37 (3.6)</td>
<td>4 (0.6)</td>
<td>33 (1.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Delirium</td>
<td>63 (6.1)</td>
<td>14 (2.0)</td>
<td>49 (13.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>420 (40.5)</td>
<td>161 (23.5)</td>
<td>259 (73.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pericardial effusion(^c)</td>
<td>132 (12.7)</td>
<td>53 (7.7)</td>
<td>82 (23.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pulmonary edema</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>171 (16.5)</td>
<td>132 (19.2)</td>
<td>39 (11.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Moderate to severe</td>
<td>264 (25.4)</td>
<td>16 (2.3)</td>
<td>248 (70.5)</td>
<td></td>
</tr>
<tr>
<td>Generalized edema</td>
<td>519 (50.0)</td>
<td>287 (41.8)</td>
<td>232 (65.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Metabolic acidosis(^d)</td>
<td>108 (10.4)</td>
<td>49 (7.1)</td>
<td>59 (16.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hyperkalemia(^e)</td>
<td>153 (14.7)</td>
<td>70 (10.2)</td>
<td>83 (23.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>General weakness</td>
<td>822 (79.2)</td>
<td>498 (72.6)</td>
<td>324 (92.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Anemia</td>
<td>82 (7.9)</td>
<td>58 (8.5)</td>
<td>24 (6.8)</td>
<td>0.36</td>
</tr>
<tr>
<td>Anorexia</td>
<td>601 (57.9)</td>
<td>409 (59.6)</td>
<td>192 (54.6)</td>
<td>0.12</td>
</tr>
<tr>
<td>Vomiting</td>
<td>303 (29.2)</td>
<td>220 (32.1)</td>
<td>83 (23.6)</td>
<td>0.004</td>
</tr>
<tr>
<td>General ache</td>
<td>37 (3.6)</td>
<td>23 (3.4)</td>
<td>14 (4.0)</td>
<td>0.61</td>
</tr>
<tr>
<td>Pruritus</td>
<td>49 (4.7)</td>
<td>35 (5.1)</td>
<td>14 (4.0)</td>
<td>0.42</td>
</tr>
<tr>
<td>Insomnia</td>
<td>47 (4.5)</td>
<td>33 (4.8)</td>
<td>14 (4.0)</td>
<td>0.54</td>
</tr>
<tr>
<td>Neuropathy</td>
<td>89 (8.6)</td>
<td>64 (9.3)</td>
<td>25 (7.1)</td>
<td>0.23</td>
</tr>
<tr>
<td>No symptom</td>
<td>69 (6.7)</td>
<td>68 (9.9)</td>
<td>1 (0.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Systemic infection</td>
<td>40 (3.9)</td>
<td>15 (2.2)</td>
<td>25 (7.1)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Data are expressed as number (%).

\(^a\)Unplanned dialysis group was defined as starting maintenance dialysis in a life-threatening situation regardless of a permanent access device in place.

\(^b\)Uremic symptoms were defined as anorexia, nausea, decreased appetite, general aches, peripheral neuropathy, pruritus, anemia despite proper medications, and other symptoms.

\(^c\)Pericardial effusion was confirmed by echocardiogram and/or computed tomography.

\(^d\)Metabolic acidosis was defined as a serum bicarbonate level below 10 mEq/L.

\(^e\)Hyperkalemia was defined as a serum potassium level greater than 6.0 mEq/L.

Table 3. The eGFR at dialysis initiation according to comorbidity index

<table>
<thead>
<tr>
<th>Davies index</th>
<th>Planned dialysis</th>
<th>Unplanned dialysis</th>
<th>eGFR difference (unplanned – planned dialysis)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. (%)</td>
<td>eGFR (mL/min/1.73 m(^2))</td>
<td>No. (%)</td>
<td>eGFR (mL/min/1.73 m(^2))</td>
</tr>
<tr>
<td>Low-risk</td>
<td>268 (39.1)</td>
<td>4.9 ± 2.5</td>
<td>71 (20.2)</td>
<td>5.7 ± 3.7</td>
</tr>
<tr>
<td>Medium-risk</td>
<td>366 (53.2)</td>
<td>6.5 ± 3.8</td>
<td>236 (67.1)</td>
<td>8.3 ± 5.3</td>
</tr>
<tr>
<td>High-risk</td>
<td>52 (7.6)</td>
<td>7.2 ± 2.9</td>
<td>45 (12.8)</td>
<td>10.1 ± 4.3</td>
</tr>
</tbody>
</table>

Data are expressed as number (%), mean ± standard deviation for eGFR, or contrast ± standard error for eGFR difference.

\(^a\)Unplanned dialysis group was defined as starting maintenance dialysis in a life-threatening situation regardless of a permanent access device in place.

\(^b\)We compared eGFR at dialysis initiation between the planned dialysis group and unplanned dialysis group.
In the peritoneal dialysis patients group, there was no difference in eGFR at dialysis initiation between the planned and unplanned groups (5.66 ± 5.06 mL/min/1.73 m² vs. 4.67 ± 0.53 mL/min/1.73 m², respectively; p < 0.001).

We also performed subgroup analysis of planned and unplanned dialysis based on age group (Supplementary Table 3, available online). There were 499 (73.4%) vs. 181 (26.6%) patients under the age of 65 years in the planned vs. unplanned dialysis groups, while there were 168 (54.4%) vs. 141 (45.6%) patients over 65 years and under 80 years in these two groups and 19 (38.8%) vs. 30 (61.2%) patients over 80 years in these two groups, respectively. In elderly patients over 80 years old, the risk of unplanned dialysis was 1.45 times higher than that of patients under 65 years of age (95% CI, 0.83–2.07; p < 0.001).

**Estimated glomerular filtration rate at dialysis initiation according to comorbidity index**

The higher the comorbidity index, the higher the eGFR at the initiation of dialysis (Table 3). The difference in eGFR at the start of dialysis increased as the number of comorbid conditions increased. Changes in eGFR at the start of dialysis according to the comorbidity index are shown for all patients except asymptomatic patients who started dialysis with progressive azotemia without specific symptoms (Supplementary Table 4, available online). The eGFR at dialysis according to the comorbidity index of patients showed no differences among patients except for the 14 patients with acute kidney injury on chronic kidney injury who start dialysis with CRRT (Supplementary Table 5, available online).

**Predialysis adverse outcomes and comorbidity index**

Analysis of the predialysis period from the time of enrollment to dialysis initiation revealed that patients with a higher comorbidity risk experienced more ischemic heart diseases such as myocardial infarction or unstable angina, and more infection events requiring hospitalization (Fig. 2). HRs of the risk groups for predialysis ischemic heart diseases were as follows: medium-risk, 4.36 (95% CI, 1.71–11.14) and high-risk, 8.84 (95% CI, 3.06–25.55) (log-rank test, global p < 0.001). HRs of each risk group for predialysis infection events were as follows: medium-risk, 2.57 (95% CI, 1.51–4.37) and high-risk,

![Figure 2. Predialysis adverse outcomes according to comorbidity index.](image-url)

(A) Ischemic heart disease-free time from study enrollment. (B) Infection-free time from study enrollment. (C) Cerebrovascular event-free time from study enrollment. X-axis represents the time (years) from the enrollment time.
3.85 (95% CI, 1.94–7.68) (log-rank test, global p < 0.001). HRs of each risk group for predialysis cerebrovascular events were as follows: medium-risk, 0.85 (95% CI, 0.36–1.99) and high-risk, 1.04 (95% CI, 0.36–1.99) (log-rank test, global p = 0.32).

**Postdialysis mortality**

Fig. 3 shows predicted survival after dialysis initiation based on comorbidity index and urgency of dialysis indications. Adjusted Cox regression prediction curves for comparisons of postdialysis survival show that mortality was higher with unplanned dialysis for the same comorbidity risk. As expected, patients with a high comorbidity risk who underwent unplanned dialysis had a higher mortality rate than patients at low risk who underwent planned dialysis (HR, 3.87; 95% CI, 1.85–8.09; p < 0.001), and the low-risk and planned dialysis group had the lowest mortality rate. Survival after dialysis initiation by RRT modality is shown in Supplementary Fig. 1 (available online). There was no difference in postdialysis mortality between hemodialysis patients and peritoneal dialysis patients (p = 0.10). Furthermore, the survival rate of peritoneal dialysis patients was better than that of hemodialysis patients up to about 5 years, but survival curves crossed over just before 5 years. It appears that the mortality rate in peritoneal dialysis patients increased with a longer observation period due to inaccurate death data in hemodialysis patients.

After adjustment for age, sex, eGFR at dialysis initiation, BMI at dialysis initiation, and unplanned dialysis initiation, there was a significant increase in the risk of death as the comorbidity index increased (medium-risk vs. low-risk: HR, 1.73; 95% CI, 1.14–2.63; p = 0.01; high-risk vs. low-risk: HR, 2.50; 95% CI, 1.47–4.27; p = 0.001) (Table 4). After adjustment for age, sex, eGFR at dialysis initiation, BMI at dialysis initiation, and comorbidity indices, HR for death after dialysis initiation in the unplanned dialysis group was 1.69 (95% CI, 1.22–2.33, p = 0.001) when compared with the planned dialysis group (Table 4). Stratified analysis by comorbidity index revealed that planned dialysis was superior to unplanned dialysis in terms of postdialysis mortality in the medium-risk group.

In the unplanned dialysis group, the mortality HR compared to planned dialysis has its immediate peak in the early postdialysis period (Fig. 4A). For patients who experience predialysis ischemic heart disease, postdialysis mortality HR also peaked in the immediate postdialysis period; interestingly, the increased HR of this group was sustained until the end of follow-up after a short neutral period (Fig. 4B).

**Discussion**

In the present study, we found that patients with more comorbidities experienced more ischemic heart diseases such as myocardial infarction or angina, and more infection events requiring hospitalization during the predialysis period than those patients with fewer comorbidities. Patients with higher comorbidity risk were also more likely to undergo unplanned dialysis despite a higher eGFR than patients with a lower comorbidity risk. The mortality rate of patients who underwent unplanned dialysis was high even after dialysis, especially in the early postdialysis period.

Early dialysis initiation (eGFR of >10 mL/min/1.73 m²) was not associated with morbidity or mortality benefits in the IDEAL study [13]. This randomized controlled trial influenced the development of the most recent European guidelines on the timing of dialysis initiation [27], which now place greater emphasis on the assessment of patient symptoms and signs rather than eGFR. It is suggested that in asymptomatic patients with stage V CKD, dialysis may be safely delayed until the eGFR is at least as low as 5 to 7 mL/min/1.73 m² if there is careful clinical follow-up and adequate patient education. In our study of 1,038 patients, mean eGFR at RRT initiation was 6.6 ± 4.2 mL/min/1.73 m². This result lends support to
Table 4. Assessment of mortality after dialysis initiation based on Cox proportional hazard assumption regression analysis

<table>
<thead>
<tr>
<th>Variable</th>
<th>Adjusted model</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex</td>
<td>1.30 (0.94–1.79)</td>
<td>0.11</td>
</tr>
<tr>
<td>Age at dialysis initiation</td>
<td>1.06 (1.04–1.07)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI at dialysis initiation (dry weight)</td>
<td>0.96 (0.91–1.01)</td>
<td>0.09</td>
</tr>
<tr>
<td>Unplanned dialysis(\text{a,b})</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Planned dialysis (all risk)</td>
<td>Reference</td>
<td>-</td>
</tr>
<tr>
<td>Unplanned dialysis (all risk)</td>
<td>1.69 (1.22–2.33)</td>
<td>0.001</td>
</tr>
<tr>
<td>Planned dialysis (low-risk(c))</td>
<td>Reference</td>
<td>-</td>
</tr>
<tr>
<td>Unplanned dialysis (low-risk(c))</td>
<td>1.89 (0.81–4.45)</td>
<td>0.14</td>
</tr>
<tr>
<td>Planned dialysis (medium-risk(c))</td>
<td>Reference</td>
<td>-</td>
</tr>
<tr>
<td>Unplanned dialysis (medium-risk(c))</td>
<td>1.72 (1.16–2.56)</td>
<td>0.007</td>
</tr>
<tr>
<td>Planned dialysis (high-risk(c))</td>
<td>Reference</td>
<td>-</td>
</tr>
<tr>
<td>Unplanned dialysis (high-risk(c))</td>
<td>1.80 (0.80–4.04)</td>
<td>0.16</td>
</tr>
<tr>
<td>Comorbidity index(d)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low-risk(c)</td>
<td>Reference</td>
<td>-</td>
</tr>
<tr>
<td>Medium-risk(c)</td>
<td>1.73 (1.14–2.63)</td>
<td>0.01</td>
</tr>
<tr>
<td>High-risk(c)</td>
<td>2.50 (1.47–4.27)</td>
<td>0.001</td>
</tr>
<tr>
<td>Predialysis ischemic heart disease(e)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>Reference</td>
<td>-</td>
</tr>
<tr>
<td>Yes</td>
<td>1.74 (1.09–2.78)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

BMI, body mass index; CI, confidence interval; HR, hazard ratio.
\(\text{a}\)Unplanned dialysis group was defined as starting maintenance dialysis in a life-threatening situation regardless of a permanent access device in place.
\(\text{b}\)Adjustment for sex, age at dialysis initiation, BMI at dialysis initiation, Davies comorbidity score, and eGFR at dialysis initiation.
\(\text{c}\)Comorbidity index was used for the Davies index and patients were divided into low, medium, and high-risk groups on the basis of this.
\(\text{d}\)Adjustment for sex, age at dialysis initiation, unplanned dialysis, BMI at dialysis initiation, and eGFR at dialysis initiation.
\(\text{e}\)Adjustment for sex, age at dialysis initiation, BMI at dialysis initiation, Davies comorbidity score, unplanned dialysis, and eGFR at dialysis initiation.

Figure 4. Time-varying hazard ratios of unplanned dialysis to postdialysis mortality. (A) Unplanned dialysis group showed an elevated hazard ratio in the early 3 years. (B) Patients who experienced predialysis ischemic heart disease had an immediate postdialysis mortality hazard ratio peak and chronically elevated hazard ratio after dialysis initiation compared to patients who did not experience predialysis ischemic heart disease. Unplanned dialysis group was defined as starting maintenance dialysis in a life-threatening situation regardless of a permanent access device in place. IHD, ischemic heart disease. Y-axis indicates the time-varying hazard ratios of risk factors of interest. Time-varying hazard ratio represents the dynamic change in hazard ratio over time.
the idea that with careful clinical management of CKD, dialysis can be delayed for some patients until the eGFR drops below 7.0 mL/min/1.73 m$^2$. The eGFR at dialysis initiation in our study was very low compared with 12.0 mL/min/1.73 m$^2$ in the early start group and 9.8 mL/min/1.73 m$^2$ in the late start group in the IDEAL study.

However, advanced CKD patients with a higher comorbidity burden may require early dialysis. In our study, eGFR at dialysis initiation in the unplanned dialysis group was 8.0 ± 5.1 mL/min/1.73 m$^2$, while eGFR at dialysis initiation in the planned dialysis group was 5.9 ± 3.4 mL/min/1.73 m$^2$ (p < 0.001). Therefore, knowledge of which comorbidities promote starting dialysis with a high eGFR could allow advanced dialysis planning for patients with these comorbidities. As shown previously, ischemic heart disease, such as myocardial infarction and angina, heart failure, and peripheral arterial occlusive disease were more prevalent in the unplanned dialysis group. In our study, unplanned dialysis was also associated with a significantly increased risk of postdialysis mortality after adjustment for comorbidities, which is a peak in the transitional period. In other words, planned dialysis may avoid the mortality hazard during the transitional period of dialysis initiation, and could have a protective effect on survival. Therefore, in patients with these comorbidities, dialysis initiation should be planned in advance for a higher eGFR. In our study, unplanned dialysis did not increase postdialysis mortality in high-risk patients (Table 4). We believe that planned dialysis is also important in high-risk patients, but the number of patients we evaluated in our study (97 of 1,038) may have been too small to obtain statistically significant results. In addition, patients in the medium-risk and unplanned dialysis group showed an eGFR overlap with those in the high-risk and planned dialysis group (Fig. 4), suggesting that unplanned dialysis is not related to postdialysis mortality in the high-risk group. Conversely, the fact that the mortality difference between planned/unplanned dialysis patients in the medium-risk group was statistically significant suggests that it is important to closely monitor medium comorbidity risk group patients so that unplanned dialysis does not occur, and to proceed with dialysis at an appropriate time without delay.

As Table 3 shows, the higher the comorbidity index, the greater the difference in eGFR at dialysis initiation between the planned dialysis group and unplanned dialysis group. Therefore, nephrologists should be alert to the need for early dialysis initiation in patients with many comorbidities. In addition, as shown in Table 2, symptoms related to volume overload occurred frequently in urgent patients. Therefore, it is important to emphasize the importance of a low salt diet and proper use of diuretics for volume control, especially in high-risk patients.

Cardiovascular disease is common in advanced CKD and ESRD patients and accounts for approximately 50% of deaths among dialysis patients [28-29]. Due to the retrospective nature of this study, we could not determine whether early dialysis planning can prevent predialysis ischemic heart disease. However, we showed that ischemic heart disease during the predialysis period is an important risk factor for postdialysis mortality even if other comorbidities are accounted for. Therefore, predialysis ischemic heart diseases are important risk factors for mortality after dialysis. As shown in Fig. 4, the risk of postdialysis mortality was high in the early period, and the risk of postdialysis mortality in patients who had predialysis ischemic heart disease was also high in the early period. Therefore, careful attention should be paid to the transitional period. In addition, predialysis ischemic heart disease was more common in the high-risk comorbidity group, and extra caution is required for patients with many comorbidities.

Infection is another important complication of CKD. In our study, more infection events requiring hospitalization occurred in patients with higher comorbidity indices during the predialysis period. About 50 years ago, it was assumed that general debility from chronic uremia increased the risk of infection and it was postulated that reversal of the uremic state would reduce the risk of infection [30]. Unfortunately, dialysis does not appear to reduce infection risk in patients with CKD [31]. ESRD may be considered a state of acquired immunodeficiency [32]. Increased risk for hospitalization with infection has also been observed among individuals with less severely decreased kidney function that does not require dialysis [33-35]. Some investigators have indicated that there may be a link between infectious events, which increase inflammatory mediators, and subsequent cardiovascular events, including myocardial infarction and congestive heart failure [36].

Our study has several limitations. First, this study was a retrospective, single-center study performed at a tertiary university hospital, and the results can therefore not be generalized. The classification of comorbidities for each patient was determined by clinical impression (based on docu-
mentation in electronic records) at the time of enrollment. This introduces the possibility of misclassification bias. Conversely, the data can be considered reliable as they were obtained by detailed chart reviews. In addition, our study did not include patients in the eGFR range of 20 to 30 mL/min/1.73 m². Furthermore, as in previous studies [7–10], we included data from only those patients who survived until initiation of dialysis therapy. RRT prevalence is used as a surrogate estimate for ESRD prevalence, but this approach ignores patients receiving conservative care. Therefore, patients with ESRD who might have experienced premature death from inadequate RRT accessibility were not analyzed in our study. Additionally, postdialysis mortality is susceptible to information censoring. Since our hospital is a tertiary university hospital, many patients transition to an outside dialysis clinic after dialysis initiation. However, early mortality during the transitional period would have had a minimal effect on information censoring bias. Another limitation of this retrospective study is the difficulty in determining a causal relationship between early planned dialysis and improved patient survival. We also did not investigate other parameters representative of nutritional status, such as serum albumin level and hsCRP, which could reflect the patient’s condition at the time of dialysis initiation. Despite these limitations, our study provided several clinically relevant points. Because of a thorough electronic medical record review, we were able to capture symptoms of patients and other clinical details. We investigated comorbidities and predialysis adverse clinical outcomes preceding initiation of dialysis. Furthermore, we investigated the association between comorbidities with eGFR at dialysis initiation.

Our study provides important information for decision-making in advanced CKD patients starting dialysis. Patients with more comorbidities experienced more adverse events during the predialysis period. In particular, unplanned dialysis was more common in patients with a history of heart failure, myocardial infarction, and peripheral arterial occlusive disease. Unplanned dialysis increased the risk of postdialysis mortality in the medium-risk comorbidity index population. Together, our findings suggest that dialysis start should be individualized based on comorbidities.

**Conflicts of interest**

All authors have no conflicts of interest to declare.

**Acknowledgments**

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**Authors’ contributions**

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

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Background: Hypertension is the most important modifiable risk factor for mortality and morbidity in chronic kidney disease and coronary artery syndrome. The effect of hypertension prior to percutaneous coronary intervention (PCI) on the development of end-stage renal disease (ESRD) is unknown.

Methods: We used nationally representative data from the Korean National Health Insurance System—140,164 subjects were enrolled during 2010–2015; they were free of ESRD at enrolment, underwent PCI, and were followed up until 2017. Blood pressure (BP) was measured within at least 2 years prior to PCI. The primary outcome was the development of ESRD.

Results: During a median follow-up of 5.4 years, 2,082 participants (1.5%) developed ESRD. The highest systolic BP group (>160 mmHg) showed a higher hazard ratio (3.69; 95% confidence interval, 2.61–5.23) than the reference group (110–119 mmHg). Similar results were observed in the highest diastolic BP group (>120 mmHg), which showed a higher hazard ratio than the reference group (70–79 mmHg). However, ESRD risk showed a J-shaped relationship with baseline systolic and diastolic BP at 113 and 74 mmHg in diabetes mellitus subgroup, respectively, after adjustment for potential confounders.

Conclusion: Our study showed that a high systolic or diastolic BP prior to PCI was independently associated with an increased incidence of ESRD.

Keywords: End-stage renal disease, Hypertension, Korean, Percutaneous coronary intervention, Risk
Introduction

Hypertension is the most important modifiable risk factor globally for overall mortality and morbidity [1]. Hypertension also plays a crucial role in the development and progression to end-stage renal disease (ESRD) [2,3]. Observational studies have shown that death due to cardiovascular (CV) disease increases progressively and linearly with blood pressure (BP) [4,5]. However, this linear theory has been challenged for nearly three decades, especially for diastolic BP (DBP) [6–9]. Physiologically, a J-shaped or U-shaped curve phenomenon would be expected to exist in vital signs such as BP and other biological signs, with increased mortality exhibited at both ends of the spectrum. The linear relationship might be true for the general population but not for patients with chronic illness. In particular, after an acute coronary syndrome, a J- or U-shaped association has been shown between BP and the risk of CV events [10,11].

Percutaneous coronary intervention (PCI) is an essential treatment modality for coronary artery disease, and following advancements in PCI techniques, its indications and applications have been widening. Although PCI is mainly performed in patients with underlying conditions such as diabetes mellitus (DM), chronic kidney disease (CKD), and hypertension, resulting in ESRD, data regarding the association between BP prior to PCI and ESRD remain insufficient. In addition, the association between BP values prior to PCI and ESRD risk has not been evaluated.

To evaluate the role of BP as a predictor of incident ESRD in patients undergoing PCI, we analyzed nationally representative data from the Korean National Health Insurance System.

Methods

Because of the confidentiality of the data used for this study and strict privacy policy from the data holder restricting data access and use to the designated research personnel only, the data cannot be provided to other people, whether or not the data are made anonymous.

Study design and database

The Korean National Health Insurance Service (KNHIS) comprises a complete set of health information of 50 million Koreans, including an eligibility database, a medical treatment database, a health examination database, and a medical care institution database [12–14]. The National Health Insurance Corporation (NHIC) is the single insurer, managed by the Korean government, to which approximately 97% of the Korean population subscribes. Enrollees in the NHIC are recommended to undergo a standardized medical examination at least every 2 years. Among 270,237 subjects who underwent PCI from 2010 to 2015 (index year), 143,981 subjects were followed up to 31 December 2017. We excluded 2,440 subjects with missing data for at least one variable. To avoid confounding effects of preexisting diseases and minimize the possible effects of reverse causality, those with a history of ESRD before the index year were also excluded (n = 1,123). Ultimately, the study population comprised 140,164 subjects (Fig. 1). We registered only de novo PCI and excluded patients with a history of PCI to avoid the effects of past coronary intervention due to coronary artery disease, including angina pectoris or myocardial infarction.

This study was approved by the Institutional Review Board.
(IRB) of Chonnam National University Hospital (No. CNUH-EXP-2019-035) and National Health Insurance Service (NHIS-2019-1-379), and it was conducted according to the principles of the Declaration of Helsinki. The need for written informed consent was waived by the IRB.

**Measurements and definitions**

In the KNHIS, the equipment used to measure BP varies between sites. However, most people received their medical examinations in the same hospital near their residence, and most BP measurements were performed using the same equipment in each individual. BP was measured by trained clinicians. Systolic BP (SBP) and DBP were measured, and the sitting brachial BP was the average of the two measurements taken after the subject had been seated for 5 minutes with an arm in the appropriate position. Body mass index (BMI) was calculated as the subject’s weight in kilograms divided by the square of the subject’s height in meters. Information on current smoking and alcohol consumption was obtained by a questionnaire. Based on alcohol consumption status, participants were categorized as non-drinker, mild drinker (<30g/day), or heavy drinker (≥30g/day). Regular exercise was defined as physical activity that was performed at least five times per week. Income level was dichotomized at the lower 25%. Blood samples for the measurement of serum glucose and total cholesterol levels were drawn after an overnight fast. Proteinuria was tested by the dipstick method and defined as negative, trace, and 1+ to 4+. Comorbidities were identified using information gathered in the 1 year before the index date. Hypertension was defined as a previous hypertension diagnosis International Classification of Diseases (ICD)-10 codes (I10–13, I15) and a history of taking at least one antihypertensive drug, a recorded SBP of ≥140 mmHg, or DBP of ≥90 mmHg in the health examination database. DM was identified using the appropriate diagnostic code (E11–14) and medical history of DM or a recorded fasting serum glucose concentration of ≥126 mg/dL in the health examination database. Dyslipidemia was identified using the appropriate diagnostic code (E78) and history of lipid-lowering drug use or a total serum cholesterol concentration of ≥240 mg/dL in the health examination database. CKD was defined as an estimated glomerular filtration rate (eGFR) of <60 mL/min/1.73 m² calculated using the CKD Epidemiology Collaboration (CKD-EPI) equation. The participants’ fasting blood glucose (mg/dL), total cholesterol (mg/dL), triglyceride (mg/dL), high-density lipoprotein cholesterol (mg/dL), and low-density lipoprotein cholesterol (mg/dL) concentrations were measured in a fasting state. The quality of the laboratory tests has been warranted by the Korean Association for Laboratory Medicine, and the hospitals participating in the National Health Insurance health checkup programs are certified by the NHIS.

**Study outcomes and follow-up**

The study population was followed from baseline to the date of ESRD diagnosis or until December 31, 2017, whichever came first. The primary endpoint was incident ESRD, which was defined using a combination of ICD-10 codes (N18-19, Z49, Z94.0, and Z99.2) and a unique code (V code) that was assigned in the initiation of renal replacement therapy (hemodialysis [HD], V001; peritoneal dialysis [PD], V003) and/or kidney transplantation (KT, V005) during hospitalization. All medical expenses for dialysis are reimbursed using the Korean Health Insurance Review and Assessment Service database. These patients are also registered as special medical aid beneficiaries. Therefore, we identified every patient with ESRD in the entire South Korean population and analyzed the data for all patients with ESRD who started dialysis. Codes for treatment or medical expense claims included V005 for KT, V001 for HD, and V003 for PD. We excluded individuals without previous CKD who had a transplant or dialysis code on the same date as an acute renal failure code. Subjects on continuous renal replacement therapy or acute PD were also excluded.

**Statistical analysis**

We report the mean ± standard deviation with intervals for continuous variables and the numbers (with percentages) for categorical variables. Participants were classified into seven groups according to the SBP and DBP levels. To identify the risk of ESRD by SBP and DBP level, we calculated the hazard ratios (HRs) with 95% confidence intervals (CIs) and analyzed these data using the Cox proportional hazard regression model. We analyzed associations between BP level and ESRD development using three models: model 1, crude model; model 2, adjusted for model 1 plus age, sex, income, DM, dyslipidemia, and hypertension; model 3, adjusted for
model 2 plus smoking, alcohol drinking, physical activity, and eGFR. We also performed subgroup analysis for DM and CKD. A p-value of <0.05 was considered to reflect statistical significance. SAS version 9.3 software and SAS survey procedures (SAS Institute, Inc., Cary, NC, USA) were used for all statistical analyses.

**Results**

**Baseline characteristics**

Table 1 shows the baseline characteristics of the participants regarding the development of ESRD. Among all the participants, 2,082 (1.5%) developed ESRD during a median follow-up duration of 5.4 years. The mean age was higher among individuals who developed ESRD than among those who did not. The proportion of low income was higher in the incident ESRD group than in the non-ESRD group. Comorbidities such as DM, hypertension, dyslipidemia, CKD, and proteinuria were more prevalent in the ESRD group than in the non-ESRD group. GFR and BMI were lower, while BP and glucose levels were higher in the ESRD group than in the non-ESRD group (Table 1).

The characteristics of participants classified by levels of SBP and DBP are presented in Tables 2 and 3, respectively. Subjects in the high SBP group were older, were more likely to be women, had a lower income, exercised less, and had a higher prevalence of DM and CKD (Table 2). BMI, waist circumference, and fasting glucose were also higher in the high SBP group. Lipid profile was higher in the high SBP group (Table 2). Subjects in the higher DBP group were younger, were more likely to be men, had a low income, exercised

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Non-ESRD</th>
<th>ESRD</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>138,082</td>
<td>2,082</td>
<td></td>
</tr>
<tr>
<td>Age (yr)</td>
<td>63.4 ± 10.6</td>
<td>65.4 ± 9.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male sex</td>
<td>97,897 (70.9)</td>
<td>1,451 (69.7)</td>
<td>0.23</td>
</tr>
<tr>
<td>Current smoker</td>
<td>41,174 (29.8)</td>
<td>539 (25.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Heavy drinker</td>
<td>8,958 (6.5)</td>
<td>76 (3.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Regular exercise</td>
<td>28,386 (20.6)</td>
<td>355 (17.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Income-low</td>
<td>29,846 (21.6)</td>
<td>552 (26.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>44,078 (31.9)</td>
<td>1,562 (75.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>95,743 (69.3)</td>
<td>1,945 (93.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>70,411 (51.0)</td>
<td>1,373 (65.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CKD*</td>
<td>19,562 (14.2)</td>
<td>1,659 (79.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>125,014 (91.2)</td>
<td>728 (35.3)</td>
<td></td>
</tr>
<tr>
<td>Trace</td>
<td>4,326 (3.2)</td>
<td>88 (4.3)</td>
<td></td>
</tr>
<tr>
<td>1+</td>
<td>4,361 (3.2)</td>
<td>296 (14.4)</td>
<td></td>
</tr>
<tr>
<td>2+</td>
<td>2,407 (1.8)</td>
<td>482 (23.4)</td>
<td></td>
</tr>
<tr>
<td>3+</td>
<td>805 (0.6)</td>
<td>369 (17.9)</td>
<td></td>
</tr>
<tr>
<td>4+</td>
<td>152 (0.1)</td>
<td>97 (4.7)</td>
<td></td>
</tr>
<tr>
<td>GFR (mL/min/1.73 m²)</td>
<td>81.8 ± 40.8</td>
<td>41.3 ± 27.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>24.7 ± 3.0</td>
<td>24.5 ± 3.2</td>
<td>0.03</td>
</tr>
<tr>
<td>Glucose (mg/dL)</td>
<td>112.2 ± 38.1</td>
<td>136.0 ± 67.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TC (mg/dL)</td>
<td>205.2 ± 46.2</td>
<td>203.6 ± 57.2</td>
<td>0.11</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>130.1 ± 15.9</td>
<td>137.5 ± 19.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>79.0 ± 10.3</td>
<td>80.1 ± 12.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Follow-up (yr)</td>
<td>5.5 ± 1.9</td>
<td>2.5 ± 2.0</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

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

CKD, chronic kidney disease; DBP, diastolic blood pressure; ESRD, end-stage renal disease; GFR, glomerular filtration rate; SBP, systolic blood pressure; TC, total cholesterol

*Estimated GFR < 60 mL/min/1.73 m².
Table 2. Baseline characteristics of participants by level of SBP

<table>
<thead>
<tr>
<th>Variable</th>
<th>Distribution of SBP (mmHg)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;110</td>
<td>≥110, &lt;120</td>
</tr>
<tr>
<td>No. of patients</td>
<td>8,177</td>
<td>22,084</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>101.4 ± 5.4</td>
<td>113.6 ± 3.5</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>64.4 ± 6.9</td>
<td>71.4 ± 6.4</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>62.5 ± 10.2</td>
<td>62.3 ± 10.5</td>
</tr>
<tr>
<td>Male sex</td>
<td>5,928 (72.5)</td>
<td>16,342 (74.0)</td>
</tr>
<tr>
<td>Smoking</td>
<td>None</td>
<td>Ex</td>
</tr>
<tr>
<td></td>
<td>3,450 (42.2)</td>
<td>9,493 (43.0)</td>
</tr>
<tr>
<td>Drinking</td>
<td>None</td>
<td>Mild</td>
</tr>
<tr>
<td></td>
<td>5,478 (67.0)</td>
<td>2,298 (28.1)</td>
</tr>
<tr>
<td></td>
<td>14,125 (64.0)</td>
<td>6,728 (30.5)</td>
</tr>
<tr>
<td></td>
<td>20,584 (63.2)</td>
<td>9,977 (30.6)</td>
</tr>
<tr>
<td></td>
<td>26,091 (62.5)</td>
<td>12,864 (30.8)</td>
</tr>
<tr>
<td></td>
<td>6,581 (64.4)</td>
<td>5,035 (28.5)</td>
</tr>
<tr>
<td></td>
<td>5,055 (65.7)</td>
<td>2,904 (28.4)</td>
</tr>
<tr>
<td></td>
<td>2,014 (26.2)</td>
<td>2,014 (26.2)</td>
</tr>
<tr>
<td></td>
<td>4,154 (50.8)</td>
<td>4,154 (50.8)</td>
</tr>
</tbody>
</table>

Data are expressed as number only, mean ± standard deviation, number (%), or mean (range).
CKD, chronic kidney disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; TC, total cholesterol; WC, waist circumference.

*Low income 25%; †geometric mean.
### Table 3. Baseline characteristics of participants by level of DBP

<table>
<thead>
<tr>
<th>Variable</th>
<th>Distribution of DBP (mmHg)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;70</td>
<td>≥70, &lt;80</td>
</tr>
<tr>
<td>No. of patients</td>
<td>18,330</td>
<td>44,011</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>63.3 ± 4.2</td>
<td>73.2 ± 3.3</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>115.5 ± 13.3</td>
<td>124.1 ± 12.2</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>66.0 ± 9.8</td>
<td>63.9 ± 10.3</td>
</tr>
<tr>
<td>Male sex</td>
<td>12,431 (67.8)</td>
<td>30,960 (70.3)</td>
</tr>
<tr>
<td>Smoking</td>
<td>8,945 (48.8)</td>
<td>21,027 (47.8)</td>
</tr>
<tr>
<td>Drinking</td>
<td>12,961 (70.7)</td>
<td>28,902 (65.7)</td>
</tr>
<tr>
<td>WC (cm)</td>
<td>83.9 ± 8.1</td>
<td>84.9 ± 7.9</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>23.9 ± 2.9</td>
<td>24.5 ± 2.9</td>
</tr>
<tr>
<td>Glucose (mg/dL)</td>
<td>111.9 ± 38.9</td>
<td>122.2 ± 38.6</td>
</tr>
<tr>
<td>TC (mg/dL)</td>
<td>195.1 ± 43.4</td>
<td>203.3 ± 47.8</td>
</tr>
<tr>
<td>HDL-C (mg/dL)</td>
<td>48.4 ± 16.9</td>
<td>49.2 ± 20.6</td>
</tr>
<tr>
<td>LDL-C (mg/dL)</td>
<td>119.0 ± 50.8</td>
<td>123.9 ± 50.6</td>
</tr>
<tr>
<td>Triglyceride (mg/dL)</td>
<td>125.2 (125.5–1274)</td>
<td>137.0 (125.9–1271)</td>
</tr>
<tr>
<td>eGFR (mL/min/1.73 m²)</td>
<td>79.8 ± 45.7</td>
<td>81.3 ± 42.1</td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>13.7 ± 1.7</td>
<td>14.1 ± 1.6</td>
</tr>
</tbody>
</table>

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

CKD, chronic kidney disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; TC, total cholesterol; WC, waist circumference.

*Low income 25%*; *geometric mean.*
less, and had a higher prevalence of CKD but a lower prevalence of DM (Table 3). BMI, waist circumference, and fasting glucose were also higher in the high SBP group. Lipid profile was higher in the high SBP group (Table 2).

**BP and the risk of ESRD**

During a median follow-up period of 5.4 years after the PCI, 2,082 participants (1.5%) developed ESRD. The highest SBP group (>160 mmHg) showed the highest HR of 3.69 (95% CI, 2.61–5.23) compared to the reference group (110–119 mmHg). Similar results were observed for the highest DBP group (≥120 mmHg) as it showed the highest HR compared to the reference group (70–79 mmHg) (Table 4, Fig. 2A, B). The risk of ESRD showed a J-shaped relationship with baseline SBP at 110 mmHg and baseline DBP at 75 mmHg (Table 4, Fig. 3A, B) after adjustment for age, sex, income, presence of DM, dyslipidemia, hypertension, smoking, alcohol drinking, physical activity, and GFR.

**Subgroup analyses**

Subgroup analyses for DM and CKD were performed. The DM cases showed a J-shaped curve with a baseline of 113 mmHg for SBP and 74 mmHg for DBP (Fig. 3C, D), while HR for incident ESRD showed a linear relationship with SBP and DBP among the non-DM cases (Fig. 3E, F). In addition, HR for incident ESRD increased only in the DBP > 120 mmHg group (HR, 2.24; 95% CI, 1.35–3.72) among the non-DM cases. However, the cases with DM showed increased HR in the DBP < 70 mmHg group (HR, 1.43; 95% CI, 1.22–1.68) and the DBP > 120 mmHg group (HR, 2.65; 95% CI, 1.44–4.88) (Table 5).

Regarding the CKD subgroup analysis, increased HR for incident ESRD was observed in the SBP > 150 mmHg group among the non-CKD cases, while increased HR for incident ESRD was observed in the SBP > 130 mmHg group among the CKD cases (Table 6; Supplementary Fig. 1A, C, available online). For DBP, HR for incident ESRD was increased in the DBP > 120 mmHg group among the non-CKD cases (HR, 5.02; 95% CI, 1.79–14.09), while the cases with CKD showed a J-shaped curve and increased HR in the DBP < 70 mmHg (HR, 1.25; 95% CI, 1.07–1.46) and DBP 110–119 mmHg groups (HR, 1.69; 95% CI, 1.13–2.54) (Table 6; Supplementary Fig. 1B, D).

**Discussion**

The present study demonstrated that increased levels of both SBP and DBP prior to PCI were associated with a higher risk of ESRD during a 5.4-year follow-up period after undergoing PCI. Both the SBP and DBP levels were associated with the ESRD risk. Moreover, patients with DM undergoing PCI showed a J-shaped relationship with SBP and DBP for ESRD risk. However, patients without DM undergoing PCI showed a linear relationship with SBP and DBP levels for ESRD risk. This association persisted after multivariable adjustment for important potential confounders.

In the last few decades, researchers have mainly focused on finding a target BP to reduce CV mortality and improve outcomes. The 2017 American Heart Association/American College of Cardiology hypertension guidelines recommended a target of <130/80 mmHg for patients with ischemic heart disease and DM [15]. The background of this guideline was that the Systolic Blood Pressure Intervention Trial (SPRINT) was prematurely ceased due to the benefits of controlling hypertensive patients’ BP levels to <120 mmHg rather than <140 mmHg, thus supporting the aim for a low SBP. The composite endpoint of acute coronary syndrome, stroke, acute decompensated heart failure, or death from CV causes was 25% less likely in those with a target BP of <120 mmHg [16]. However, only a few studies have investigated the association of BP and ESRD risk in patients undergoing PCI. Our data showed that the risk of ESRD is associated with increased SBP and DBP. Especially, DBP of PCI with DM group showed a J-shape at a baseline DBP of 74 mmHg. Böhm et al. [17] reported a significant increase in adverse events for SBP below 120 mmHg, potentially due to poor perfusion leading to an increased risk of ischemic events. White et al. [11] also reported that in patients with type 2 DM and recent acute coronary syndrome, an average BP of <130/80 mmHg was associated with worsened CV outcomes. Similarly, despite the lack of studies on the adverse effects of low BP on ESRD, our results suggest that low BP is a poor prognostic factor for ESRD in DM patients who underwent PCI. Analyses from other preventive cardiology clinical trials support our findings. The Avoiding Cardiovascular Events Through Combination Therapy in Patients Living with Systolic Hypertension trial also showed similar results. This trial included patients with hypertension and increased CV risk and found that, compared with an SBP of...
Figure 2. Incidence rates, HRs, and 95% CIs of ESRD by deciles of SBP (A) and DBP (B). Adjusted for age, sex, income-low 25%, diabetes mellitus, hypertension, dyslipidemia, current smoker, alcohol consumption, regular exercise, and estimated glomerular filtration rate.

CI, confidence interval; DBP, diastolic blood pressure; ESRD, end-stage renal disease; HR, hazard ratio; SBP, systolic blood pressure.

Figure 3. Cubic spline curves depicting the relationship between SBP or DBP and ESRD risk. (A, B) In total, (C, D) diabetes mellitus, and (D, F) non-DM subgroup. Adjusted for age, sex, income, DM, dyslipidemia, and hypertension, smoking, alcohol drinking, physical activity, and estimated glomerular filtration rate.

CI, confidence interval; DBP, diastolic blood pressure; DM, diabetes mellitus; ESRD, end-stage renal disease; HR, hazard ratio; SBP, systolic blood pressure; Ref, reference.
Table 4. Multivariate Cox analysis for incident ESRD by level of SBP and DBP in underwent PCI patients

<table>
<thead>
<tr>
<th>BP group (mmHg)</th>
<th>Total (n)</th>
<th>ESRD (n)</th>
<th>Duration (person × yr)</th>
<th>IR</th>
<th>Hazard ratio (95% confidence interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Model 1</td>
</tr>
<tr>
<td>SBP</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;110</td>
<td>8,177</td>
<td>90</td>
<td>43,605</td>
<td>2.06</td>
<td>1.19 (0.93–1.53)</td>
</tr>
<tr>
<td>≥110, &lt;120</td>
<td>22,084</td>
<td>208</td>
<td>120,898</td>
<td>1.72</td>
<td>1.00 (reference)</td>
</tr>
<tr>
<td>≥120, &lt;130</td>
<td>32,562</td>
<td>331</td>
<td>177,551</td>
<td>1.86</td>
<td>1.08 (0.91–1.29)</td>
</tr>
<tr>
<td>≥130, &lt;140</td>
<td>41,759</td>
<td>544</td>
<td>230,005</td>
<td>2.37</td>
<td>1.38 (1.17–1.62)</td>
</tr>
<tr>
<td>≥140, &lt;150</td>
<td>17,669</td>
<td>339</td>
<td>95,530</td>
<td>3.55</td>
<td>2.06 (1.73–2.45)</td>
</tr>
<tr>
<td>≥150, &lt;160</td>
<td>10,222</td>
<td>258</td>
<td>55,159</td>
<td>4.68</td>
<td>2.72 (2.26–3.26)</td>
</tr>
<tr>
<td>≥160</td>
<td>7,691</td>
<td>312</td>
<td>41,459</td>
<td>7.53</td>
<td>4.38 (3.68–5.22)</td>
</tr>
<tr>
<td>p for trend</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>DBP</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;70</td>
<td>18,330</td>
<td>308</td>
<td>96,109</td>
<td>3.20</td>
<td>1.37 (1.19–1.57)</td>
</tr>
<tr>
<td>≥70, &lt;80</td>
<td>44,011</td>
<td>555</td>
<td>238,017</td>
<td>2.33</td>
<td>1.05 (0.94–1.17)</td>
</tr>
<tr>
<td>≥80, &lt;90</td>
<td>54,023</td>
<td>724</td>
<td>298,763</td>
<td>2.42</td>
<td>1.52 (1.33–1.74)</td>
</tr>
<tr>
<td>≥90, &lt;100</td>
<td>17,124</td>
<td>333</td>
<td>94,355</td>
<td>3.53</td>
<td>1.66 (1.36–2.04)</td>
</tr>
<tr>
<td>≥100, &lt;110</td>
<td>5,328</td>
<td>114</td>
<td>29,658</td>
<td>3.84</td>
<td>2.52 (1.76–3.60)</td>
</tr>
<tr>
<td>≥110, &lt;120</td>
<td>1,006</td>
<td>32</td>
<td>5,471</td>
<td>5.85</td>
<td>3.75 (2.28–6.17)</td>
</tr>
<tr>
<td>≥120</td>
<td>342</td>
<td>16</td>
<td>1,834</td>
<td>8.72</td>
<td>3.75 (2.28–6.17)</td>
</tr>
<tr>
<td>p for trend</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

BP, blood pressure; DBP, diastolic BP; ESRD, end-stage renal disease; IR, incidence rate (per 1000 person-years); PCI, percutaneous coronary intervention; SBP, systolic BP.

Model 1: crude model. Model 2: adjusted for age, sex, income, diabetes mellitus, dyslipidemia, and hypertension. Model 3: adjusted for model 2 plus smoking, alcohol drinking, regular exercise, and glomerular filtration rate. Model 4: adjusted for model 3 plus body mass index, waist circumferences. Model 5: adjusted for model 4 plus number of PCI received.
≥140 mmHg, achieving <140 mmHg produced significant benefits in the CV outcome, but there was no further benefit at lower SBP levels [18].

Recent post hoc and secondary analyses of SPRINT have shown that patients with low baseline CV risk had less benefit and more adverse renal events in the intensively treated group than in the standard group [19]. Furthermore, those patients in the lowest quintile of DBP at baseline (61 mmHg) had higher rates of CV events, but intensive lowering of SBP in this group was still beneficial relative to the low DBP.

Table 5. Multivariate Cox analysis for incident ESRD by level of SBP and DBP in underwent PCI patients (subgroup analysis for DM)

<table>
<thead>
<tr>
<th>BP group (mmHg)</th>
<th>Total (n)</th>
<th>ESRD (n)</th>
<th>Duration (person × yr)</th>
<th>IR</th>
<th>Hazard ratio (95% confidence interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Model 1</td>
</tr>
<tr>
<td>SBP</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-DM</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;110</td>
<td>5,644</td>
<td>15</td>
<td>30,642</td>
<td>0.49</td>
<td>0.79 (0.44–1.39)</td>
</tr>
<tr>
<td>≥110, &lt;120</td>
<td>15,370</td>
<td>53</td>
<td>85,321</td>
<td>0.62</td>
<td>1.00 (reference)</td>
</tr>
<tr>
<td>≥120, &lt;130</td>
<td>22,370</td>
<td>79</td>
<td>123,443</td>
<td>0.64</td>
<td>1.03 (0.73–1.46)</td>
</tr>
<tr>
<td>≥130, &lt;140</td>
<td>28,401</td>
<td>162</td>
<td>158,921</td>
<td>1.02</td>
<td>1.64 (1.21–2.24)</td>
</tr>
<tr>
<td>≥140, &lt;150</td>
<td>11,411</td>
<td>76</td>
<td>62,928</td>
<td>1.20</td>
<td>1.94 (1.37–2.76)</td>
</tr>
<tr>
<td>≥150, &lt;160</td>
<td>6,532</td>
<td>60</td>
<td>36,089</td>
<td>1.66</td>
<td>2.68 (1.85–3.87)</td>
</tr>
<tr>
<td>≥160</td>
<td>4,796</td>
<td>75</td>
<td>26,808</td>
<td>2.80</td>
<td>4.51 (3.18–6.42)</td>
</tr>
<tr>
<td>DM</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;110</td>
<td>2,533</td>
<td>75</td>
<td>12,963</td>
<td>5.79</td>
<td>1.32 (1.00–1.74)</td>
</tr>
<tr>
<td>≥110, &lt;120</td>
<td>6,714</td>
<td>155</td>
<td>35,577</td>
<td>4.36</td>
<td>1.00 (reference)</td>
</tr>
<tr>
<td>≥120, &lt;130</td>
<td>10,192</td>
<td>252</td>
<td>54,108</td>
<td>4.66</td>
<td>1.07 (0.88–1.31)</td>
</tr>
<tr>
<td>≥130, &lt;140</td>
<td>13,358</td>
<td>382</td>
<td>71,084</td>
<td>5.37</td>
<td>1.24 (1.03–1.49)</td>
</tr>
<tr>
<td>≥140, &lt;150</td>
<td>6,258</td>
<td>263</td>
<td>36,089</td>
<td>8.07</td>
<td>1.85 (1.52–2.25)</td>
</tr>
<tr>
<td>≥150, &lt;160</td>
<td>3,690</td>
<td>198</td>
<td>19,070</td>
<td>10.38</td>
<td>2.38 (1.93–2.93)</td>
</tr>
<tr>
<td>≥160</td>
<td>2,895</td>
<td>237</td>
<td>14,651</td>
<td>16.18</td>
<td>4.51 (3.18–6.42)</td>
</tr>
<tr>
<td>p for interaction</td>
<td>0.09</td>
<td>0.10</td>
<td>0.11</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DBP</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-DM</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;70</td>
<td>11,515</td>
<td>60</td>
<td>61,701</td>
<td>0.97</td>
<td>1.10 (0.82–1.49)</td>
</tr>
<tr>
<td>≥70, &lt;80</td>
<td>29,440</td>
<td>142</td>
<td>161,769</td>
<td>0.88</td>
<td>1.00 (reference)</td>
</tr>
<tr>
<td>≥80, &lt;90</td>
<td>37,331</td>
<td>200</td>
<td>209,254</td>
<td>0.96</td>
<td>1.09 (0.88–1.35)</td>
</tr>
<tr>
<td>≥90, &lt;100</td>
<td>11,559</td>
<td>82</td>
<td>64,918</td>
<td>1.26</td>
<td>1.44 (1.10–1.90)</td>
</tr>
<tr>
<td>≥100, &lt;110</td>
<td>3,727</td>
<td>23</td>
<td>21,201</td>
<td>1.09</td>
<td>1.24 (0.80–1.93)</td>
</tr>
<tr>
<td>≥110, &lt;120</td>
<td>701</td>
<td>8</td>
<td>3,912</td>
<td>2.05</td>
<td>2.34 (1.15–4.76)</td>
</tr>
<tr>
<td>≥120</td>
<td>251</td>
<td>5</td>
<td>1,397</td>
<td>3.58</td>
<td>4.08 (1.67–9.94)</td>
</tr>
<tr>
<td>p for trend</td>
<td>0.55</td>
<td>0.34</td>
<td>0.32</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

BP, blood pressure; DBP, diastolic BP; DM, diabetes mellitus; ESRD, end-stage renal disease; IR, incidence rate (per 1000 person-years); PCI, percutaneous coronary intervention; SBP, systolic BP.

Table 6. Multivariate Cox analysis for incident ESRD by level of SBP and DBP in underwent PCI patients (subgroup analysis for CKD)

<table>
<thead>
<tr>
<th>BP group (mmHg)</th>
<th>Total (n)</th>
<th>ESRD (n)</th>
<th>Duration (person × yr)</th>
<th>IR</th>
<th>Hazard ratio (95% confidence interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Model 1</td>
</tr>
<tr>
<td>SBP</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Model 1</td>
</tr>
<tr>
<td>Non-CKD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;110, &lt;120</td>
<td>6,907</td>
<td>20</td>
<td>37,378</td>
<td>0.54</td>
<td>1.16 (0.69–1.95)</td>
</tr>
<tr>
<td>≥120, &lt;130</td>
<td>19,127</td>
<td>49</td>
<td>105,460</td>
<td>0.46</td>
<td>1.00 (reference)</td>
</tr>
<tr>
<td>≥130, &lt;140</td>
<td>28,120</td>
<td>77</td>
<td>154,889</td>
<td>0.50</td>
<td>1.07 (0.75–1.53)</td>
</tr>
<tr>
<td>≥140, &lt;150</td>
<td>35,854</td>
<td>126</td>
<td>199,710</td>
<td>0.63</td>
<td>1.35 (0.97–1.88)</td>
</tr>
<tr>
<td>≥150, &lt;160</td>
<td>14,561</td>
<td>62</td>
<td>80,119</td>
<td>0.77</td>
<td>1.67 (1.15–2.42)</td>
</tr>
<tr>
<td>≥160</td>
<td>8,350</td>
<td>45</td>
<td>46,148</td>
<td>0.98</td>
<td>2.09 (1.40–3.14)</td>
</tr>
<tr>
<td>CKD</td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>&lt;110, &lt;120</td>
<td>1,270</td>
<td>70</td>
<td>6,227</td>
<td>11.24</td>
<td>1.07 (0.81–1.42)</td>
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<tr>
<td>≥120, &lt;130</td>
<td>2,957</td>
<td>159</td>
<td>15,437</td>
<td>10.30</td>
<td>1.00 (reference)</td>
</tr>
<tr>
<td>≥130, &lt;140</td>
<td>4,442</td>
<td>254</td>
<td>22,662</td>
<td>11.21</td>
<td>1.08 (0.89–1.32)</td>
</tr>
<tr>
<td>≥140, &lt;150</td>
<td>5,905</td>
<td>418</td>
<td>22,662</td>
<td>13.80</td>
<td>1.33 (1.11–1.60)</td>
</tr>
<tr>
<td>≥150, &lt;160</td>
<td>1,872</td>
<td>213</td>
<td>9,012</td>
<td>23.64</td>
<td>2.25 (1.83–2.77)</td>
</tr>
<tr>
<td>≥160</td>
<td>1,667</td>
<td>268</td>
<td>7,789</td>
<td>34.41</td>
<td>3.28 (2.69–3.99)</td>
</tr>
<tr>
<td>p for interaction</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DBP</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-CKD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>&lt;70</td>
<td>14,929</td>
<td>50</td>
<td>79,703</td>
<td>0.63</td>
<td>1.03 (0.74–1.44)</td>
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<tr>
<td>≥70, &lt;80</td>
<td>37,519</td>
<td>117</td>
<td>205,455</td>
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<td>1.00 (reference)</td>
</tr>
<tr>
<td>≥80, &lt;90</td>
<td>46,407</td>
<td>254</td>
<td>22,662</td>
<td>11.21</td>
<td>1.08 (0.85–1.37)</td>
</tr>
<tr>
<td>≥90, &lt;100</td>
<td>14,433</td>
<td>72</td>
<td>80,966</td>
<td>0.89</td>
<td>1.30 (0.88–1.91)</td>
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<tr>
<td>≥100, &lt;110</td>
<td>4,528</td>
<td>19</td>
<td>25,652</td>
<td>0.74</td>
<td>1.18 (0.68–2.03)</td>
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<td>≥110, &lt;120</td>
<td>857</td>
<td>5</td>
<td>4,788</td>
<td>1.04</td>
<td>1.65 (0.65–4.19)</td>
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<tr>
<td>≥120</td>
<td>270</td>
<td>4</td>
<td>1,490</td>
<td>2.41</td>
<td>4.91 (1.75–13.75)</td>
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<tr>
<td>CKD</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;70</td>
<td>3,401</td>
<td>258</td>
<td>16,407</td>
<td>15.73</td>
<td>1.25 (1.07–1.46)</td>
</tr>
<tr>
<td>≥70, &lt;80</td>
<td>4,692</td>
<td>438</td>
<td>32,516</td>
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<td>1.00 (reference)</td>
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<td>≥80, &lt;90</td>
<td>7,616</td>
<td>568</td>
<td>39,444</td>
<td>14.40</td>
<td>0.98 (0.86–1.11)</td>
</tr>
<tr>
<td>≥90, &lt;100</td>
<td>2,691</td>
<td>261</td>
<td>13,389</td>
<td>19.49</td>
<td>0.83 (0.70–1.00)</td>
</tr>
<tr>
<td>≥100, &lt;110</td>
<td>800</td>
<td>95</td>
<td>4,005</td>
<td>23.72</td>
<td>0.96 (0.75–1.22)</td>
</tr>
<tr>
<td>≥110, &lt;120</td>
<td>149</td>
<td>27</td>
<td>683</td>
<td>39.52</td>
<td>1.63 (1.09–2.43)</td>
</tr>
<tr>
<td>≥120</td>
<td>72</td>
<td>12</td>
<td>344</td>
<td>34.89</td>
<td>1.32 (0.74–2.37)</td>
</tr>
<tr>
<td>p for trend</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.70</td>
</tr>
</tbody>
</table>

BP, blood pressure; CKD, chronic kidney disease; DBP, diastolic BP; ESRD, end-stage renal disease; IR, incidence rate (per 1000 person-years); PCI, percutaneous coronary intervention; SBP, systolic BP.


A linear relationship between levels of BP and CV outcomes has been observed in the general hypertensive population, particularly for stroke; however, in patients with coronary artery disease, the relationship of BP and CV outcomes often shows a J-shaped curve with higher CV event rates at lower levels of BP [21]. Several pathophysiological mechanisms have been proposed to explain the existence of a J-shaped curve. The J-shaped curve may represent an epiphenomenon of increased arterial stiffness; thus, a low DBP level might be
a marker of high pulse pressure and increased mortality because coronary perfusion occurs during diastole [22]. In our analyses, we noticed a J-shaped curve phenomenon just for DBP but not for SBP in patients with DM, for which the pulse pressure theory would be applicable. However, the hypothesis that a J-shaped curve might be an epiphenomenon of severe underlying chronic illness or inflammation seems more convincing.

Unfortunately, there is no published research on the measurement of BP during health check-ups prior to PCI and ESRD prognosis after PCI. High SBP increases cardiac afterload, whereas low DBP may lead to impaired coronary perfusion. Therefore, the higher the pulse pressure immediately before PCI, the worse the prognosis after PCI [23]. However, it is difficult to determine whether the previous study’s mechanism is the same as that of the current study due to different participant characteristics and methodology. Further research on the mechanism of why BP measured within two years prior to PCI affects the progression to ESRD after PCI is warranted. However, high BP progressively leads to the development of acute coronary syndrome; thus, it can be considered an ESRD progression factor.

This study has several limitations. First, the study population comprised Korean men and women; hence, it is uncertain whether these findings can be generalized to other ethnic groups. Second, different BP devices were used to measure BP, and no standardized protocols were used in each center. Third, antihypertensive drugs, such as renin-angiotensin-aldosterone system blockers, are known to delay the progression of CKD, but these antihypertensive medication effects were not considered in this study. Fourth, there are various time differences between BP measurement and PCI. The maximal time difference was two years, and the average time difference was 1.04 ± 0.57 years. However, the time difference effects were not considered in this study.

In conclusion, our study showed that a high SBP or DBP prior to PCI was independently associated with an increased incidence of ESRD and low DBP also risk for ESRD in PCI patients with DM.

Conflicts of interest

All authors have no conflicts of interest to declare.

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Authors’ contributions

Conceptualization: EHB, SYL
Data curation: BK, KDH
Formal analysis: TRO, HSC
Funding acquisition: SWK
Investigation: BK, KDH
Project administration: EHB, SYL
Visualization: CSK, SKM
Writing–original draft: EHB, SYL
Writing–review & editing: CSK, SKM
All authors read and approved the final manuscript.

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References


Mixed- versus predilution hemodiafiltration effects on convection volume and small and middle molecule clearance in hemodialysis patients: a prospective randomized controlled trial

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\section*{Background} The use of newly developed mixed-dilution hemodiafiltration (HDF) can supplement the weaknesses of pre- and postdilution HDF. However, it is unclear whether mixed-HDF performs well compared to predilution HDF.

\section*{Methods} We conducted a prospective, open-labeled, randomized controlled trial from two hemodialysis centers in Korea. Between January 2017 and September 2019, 60 patients who underwent chronic hemodialysis were randomly assigned at a 1:1 ratio to receive either predilution HDF (n = 30) or mixed-HDF (n = 30) for 6 months. We compared convection volume, changes in small- and medium-sized molecule clearance, high-sensitive C-reactive protein (hs-CRP) level, and dialysis-related parameters between the two dialysis modalities.

\section*{Results} A mean effective convection volume of 41.0 $\pm$ 10.3 L/session in the predilution HDF group and 51.5 $\pm$ 9.0 L/session in the mixed-HDF group was obtained by averaging values of three time-points. The difference in effective convection volume between the groups was 10.5 $\pm$ 1.3 L/session. This met the preset noninferiority criteria, suggesting that mixed-HDF was noninferior to predilution HDF. Moreover, the $\beta_2$-microglobulin reduction rate was greater in the mixed-HDF group than in the predilution HDF group, while mixed-HDF provided greater transmembrane pressure. There were no significant between-group differences in Kt/V urea levels, changes in predialysis hs-CRP levels, proportions of overhydration, or blood pressure values. Symptomatic intradialytic hypotension episodes and other adverse events occurred similarly in the two groups.

\section*{Conclusion} Use of mixed-HDF was comparable to predilution HDF in terms of delivered convection volume and clinical parameters. Moreover, mixed-HDF provided better $\beta_2$-microglobulin clearance than predilution HDF.

\section*{Keywords} Convective volume, Hemodiafiltration, Online hemodiafiltration, Randomized controlled trial

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Introduction

Remarkable technical advances have been made with regard to dialysis membranes and hemodialysis (HD) machines in recent decades. In spite of such improvements, mortality rates remain high, and the overall 5-year survival rate in patients of kidney failure with replacement therapy (KFRT) is 30% in the United States [1]. Unfortunately, dialysis treatment alone cannot improve clinical outcomes, and a comprehensive approach is required. Such an approach should include blood pressure control, appropriate body fluid control, elimination of middle-sized molecules, removal of inflammatory substances, osteoporosis and anemia management, and the provision of sufficient nourishment. Hemodiafiltration (HDF) can facilitate the achievement of these diverse goals [2-5]. In fact, HDF has many advantages over conventional HD, which include its higher clearance of low and middle molecules and inflammatory cytokines, improvement of anemia, and maintenance of hemodynamic stability [6,7]. Notably, recent clinical trials have shown that HDF increased patient survival rates compared to conventional HD, especially in patients who received high-volume convective therapy [7,8].

There are two representative HDF modes: pre- and postdilution. Each has strengths and limitations. Postdilution HDF is the most effective way to maximize molecule clearance. However, blood concentrations can be elevated using HDF, which can cause thrombosis. On the other hand, predilution HDF can resolve this problem [9] but requires about three times more purified water than postdilution HDF and does not guarantee maximal clearance. Therefore, the use of mixed-HDF emerged to compensate for the shortcomings of the other two HDF modalities [10,11]. In mixed-HDF, the substitution fluid required for dialysis is injected at both the entrance and exit of the dialysis membrane. Using a continuous monitoring and feedback system to assess transmembrane pressure (TMP) in the dialyzer, dialysis is automatically switched to either pre- or postdilution HDF mode and optimizes TMP during HD [12]. Despite these advantages of mixed-HDF, clinical studies testing the efficacy of mixed-HDF versus pre- or postdilution HDF are lacking. Several studies have reported that the efficiencies of small- or large-sized molecule removal between mixed-HDF and pre- or postdilution HDF are comparable. Also, TMP is maintained at a more stable level in mixed-HDF compared with postdilution HDF [13-15]. In parts of East Asia such as Japan, most HD units tend to use predilution HDF due to intrinsic problems with postdilution HDF, including high TMP and the tendency to promote clot formation [11,16]. This is also true in Korea, where utilization of predilution HDF is increasing [8]. However, whether mixed-HDF performs well in comparison to predilution HDF remains unknown. Therefore, we conducted a randomized controlled trial to compare predilution HDF with mixed-HDF in Korean patients with KFRT.

Methods

Study design and participants

This study was a prospective, randomized, open-label trial conducted at two hospitals in Korea (Severance Hospital, Seoul; National Health Insurance Service [NHIS] Ilsan Hospital, Goyang). Individuals aged 20 to 75 years who had received HD 3 times weekly for ≥3 months were allowed to participate in the study. Exclusion criteria were as follows: (1) life expectancy < 12 months, (2) dialysis treatment received for less than 3 months or initiated due to acute kidney injury, (3) current history of malignancy, (4) pregnancy, (5) contraindication to anticoagulants, (6) systemic blood pressure < 90 mmHg, and (7) previously received HDF before enrollment. The study was conducted in accordance with the principles of the Declaration of Helsinki, and the study protocol was approved by the Institutional Review Board at each center (No. 4-2016-0702 for Severance Hospital; No. 2018-11-002 for NHIS Ilsan Hospital). All participants provided informed consent when enrolled in the study.

Between January 2017 and December 2019, a total of 66 patients was screened. After a 1-month screening period, 60 patients were randomly assigned at a 1:1 ratio to receive either mixed-HDF or predilution HDF for 6 months. The random assignment was performed using a web-based, random allocation table that considered institution, sex, and causative disease of KFRT (Fig. 1).

Treatment procedures

All participants received thrice-weekly dialysis for at least 3 hours. Both groups were treated with the 5008 or 5008S dialysis system using Cordia dialyzer (Fresenius Medical Care, Bad Homburg, Germany) and maintained a blood
flow rate of 250 mL/min and dialysate flow rate of 700 mL/min. TMP was not expected to exceed 400 mmHg in either predilution HDF or mixed-HDF patients. Prescribed ultrafiltration rate and substitution fluid in both predilution and mixed-HDF groups were calculated using previously reported equations [17].

**Study variables**

The demographic and medical history of participants was collected at enrollment. We recorded dialysis-related information at baseline and every 3 months thereafter. Information collected included dialyzer characteristics, dialysis time, dialysis machine, blood and dialysate flows, substitution volume, TMP, height, dry body weight, pre- and postdialysis body weight, delivered convective volume, net ultrafiltration volume, and predialysis systolic and diastolic blood pressure. Further, the following laboratory data were measured at 0, 3, and 6 months after initiation of this research: hemoglobin, hematocrit, white blood cell differential count, platelet count, predialysis urea concentration, creatinine, sodium, potassium, concentration of bicarbonate using total carbon dioxide, calcium, phosphate, intact parathyroid hormone, high-sensitivity C-reactive protein (hs-CRP), albumin, and fasting glucose. To determine the reduction ratio (RR) of β2-microglobulin at pre- and postdialysis, serum β2-microglobulin level was measured at 0 and 6 months. All laboratory tests were performed locally using standard procedures in certified laboratories. The RR of β2-microglobulin was calculated using pre- and postdialysis serum β2-microglobulin levels and the following formula: $\text{RR} (%) = [1 - (\text{concentration of serum } \beta_2\text{-microglobulin obtained after dialysis/}\text{concentration of serum } \beta_2\text{-microglobulin obtained before dialysis})] \times 100$. Extracellular fluid and total body water volumes were measured via multiple frequency bioelectrical impedance analysis (BCM; Fresenius Medical Care). Measured extracellular fluid volume is presented as overhydrated (L). Measured relative extracellular fluid volume considering total body water fluid volume is presented as overhydrated-extra- cellular fluid (%).

**Outcomes**

The primary outcome assessed was the delivered convection volume difference between mixed-HDF and predilution HDF treatment methods [18]. Since the predilution mode of therapy used twice as much replacement fluid as the postdilution mode, we calculated effective convection volume ratios for mixed-HDF as follows: effective convection volume = substitution volume in predilution mode + 2 × substitution volume in postdilution mode + ultrafiltration volume. In addition, we compared convection volume adjusted for body surface area between two groups. Secondary outcomes included middle- (RR of β2-microglobulin) and small-sized
molecule clearance (Kt/V urea), changes in predialysis levels of an inflammatory marker (hs-CRP) and phosphate, TMP, blood pressure, and intradialysis tolerance.

Power calculation

The total substitution fluid volume is always greater when using predilution HDF versus mixed-HDF. Because mixed-HDF uses both pre- and postdilution modes during the dialysis session, we hypothesized that the effective convective volume in mixed-HDF would be 120% of that of predilution HDF, and the difference in convective fluid would be approximately 7.5 L, which was used as a noninferiority limit. Thus, it was determined that 25 patients within each group were needed to detect a 10-L delivered convective volume difference between the two groups assessed with a power of 90% and an α-value of 0.05. Considering a dropout percentage of 20%, the number needed per group was 30 patients.

Statistical analyses

All data were analyzed according to the per-protocol principle. Data are expressed as mean ± standard deviation or as median (range) for skewed data. Baseline clinical data and laboratory findings, measured at the time of random group assignment, were compared using the t-test and chi-square test. In addition, changes in primary and secondary outcome parameters were analyzed using repeated measures analysis of variance (ANOVA). Continuous variables were assessed using a mixed model approach for repeated measures, after adjustment for age, sex, serum albumin and hemoglobin levels, systolic blood pressure (SBP), predialysis serum β2-microglobulin concentration, and dialysis blood flow. A two-sided significance test was used throughout the analysis, and values of p < 0.05 were considered significant. All statistical analyses were performed using the STATA version 16 statistical package (StataCorp, College Station, TX, USA).

Results

Baseline patient characteristics

The baseline characteristics of patients and treatment parameters are summarized in Table 1. The mean age was 59.7 years, and 50.9% of study participants were male. All patients had been on dialysis treatment for 2 years (range, 1–4 years). Overall, there were no differences in baseline characteristics observed between the two groups. However, the serum β2-microglobulin level of the mixed-HDF group was significantly higher than that of the predilution HDF group. Among dialysis parameters, dialysis time, TMP, dialysis flow rate, and net ultrafiltration did not differ between the two groups. However, the mixed-HDF group had slightly lower blood flow rate than the predilution HDF group.

Primary outcome

Table 2 and Supplementary Fig. 1A (available online) show convection volumes of the two HDF groups during the 6-month period considered. In the predilution HDF group, the mean convective volume determined by averaging values from three time points was 41.0 ± 10.3 L/session, and the convective volume was constantly delivered during follow-up. In the mixed-HDF group, the switch to predilution mode was successfully accomplished depending on TMP level during the dialysis session. In this group, the total effective convection volume delivered was 51.5 ± 9.0 L/session in the mixed-HDF group, which was approximately 20% higher than that of the predilution HDF group. The difference in effective convection volume between the two groups was 10.5 ± 1.3 L/session, which met our preset noninferiority criteria (Fig. 2B, Supplementary Fig. 1B). This finding suggests that mixed-HDF is comparable to predilution HDF with respect to convection volume. Repeated ANOVA analysis and linear mixed model assessment also showed that effective convection volume was greater in the mixed-HDF group than in the predilution HDF group throughout the study period. These results were similar when body surface area-adjusted volumes were compared (Table 2 and Fig. 2).

Secondary outcomes

In secondary outcome analyses, we first compared middle- and small-molecule clearance rates of mixed-HDF and predilution HDF groups. The predialysis serum β2-microglobulin level was significantly higher in the mixed-HDF group than the predilution HDF group during the study period. However, serum β2-microglobulin level of the mixed-HDF group significantly decreased from the baseline value.
(25.4 ± 5.6 mg/L to 22.2 ± 4.4 mg/L), while they remained relatively constant in the predilution HDF group at the same time period (p for intergroup difference = 0.02) (Table 3, Supplementary Fig. 2A). The β2-microglobulin RRs

Table 1. Baseline characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Predilution HDF (n = 27)</th>
<th>Mixed-HDF (n = 26)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>59.0 ± 1.3</td>
<td>60.5 ± 1.1</td>
<td>0.63</td>
</tr>
<tr>
<td>Male sex</td>
<td>16 (59.3)</td>
<td>11 (42.3)</td>
<td>0.22</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>23.7 ± 3.4</td>
<td>22.6 ± 3.9</td>
<td>0.25</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>16 (59.3)</td>
<td>14 (53.8)</td>
<td>0.69</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>10 (37.0)</td>
<td>4 (15.4)</td>
<td>0.07</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>12 (44.4)</td>
<td>10 (38.5)</td>
<td>0.66</td>
</tr>
<tr>
<td>CCI</td>
<td>2 (2–3)</td>
<td>3 (2–3)</td>
<td>0.14</td>
</tr>
<tr>
<td>Cause of KFRT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>16 (59.3)</td>
<td>12 (46.2)</td>
<td>0.46</td>
</tr>
<tr>
<td>Hypertension</td>
<td>9 (33.3)</td>
<td>10 (38.5)</td>
<td>0.34</td>
</tr>
<tr>
<td>Glomerulonephritis</td>
<td>1 (3.7)</td>
<td>3 (11.5)</td>
<td>0.34</td>
</tr>
<tr>
<td>Others</td>
<td>1 (3.7)</td>
<td>1 (3.8)</td>
<td>0.25</td>
</tr>
<tr>
<td>BP-lowering drug</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ARB</td>
<td>17 (63.0)</td>
<td>17 (65.4)</td>
<td>0.85</td>
</tr>
<tr>
<td>CCB</td>
<td>11 (40.7)</td>
<td>14 (53.8)</td>
<td>0.34</td>
</tr>
<tr>
<td>β-Blocker</td>
<td>12 (44.4)</td>
<td>15 (57.7)</td>
<td>0.34</td>
</tr>
<tr>
<td>α-Blocker</td>
<td>3 (11.1)</td>
<td>6 (23.1)</td>
<td>0.25</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>147.0 ± 25.7</td>
<td>148.1 ± 22.6</td>
<td>0.87</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>73.5 ± 17.4</td>
<td>72.8 ± 13.9</td>
<td>0.86</td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>10.6 ± 1.1</td>
<td>10.2 ± 1.3</td>
<td>0.32</td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>3.9 ± 0.3</td>
<td>3.9 ± 0.3</td>
<td>0.57</td>
</tr>
<tr>
<td>hs-CRP (mg/dL)</td>
<td>0.7 (0.11–1.4)</td>
<td>0.8 (0.23–1.5)</td>
<td>0.87</td>
</tr>
<tr>
<td>Sodium (mmol/L)</td>
<td>137.7 ± 2.8</td>
<td>134.0 ± 17.7</td>
<td>0.29</td>
</tr>
<tr>
<td>Potassium (mmol/L)</td>
<td>5.1 ± 0.7</td>
<td>4.9 ± 0.7</td>
<td>0.35</td>
</tr>
<tr>
<td>Bicarbonate (mmol/L)</td>
<td>23.6 ± 4.6</td>
<td>23.8 ± 2.6</td>
<td>0.89</td>
</tr>
<tr>
<td>PTH (pg/mL)</td>
<td>255.5 (188.7–395.6)</td>
<td>265.8 (169.6–451.9)</td>
<td>0.75</td>
</tr>
<tr>
<td>Calcium (mg/dL)</td>
<td>8.6 ± 1.3</td>
<td>8.9 ± 0.6</td>
<td>0.26</td>
</tr>
<tr>
<td>Phosphate (mg/dL)</td>
<td>5.4 ± 1.8</td>
<td>5.2 ± 1.3</td>
<td>0.73</td>
</tr>
<tr>
<td>BUN (mg/dL)</td>
<td>62.1 ± 15.8</td>
<td>58.8 ± 16.8</td>
<td>0.47</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>10.1 ± 2.4</td>
<td>10.0 ± 4.4</td>
<td>0.88</td>
</tr>
<tr>
<td>B2MG (mg/L)</td>
<td>21.7 (19.7–23.4)</td>
<td>25.6 (21.4–28.0)</td>
<td>0.006</td>
</tr>
<tr>
<td>Glucose (mg/dL)</td>
<td>138.6 ± 58.9</td>
<td>132.2 ± 73.2</td>
<td>0.73</td>
</tr>
<tr>
<td>Dialysate parameter</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vintage (yr)</td>
<td>1.5 (1.0–4.25)</td>
<td>3 (1–4)</td>
<td>0.89</td>
</tr>
<tr>
<td>Dialysis time (min)</td>
<td>241.0 ± 0.9</td>
<td>241.6 ± 2.5</td>
<td>0.52</td>
</tr>
<tr>
<td>TMP (mmHg)</td>
<td>150.2 ± 47.6</td>
<td>162.5 ± 51.2</td>
<td>0.37</td>
</tr>
<tr>
<td>Blood flow (mL/min)</td>
<td>272.8 ± 39.7</td>
<td>256.2 ± 31.8</td>
<td>0.005</td>
</tr>
<tr>
<td>Heparin dose (IU/session)</td>
<td>2,205.6 (1,201.7–2,213.9)</td>
<td>1,899.4 (1,603.3–2,209.5)</td>
<td>0.48</td>
</tr>
<tr>
<td>Dialysate flow (mL/min)</td>
<td>607.0 ± 90.5</td>
<td>589.5 ± 113.3</td>
<td>0.54</td>
</tr>
<tr>
<td>Net ultrafiltration (L/session)</td>
<td>2.3 ± 1.0</td>
<td>2.3 ± 1.1</td>
<td>0.91</td>
</tr>
</tbody>
</table>

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

ARB, angiotensin receptor blocker; B2MG, β2-microglobulin; BP, blood pressure; BUN, blood urea nitrogen; CCB, calcium channel blocker; CCI, Charlson comorbidity index; DBP, diastolic blood pressure; HDF, hemodiafiltration; hs-CRP, high-sensitivity C-reactive protein; KFRT, kidney failure with replacement therapy; PTH, parathyroid hormone; SBP, systolic blood pressure; TMP, transmembrane pressure.
at baseline did not differ between the two groups (75.2% ± 4.9% in the predilution HDF group vs. 76.0% ± 4.8% in the mixed-HDF group). The RR significantly decreased in the predilution HDF group at 6 months, whereas it increased in the mixed-HDF group (p for intergroup difference = 0.01) (Table 3, Fig. 3). Kt/V urea values, used as a traditional index for small-molecule clearance, were similar between the two groups throughout the study period (Table 3, Supplementary Fig. 2B). We also monitored TMP level during dialysis sessions because the mixed-HDF technique involves switching of HDF mode based on TMP level. The mixed-HDF group had consistently higher TMP level compared to the predilution HDF group during the 6-month study period (p for intergroup difference = 0.001) (Table 3, Supplementary Fig. 2C).

During the study period, there were no significant between-group differences in terms of serum hs-CRP, albumin, phosphate, sodium, potassium, and bicarbonate concentrations (Table 3). Out of 53 patients, 47 had available bioimpedance analysis data. As shown in Table 3, the proportions of overhydration status did not differ between the groups.

At baseline, SBP for the predilution HDF and mixed-HDF groups were 147 ± 25.7 and 148.1 ± 22.6 mmHg, respectively. SBP increased at 3 months relative to baseline but then decreased at 6 months relative to the increase observed at 3 months in both groups. The difference observed between the two groups did not reach statistical significance. DBP of both groups remained similar throughout the 6-month study period (Table 3). Most patients tolerated HDF therapy well, and the symptomatic adverse event rate was remarkably low. The most common adverse effect observed was an asymptomatic decrease in SBP by >10 mmHg during a dialysis session, which occurred in 44% of all patients. However, symptomatic intradialytic hypotension was rarely observed in either group (3.7% versus 1.3% in predilution and mixed-HDF, respectively). There were no differences in any other event rates observed between the two groups (Table 4).

**Discussion**

In this randomized controlled study, we demonstrated that mixed-HDF therapy produces outcomes similar to predilution HDF. Convective volume was delivered well in the mixed-HDF group, and the difference in effective convec-

### Table 2. Primary outcome analysis: the differences in convection volume between predilution HDF and mixed-HDF

<table>
<thead>
<tr>
<th>Variable</th>
<th>Treatment</th>
<th>Mean value during 6 mo</th>
<th>Baseline</th>
<th>Month 3</th>
<th>Month 6</th>
<th>Between-group</th>
<th>Within-group</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Convection volume (L/session)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absolute</td>
<td>Predilution</td>
<td>41.0 ± 10.3</td>
<td>40.4 ± 8.0</td>
<td>39.1 ± 8.7</td>
<td>40.3 ± 7.2</td>
<td>0.17</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mixed</td>
<td>35.0 ± 5.7</td>
<td>32.6 ± 7.8</td>
<td>36.3 ± 4.2</td>
<td>36.1 ± 3.7</td>
<td>&lt;0.001</td>
<td>0.01</td>
</tr>
<tr>
<td>Effective</td>
<td>Predilution</td>
<td>41.0 ± 10.3</td>
<td>40.4 ± 8.0</td>
<td>39.1 ± 8.7</td>
<td>40.3 ± 7.2</td>
<td>0.17</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mixed</td>
<td>51.5 ± 9.0</td>
<td>47.9 ± 10.4</td>
<td>53.3 ± 7.6</td>
<td>53.2 ± 7.4</td>
<td>&lt;0.001</td>
<td>0.003</td>
</tr>
<tr>
<td><strong>Substitution volume (L/session)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Via predilution mode</td>
<td>Predilution</td>
<td>38.8 ± 10.5</td>
<td>37.7 ± 8.0</td>
<td>36.8 ± 8.9</td>
<td>41.8 ± 13.4</td>
<td>0.16</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mixed</td>
<td>16.6 ± 4.2</td>
<td>15.6 ± 6.8</td>
<td>17.1 ± 2.3</td>
<td>17.1 ± 2.1</td>
<td>0.44</td>
<td></td>
</tr>
<tr>
<td>Via postdilution mode</td>
<td>Predilution</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mixed</td>
<td>16.3 ± 2.5</td>
<td>14.8 ± 2.6</td>
<td>16.9 ± 2.2</td>
<td>17.1 ± 2.1</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td><strong>Net ultrafiltration (L/session)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Predilution</td>
<td>2.3 ± 1.1</td>
<td>2.3 ± 1.0</td>
<td>2.3 ± 1.1</td>
<td>2.2 ± 1.1</td>
<td>0.72</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mixed</td>
<td>2.2 ± 1.1</td>
<td>2.3 ± 1.1</td>
<td>2.3 ± 1.0</td>
<td>1.9 ± 1.1</td>
<td>0.73</td>
<td>0.06</td>
<td></td>
</tr>
<tr>
<td><strong>Convection volumes adjusted for body surface area (L/m² per session)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absolute</td>
<td>Predilution</td>
<td>24.5 ± 3.8</td>
<td>24.4 ± 5.1</td>
<td>23.1 ± 5.5</td>
<td>25.8 ± 7.8</td>
<td>0.27</td>
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</tr>
<tr>
<td></td>
<td>Mixed</td>
<td>20.6 ± 5.5</td>
<td>18.0 ± 5.1</td>
<td>20.0 ± 4.1</td>
<td>23.8 ± 10.5</td>
<td>0.004</td>
<td>0.004</td>
</tr>
<tr>
<td>Effective</td>
<td>Predilution</td>
<td>24.5 ± 3.8</td>
<td>24.4 ± 5.1</td>
<td>23.1 ± 5.5</td>
<td>25.8 ± 7.8</td>
<td>0.60</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mixed</td>
<td>31.5 ± 5.3</td>
<td>27.5 ± 5.4</td>
<td>32.6 ± 4.6</td>
<td>34.4 ± 11.2</td>
<td>&lt;0.001</td>
<td>0.003</td>
</tr>
</tbody>
</table>

Data are presented as mean ± standard deviation. All analyses were conducted using repeated measures analysis of variance. HDF, hemodiafiltration; NA, not available.
Figure 2. Changes and difference in effective convection volume. (A) Effective convection volume over 6 months (p for intergroup difference < 0.001). (B) Noninferiority of mixed-HDF compared with predilution HDF. The gray line indicates predilution HDF, and the black line indicates mixed-HDF. HDF, hemodiafiltration.

Figure 3. Changes in reduction ratios of B2MG during the study period (p for intergroup difference = 0.01). The yellow line indicates predilution HDF, and the red line indicates mixed-HDF. HDF, hemodiafiltration; B2MG, β2-microglobulin.
<table>
<thead>
<tr>
<th>Variable</th>
<th>Treatment</th>
<th>Observed data</th>
<th>Observed data</th>
<th>Observed data</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Mean value of three time points</td>
<td>Baseline</td>
<td>Month 3</td>
<td>Month 6</td>
</tr>
<tr>
<td>Predialysis B2MG (mg/L)</td>
<td>Predilution</td>
<td>21.2 ± 4.8</td>
<td>21.5 ± 3.5</td>
<td>21.2 ± 6.3</td>
<td>20.9 ± 4.5</td>
</tr>
<tr>
<td></td>
<td>Mixed</td>
<td>23.6 ± 4.7</td>
<td>25.4 ± 5.6</td>
<td>23.3 ± 3.6</td>
<td>22.2 ± 4.4</td>
</tr>
<tr>
<td>Reduction ratio of B2MG (%)</td>
<td>Predilution</td>
<td>73.9 ± 6.6</td>
<td>75.2 ± 4.9</td>
<td>NA</td>
<td>78.4 ± 7.9</td>
</tr>
<tr>
<td></td>
<td>Mixed</td>
<td>76.5 ± 5.9</td>
<td>76.0 ± 4.8</td>
<td>NA</td>
<td>78.7 ± 5.1</td>
</tr>
<tr>
<td>Kt/V urea</td>
<td>Predilution</td>
<td>1.53 ± 0.2</td>
<td>1.53 ± 0.3</td>
<td>1.49 ± 0.2</td>
<td>1.57 ± 0.2</td>
</tr>
<tr>
<td></td>
<td>Mixed</td>
<td>1.56 ± 0.3</td>
<td>1.51 ± 0.3</td>
<td>1.59 ± 0.25</td>
<td>1.57 ± 0.3</td>
</tr>
<tr>
<td>TMP (mmHg)</td>
<td>Predilution</td>
<td>139.6 ± 42.0</td>
<td>150.2 ± 47.6</td>
<td>135.7 ± 36.9</td>
<td>132.9 ± 40.3</td>
</tr>
<tr>
<td></td>
<td>Mixed</td>
<td>176.2 ± 51.9</td>
<td>162.5 ± 51.2</td>
<td>192.7 ± 42.4</td>
<td>173.1 ± 59.1</td>
</tr>
<tr>
<td>hs-CRP (mg/dL)</td>
<td>Predilution</td>
<td>0.6 (0.1–1.7)</td>
<td>0.7 (0.1–1.4)</td>
<td>0.6 (0.2–2.2)</td>
<td>0.6 (0.1–3.3)</td>
</tr>
<tr>
<td></td>
<td>Mixed</td>
<td>0.9 (0.3–2.0)</td>
<td>0.8 (0.2–1.5)</td>
<td>1.1 (0.3–2.0)</td>
<td>0.9 (0.3–3.5)</td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>Predilution</td>
<td>3.9 ± 0.3</td>
<td>3.9 ± 0.3</td>
<td>4.0 ± 0.4</td>
<td>3.9 ± 0.3</td>
</tr>
<tr>
<td></td>
<td>Mixed</td>
<td>3.8 ± 0.4</td>
<td>3.9 ± 0.3</td>
<td>3.8 ± 0.4</td>
<td>3.8 ± 0.4</td>
</tr>
<tr>
<td>Phosphate (mg/dL)</td>
<td>Predilution</td>
<td>5.1 ± 1.7</td>
<td>5.4 ± 1.8</td>
<td>5.0 ± 1.4</td>
<td>4.8 ± 1.7</td>
</tr>
<tr>
<td></td>
<td>Mixed</td>
<td>5.0 ± 1.4</td>
<td>5.2 ± 1.3</td>
<td>4.9 ± 1.5</td>
<td>4.8 ± 1.3</td>
</tr>
<tr>
<td>Sodium (mmol/L)</td>
<td>Predilution</td>
<td>137.7 ± 4.2</td>
<td>137.7 ± 2.9</td>
<td>138.3 ± 3.1</td>
<td>137.2 ± 6.0</td>
</tr>
<tr>
<td></td>
<td>Mixed</td>
<td>137.3 ± 3.5</td>
<td>137.9 ± 4.3</td>
<td>136.7 ± 3.3</td>
<td>137.3 ± 2.7</td>
</tr>
<tr>
<td>Potassium (mmol/L)</td>
<td>Predilution</td>
<td>5.0 ± 0.8</td>
<td>5.1 ± 0.7</td>
<td>5.0 ± 0.8</td>
<td>4.9 ± 0.8</td>
</tr>
<tr>
<td></td>
<td>Mixed</td>
<td>5.0 ± 0.7</td>
<td>4.9 ± 0.7</td>
<td>4.9 ± 0.8</td>
<td>5.2 ± 0.6</td>
</tr>
<tr>
<td>Bicarbonate (mmol/L)</td>
<td>Predilution</td>
<td>23.4 ± 4.0</td>
<td>23.6 ± 4.6</td>
<td>23.4 ± 3.5</td>
<td>23.3 ± 3.9</td>
</tr>
<tr>
<td></td>
<td>Mixed</td>
<td>23.4 ± 3.0</td>
<td>23.8 ± 2.6</td>
<td>23.4 ± 3.7</td>
<td>22.9 ± 2.8</td>
</tr>
<tr>
<td>Bioimpedance parameter</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OH (L)</td>
<td>Predilution</td>
<td>0.8 (–0.9 to 1.2)</td>
<td>NA</td>
<td>1.0 (–0.3 to 2.7)</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td></td>
<td>Mixed</td>
<td>0.3 (–0.2 to 1.23)</td>
<td>NA</td>
<td>0.7 (–0.6 to 2.9)</td>
<td>0.32</td>
</tr>
<tr>
<td>OH-ECW (%)</td>
<td>Predilution</td>
<td>4.5 (–5.6 to 9.1)</td>
<td>NA</td>
<td>7.1 (–1.9 to 14.6)</td>
<td>0.98</td>
</tr>
<tr>
<td></td>
<td>Mixed</td>
<td>2.7 (–1.2 to 8.0)</td>
<td>NA</td>
<td>4.1 (–4.5 to 18.2)</td>
<td>0.33</td>
</tr>
<tr>
<td>Predialysis blood pressure (mmHg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP</td>
<td>Predilution</td>
<td>147.0 ± 25.7</td>
<td>155.8 ± 25.5</td>
<td>149.2 ± 26.0</td>
<td>149.2 ± 26.0</td>
</tr>
<tr>
<td></td>
<td>Mixed</td>
<td>148.1 ± 22.6</td>
<td>156.1 ± 24.7</td>
<td>153.9 ± 28.8</td>
<td>153.9 ± 28.8</td>
</tr>
<tr>
<td>DBP</td>
<td>Predilution</td>
<td>73.5 ± 17.2</td>
<td>74.0 ± 14.6</td>
<td>73.9 ± 18.6</td>
<td>73.9 ± 18.6</td>
</tr>
<tr>
<td></td>
<td>Mixed</td>
<td>72.8 ± 13.9</td>
<td>74.9 ± 15.9</td>
<td>74.1 ± 13.4</td>
<td>74.1 ± 13.4</td>
</tr>
</tbody>
</table>

Data are presented as mean ± standard deviation or median (interquartile range). B2MG, β2-microglobulin; DBP, diastolic blood pressure; hs-CRP, high-sensitive C-reactive protein; NA, not available; OH-ECW, overhydration/extracellular water; OH, overhydration; SBP, systolic blood pressure; TMP, transmembrane pressure. All analyses were conducted using repeated measures analysis of variance.

pared with conventional HD when an optimal convective substitution fluid was used [21–25]. Such proven benefits have resulted in the increased utilization of HDF in European countries [26]. There have been remarkable advances in HDF techniques, and several HDF methods have been implemented in clinical practice, including predilution, postdilution, and mixed modes. Most trials to date have tested the effects of postdilution HDF, and studies on other HDF modes are lacking. Interestingly, in East Asian countries, predilution HDF with a low access blood flow rate has been widely used [8]. A recently published observational study in Japan, where predilution HDF is preferred in most centers, suggested that this HDF mode was significantly associated with improved overall and cardiovascular survival compared with conventional HD [27]. Both pre- and postdilution HDF modes have pros and cons. Although the postdilution HDF mode, which is being recommended to most patients in Western countries, is associated with a highly efficient clearance of uremic toxins with a relatively small substitution volume, the limitation of
the method is that blood flow should be maintained at a certain speed to reduce risk of blood clot formation. Patients in East Asian countries, who have relatively low blood flow of arteriovenous access, prefer predilution HDF mode to postdilution HDF, due to lower risk of clotting events in the former mode [6]. Recently, a new mode called mixed-HDF was developed to address the drawbacks of pre- and postdilution HDF. Mixed-HDF monitors optimal TMP and automatically switches to pre- or postdilution mode when the TMP level reaches a particular threshold, before a clotting issue occurs [15,28]. This process can compensate for the weaknesses of each HDF mode. Although few studies have compared the efficacy of mixed-HDF versus other HDF modes, Pedrini and De Cristofaro [2] reported that mixed-HDF had a better β2-microglobulin removal rate than postdilution HDF. In addition, de Sequera et al. [29] showed that mixed-HDF was comparable to postdilution HDF with regard to small and medium-sized and protein-bound molecule clearance.

Delivered convective volume is considered a crucial factor that influences HDF therapy. Mixed-HDF is a new concept of high-efficiency HDF in which predilution and postdilution modes are mixed, and it is difficult to compare quantitatively absolute substitution fluid with those of the predilution mode. Given that a greater volume of substitution fluid is required in predilution mode versus postdilution HDF mode, we hypothesized that the effective convection volume via mixed-HDF mode consisted of a sum of the substitution volume in postdilution mode times two, substitution volume in predilution mode, and ultrafiltration volume. Although the absolute convection volume was higher in predilution HDF, we showed that the effective convection volume delivered by mixed-HDF was greater than that of predilution HDF. The effective convection volume from mixed-HDF was approximately 20% higher than that of predilution HDF. The optimal convection volume delivered by mixed-HDF remains unknown because no studies have yet examined mixed-HDF outcomes such as mortality or cardiovascular events based on convection volume. In this regard, the concept of effective convection volume might be an alternative tool for the comparison of convection volumes for predilution and mixed-HDF. Notably, differences in effective convection volume might result in improved β2-microglobulin clearance by mixed-HDF. This is important because the accumulation of middle molecules, such as β2-microglobulin, is an independent predictor of mortality [30–32], and β2-microglobulin clearance correlates well with convection volume [33]. In addition, dialysis tolerance of patients was similar for the two HDF modes. All adverse events were minor, and the event rates of both groups were similar. Taken together, these findings suggest that mixed-HDF can be an alternative dialysis tool for patients who frequently experience dialysis-related symptoms such as intradialysis hypotension, muscle cramping, and arrhythmia [25].

This study has limitations. First, the sample size was small,

<table>
<thead>
<tr>
<th>Variable</th>
<th>Predilution HDF (n = 81)</th>
<th>Mixed-HDF (n = 78)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of adverse events</td>
<td>42 (51.9)</td>
<td>40 (51.3)</td>
<td>0.94</td>
</tr>
<tr>
<td>At least one event</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A decrease in SBP &gt;10 mmHg without symptoms</td>
<td>36 (44.4)</td>
<td>34 (43.6)</td>
<td>0.73</td>
</tr>
<tr>
<td>Symptomatic intradialytic hypotension*</td>
<td>3 (3.7)</td>
<td>1 (1.3)</td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>1 (1.2)</td>
<td>2 (2.6)</td>
<td></td>
</tr>
<tr>
<td>Muscle cramps</td>
<td>2 (2.5)</td>
<td>1 (1.3)</td>
<td></td>
</tr>
<tr>
<td>Nausea, vomiting</td>
<td>0</td>
<td>1 (1.3)</td>
<td></td>
</tr>
<tr>
<td>Fever</td>
<td>0</td>
<td>1 (1.3)</td>
<td></td>
</tr>
<tr>
<td>Chest pain</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arrhythmia</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Data are presented as number (%). The percentages were calculated with number of adverse events per dialysis sessions during study period. HDF, hemodiafiltration; SBP, systolic blood pressure.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>*Symptomatic intradialytic hypotension is defined as a decrease in SBP by ≥20 mmHg associated with symptoms that include abdominal discomfort, yawning, sighing, nausea, vomiting, muscle cramps, restlessness, dizziness or fainting, and anxiety.</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 4. Adverse event rates

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and only two centers participated. Therefore, selection bias could not be excluded. Second, we could not determine optimal convection volume. It should be noted that many previous trials with postdilution HDF consistently showed improved patient survival rate compared with conventional HD in patients with adequately delivered convection volume. To date, there has been no randomized controlled trial that has assessed the delivered convection volume in patients given predilution HDF or mixed-HDF therapy. Future studies with larger sample sizes will be needed to address this. Third, we measured β2-microglobulin and hs-CRP levels as representative middle molecule and inflammatory markers, although other uremic toxins with deleterious effects exist. Because the predilution mode has an intrinsic limitation in the degree of clearance compared with postdilution HDF, the performance of mixed-HDF should be further tested using other molecules. Fourth, we used a simple equation of RR of β2-microglobulin, which was not calibrated for body fluid reduction during dialysis. However, as there was no significant difference in ultrafiltration volume between the predilution and mixed-HDF groups, ultrafiltration volume is unlikely to alter the outcomes. Finally, we did not evaluate albumin loss via dialyzer during the study. Albumin loss via HDF can differ depending on the dialyzer, dialysis modalities, and convection volumes. Previous studies have reported a wide range of albumin loss between 0.5 and 4.5 g per session in postdilution HDF [34–36]. The amount of albumin loss in mixed-HDF is not well known. Although albumin loss is less severe in predilution HDF than in postdilution HDF, albumin loss via HDF can be especially important for patients with marked hypoalbuminemia. However, in this study, the two groups used the same dialyzer that has a very low albumin-sieving coefficient according to the manufacturer. Moreover, serum albumin levels were comparable between the two groups. Thus, albumin loss was unlikely to affect the study results.

In conclusion, we demonstrated that mixed-HDF performed well with regard to convective volume delivery and provided better middle molecule clearance than predilution HDF. For the implementation of mixed-HDF in clinical practice, further studies should explore whether the use of mixed-HDF is advantageous over other dialysis modes with regard to its cost-effectiveness and long-term outcomes.

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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Authors’ contributions
Conceptualization: SHH
Data collection and curation: All authors
Formal analysis: KSP
Funding acquisition: SHH
Investigation: KSP, WJ
Writing - original draft: KSP
Writing - review & editing: SHH
All authors read and approved the final manuscript.

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Effect of Phoxilium on prognostic predictors in patients undergoing continuous venovenous hemodiafiltration

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Background: Phosphorus-containing dialysis solution is used to prevent hypophosphatemia in patients undergoing continuous venovenous hemodiafiltration (CVVHDF). This study evaluated the effect of phosphorus-containing dialysis solution on mortality in patients undergoing CVVHDF based on changes in phosphorus and red cell distribution width-coefficient of variation (RDW-CV) levels.

Methods: We included 272 patients with acute kidney injury (AKI) who underwent CVVHDF at the medical intensive care unit from 2017 to 2019 and classified them according to Phoxilium (Baxter Healthcare Ltd.), as a phosphorus-containing dialysis solution, use within 48 hours after CVVHDF initiation. Clinical data were collected at baseline and 48 hours after CVVHDF initiation. The primary outcome was all-cause mortality during the follow-up period.

Results: The non-Phoxilium (NP) group had higher phosphorus and lower RDW-CV levels than the Phoxilium (P) group (phosphorus, 7.3 ± 4.3 vs. 5.0 ± 2.8 mg/dL; RDW-CV, 14.6 ± 1.9 vs. 15.7 ± 2.6%; all p < 0.001). In the multivariable Cox proportional hazard regression of the NP group, an increase in phosphorus and RDW-CV at 48 hours of CVVHDF was associated with mortality (delta phosphorus: median, >0 mg/dL vs. <–2.0 mg/dL; hazard ratio [HR], 8.62; 95% confidence interval [CI], 2.10–35.32; p = 0.003/delta RDW-CV: median, >0% vs. <–0.2%; HR, 4.34; 95% CI, 1.49–13.18; p = 0.008). Meanwhile, in the P group, an increase in delta RDW-CV was associated with mortality (delta RDW-CV: >0% vs. >–0.2% and <0%; HR, 2.65; 95% CI, 1.12–6.24; p = 0.03), while an increase in delta phosphorus was not.

Conclusion: In patients with AKI undergoing CVVHDF, the risk factors for all-cause mortality differed according to the initial phosphorus levels and use of Phoxilium.

Keywords: Continuous renal replacement therapy, Continuous venovenous hemodiafiltration, Phoxilium, Phosphorus, Red cell distribution width
Electrolyte imbalances, including that of phosphorus, frequently occur during continuous renal replacement therapy (CRRT) in critically ill patients with acute kidney injury (AKI) [1]. Hypophosphatemia is reported in 11% to 65% of patients undergoing CRRT [2]. Severe hypophosphatemia can cause respiratory muscle weakness and decreased cardiac output [2–4]. Hypophosphatemia occurs when phosphorus is removed via CRRT and the intake of phosphorus is reduced. The removal of 57 mmol of phosphorus was observed during a single session of continuous venovenous hemodialysis [5]. Several studies have been conducted to treat hypophosphatemia by replacing phosphorus with dialysate and replacement solutions [6–8]. Thus, Phoxilium (Baxter Healthcare Ltd., Norfolk, UK), a commercially available phosphorus-containing dialysis solution, is now used in patients who require phosphorus supplementation during CRRT.

At present, several prognostic markers for patients on CRRT have been described based on cross-sectional and retrospective studies [4,9,10]. Among these, hyperphosphatemia and high red cell distribution width-coefficient of variation (RDW-CV) are predictors of all-cause mortality [4,9]. RDW-CV, expressed as the standard deviation of erythrocyte size divided by the mean corpuscular volume, is a measure of the variation in the red blood cell volumes. In elderly patients with septic shock and an RDW-CV level >15%, the continuous increase in RDW-CV is a more useful marker for predicting hospital death than the level of RDW-CV itself [11]. In previous studies assessing red cell properties and phosphorus homeostasis, a correlation was observed between CRRT-induced phosphorus depletion and the reduction of RBC 2,3-diphosphoglycerate concentration [2,12–14].

Phoxilium contains phosphorus but less bicarbonate than Hemosol-B0 (Baxter Healthcare Ltd.). In a previous study, after 36 to 42 hours of CRRT, Phoxilium increased serum phosphorus level, while Hemosol-B0 decreased phosphorus level. Additionally, Phoxilium decreased serum bicarbonate level further than Hemosol-B0 [15]. Thus, dialysates and replacement fluids with phosphorus may affect the prognosis of CRRT patients. However, the effect of Phoxilium on prognostic predictors in AKI patients undergoing CRRT has rarely been addressed. Therefore, we aimed to evaluate the effect of Phoxilium use on prognostic predictors for all-cause mortality in AKI patients undergoing CRRT in an intensive care unit (ICU) in Korea.

Methods

Study design and subjects

This was a retrospective single-center study. Data from the medical records of 1,213 patients who underwent CRRT from January 2017 to December 2019 in the ICU of a single-center, university-affiliated hospital were reviewed (Fig. 1). All patients were older than 18 years. The exclusion criteria were as follows: non-internal medicine ICU, history of end-stage kidney disease requiring maintenance dialysis, active malignancies, use of Phoxilium 48 hours after CRRT initiation, and insufficient data. Among the 1,213 patients, only 272 were included in the analysis after applying the exclusion criteria. Patients were categorized into two groups according to the use of Phoxilium within 48 hours after CRRT initiation: the non-Phoxilium group (NP group, n = 96) and the Phoxilium group using Phoxilium as a dialysate or replacement solution or both (P group, n = 176). The composition of the CRRT fluid is described in Supplementary Table 1 (available online). Phoxilium is the only phosphorus-containing solution among all dialysates and contains 4 mmol/L potassium. Hemosol-B0 contained neither phosphorus nor potassium. PrismaSol 2 and PrismaSol 4 (Baxter Healthcare Ltd.) contained 2 and 4 mmol/L potassium, respectively. Phoxilium contains less bicarbonate and calcium than Hemosol-B0 or PrismaSol 2 and PrismaSol 4. The dialysate and replacement solutions were selected based on serum phosphorus and potassium levels according to our hospital protocol (Supplementary Table 2, available online).

The study was approved by the Institutional Review Board of Pusan National University Hospital (No. 2005-005-090), which waived the requirement for informed patient consent because of the retrospective design of the study. All clinical investigations were conducted in accordance with the principles of the Declaration of Helsinki.

Clinical data collection and laboratory measurements

The demographic and clinical data including age, sex, body mass index (BMI), causes of AKI, and comorbidities at the time of CRRT initiation were reviewed. Laboratory tests were performed in all patients at the time of CRRT initiation and
48 hours after CRRT initiation. The levels of white blood cells, hemoglobin, RDW-CV, albumin, potassium, bicarbonate, serum blood urea nitrogen, creatinine, phosphorus, calcium, and C-reactive protein (CRP) were measured. The Sequential Organ Failure Assessment (SOFA) score and Acute Physiology and Chronic Health Evaluation II (APACHE II) scores were calculated to assess the severity of the disease [16]. Hyperphosphatemia was defined as a phosphorus level higher than 4.5 mg/dL and hypophosphatemia as a phosphorus level lower than 2.0 mg/dL.

**CRRT protocol**

Among critically ill patients with AKI, patients who had sustained oliguria, uncontrolled volume overload, intractable hyperkalemia, severe metabolic acidosis, or other conditions, including uremic encephalopathy, were subjected to CRRT according to the discretion of their physicians. All patients received continuous venovenous hemodiafiltration (CVVHDF) through the internal jugular or femoral vein. The Prismaflex (Gambro Lundia AB, Lund, Sweden) CRRT machine and AN 69 ST 100 filter set (1.0 m², Gambro Lundia AB) were used. The initial effluent flow rates were 30 to 35 mL/kg/hr, and additional adjustments were made according to the catabolic state or the presence of hyperkalemia and metabolic acidosis. The actual delivered dose was calculated as the mean value of the effluent volume divided by the weight of the patient during the entire CRRT period. Down time was calculated by adding all the time (hours) for which the CRRT was interrupted during the entire CRRT period. The patients’ body weights were measured consecutively during the CRRT period. The blood flow rate was started at 150 mL/min and adjusted according to patients’ metabolic demands and hemodynamic instabilities. Heparin-free, heparin, or nafamostat mesylate were selected to maintain patency of the extracorporeal circuit while minimizing patient complications according to the bleeding risks of the patients.
Outcomes

Patients were followed until February 2020. The primary outcome of the study was all-cause mortality during the follow-up period.

Statistical analysis

Continuous variables were expressed as the mean ± standard deviation or median (interquartile range), while categorical variables were expressed as number (percentage). Comparisons between the two groups were performed using Student t test or the Mann-Whitney U test for continuous variables and the chi-square test for categorical variables. Cumulative patient survival curves were derived using the Kaplan-Meier method, and the differences between the curves were analyzed using the log-rank test. The Cox proportional hazards model was used to determine the hazard ratio (HR) of variables related to mortality in the univariable and multivariable analyses. Variables were selected for multivariate analysis according to the study’s interest and were serially adjusted. The results are reported as HR and 95% confidence interval (CI). We applied the same univariable and multivariable Cox proportional hazard regression analyses to variables at 0 and 48 hours of CRRT in the NP and P groups. Variables in the multivariable Cox regression analysis were sequentially entered into three models. Model 1 was unadjusted. Model 2 was adjusted for age, sex, BMI, phosphorus level, and RDW-CV. In model 3, the SOFA score as well as bicarbonate and albumin levels were added to the covariates in model 2. We also categorized patients into three groups according to the changes in phosphorus and RDW-CV levels over a 48-hour period after CRRT initiation: delta phosphorus = phosphorus measured at 48 hours (referred to as phosphorus_48hr) – phosphorus measured at 0 hr (referred to as phosphorus_0hr) and delta RDW-CV = RDW-CV at 48 hours (referred to as RDW-CV_48hr) – RDW-CV at 0 hr (referred to as RDW-CV_0hr). Delta phosphorus groups were categorized as increased (delta phosphorus > 0), stable (delta phosphorus between median and 0), and decreased (delta phosphorus < median). Similarly, delta RDW-CV groups were categorized as increased (delta RDW-CV > 0), stable (delta RDW-CV between median and 0), and decreased (delta RDW-CV < median). We divided the stable and decreased phosphorus and RDW-CV groups using the median values of the changes at -2.0 mg/dL and −0.2%, respectively. Then, we performed univariable and multivariable Cox proportional hazard regression analysis adjusting for the age, sex, BMI, SOFA score, bicarbonate level, and albumin level at 0 hour. All probabilities were two-tailed, and the level of statistical significance was defined as p < 0.05. All statistical analyses were performed using IBM SPSS version 20.0 (IBM Corp., Armonk, NY, USA).

Results

Baseline clinical characteristics of patients

The baseline clinical characteristics according to Phoxilium use are presented in Table 1. The mean age of patients was

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All</th>
<th>Phoxilium (–)</th>
<th>Phoxilium (+)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>272</td>
<td>96</td>
<td>176</td>
<td></td>
</tr>
<tr>
<td>Age (yr)</td>
<td>67.0 ± 13.6</td>
<td>67.4 ± 12.2</td>
<td>66.7 ± 14.3</td>
<td>0.67</td>
</tr>
<tr>
<td>Male sex</td>
<td>161 (59.2)</td>
<td>62 (64.6)</td>
<td>99 (56.3)</td>
<td>0.18</td>
</tr>
<tr>
<td>Underlying comorbidity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>157 (57.7)</td>
<td>62 (64.6)</td>
<td>95 (54.0)</td>
<td>0.09</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>141 (51.8)</td>
<td>53 (55.2)</td>
<td>88 (50.0)</td>
<td>0.41</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>138 (50.7)</td>
<td>54 (56.3)</td>
<td>84 (47.7)</td>
<td>0.18</td>
</tr>
<tr>
<td>Liver disease</td>
<td>39 (14.3)</td>
<td>11 (11.5)</td>
<td>28 (15.9)</td>
<td>0.32</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>23.3 ± 4.3</td>
<td>23.0 ± 4.2</td>
<td>23.5 ± 4.4</td>
<td>0.36</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>113.4 ± 24.5</td>
<td>111.9 ± 18.9</td>
<td>114.2 ± 27.1</td>
<td>0.42</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>65.5 ± 15.1</td>
<td>66.7 ± 12.9</td>
<td>64.9 ± 16.2</td>
<td>0.33</td>
</tr>
</tbody>
</table>

(Continued to the next page)
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All</th>
<th>Phoxilium (–)</th>
<th>Phoxilium (+)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean arterial pressure (mmHg)</td>
<td>81.6 ± 16.1</td>
<td>81.8 ± 13.3</td>
<td>81.6 ± 17.5</td>
<td>0.92</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>97.1 ± 25.5</td>
<td>93.4 ± 24.9</td>
<td>99.2 ± 25.7</td>
<td>0.08</td>
</tr>
<tr>
<td>ICU risk factor</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ventilator use</td>
<td>122 (44.9)</td>
<td>43 (44.8)</td>
<td>79 (44.9)</td>
<td>0.99</td>
</tr>
<tr>
<td>Vasopressor use</td>
<td>166 (61.0)</td>
<td>62 (64.6)</td>
<td>104 (59.1)</td>
<td>0.34</td>
</tr>
<tr>
<td>SOFA_Ohr</td>
<td>9.2 ± 3.2</td>
<td>8.7 ± 3.4</td>
<td>9.4 ± 3.1</td>
<td>0.08</td>
</tr>
<tr>
<td>APACHE II score</td>
<td>22.6 ± 6.3</td>
<td>22.9 ± 7.0</td>
<td>22.4 ± 6.0</td>
<td>0.54</td>
</tr>
<tr>
<td>6-Hr urine output before CRRT (mL)</td>
<td>125.0 (37.5–310.0)</td>
<td>110.0 (20.0–300.0)</td>
<td>130.0 (50.0–342.5)</td>
<td>0.24</td>
</tr>
<tr>
<td>CRRT indication (overlapped)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sustained oliguria</td>
<td>187 (68.8)</td>
<td>58 (60.4)</td>
<td>129 (73.3)</td>
<td>0.03</td>
</tr>
<tr>
<td>Uncontrolled volume overload</td>
<td>76 (27.9)</td>
<td>22 (22.9)</td>
<td>54 (30.7)</td>
<td>0.17</td>
</tr>
<tr>
<td>Intractable hyperkalemia</td>
<td>38 (14.0)</td>
<td>26 (27.1)</td>
<td>12 (6.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Severe metabolic acidosis</td>
<td>124 (45.6)</td>
<td>41 (42.7)</td>
<td>83 (47.2)</td>
<td>0.48</td>
</tr>
<tr>
<td>Others</td>
<td>10 (3.7)</td>
<td>7 (7.3)</td>
<td>3 (1.7)</td>
<td>0.02</td>
</tr>
<tr>
<td>Causes of AKI</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Septic</td>
<td>103 (37.9)</td>
<td>24 (25.0)</td>
<td>79 (44.9)</td>
<td>0.001</td>
</tr>
<tr>
<td>Cardiogenic</td>
<td>76 (27.9)</td>
<td>30 (31.3)</td>
<td>46 (26.1)</td>
<td>0.40</td>
</tr>
<tr>
<td>Nephrotoxic</td>
<td>10 (3.7)</td>
<td>6 (6.3)</td>
<td>4 (2.3)</td>
<td>0.10</td>
</tr>
<tr>
<td>Postoperative</td>
<td>5 (1.8)</td>
<td>2 (2.1)</td>
<td>3 (1.7)</td>
<td>0.82</td>
</tr>
<tr>
<td>Others</td>
<td>78 (28.7)</td>
<td>34 (35.4)</td>
<td>44 (25.0)</td>
<td>0.07</td>
</tr>
<tr>
<td>CRRT duration (hr)</td>
<td>51.0 (23.8–94.0)</td>
<td>22.0 (14.0–42.8)</td>
<td>70.0 (36.0–122.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Down time (hr)</td>
<td>2.0 (0.0–4.0)</td>
<td>0.0 (0.0–2.0)</td>
<td>3.0 (1.0–7.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Prescribed dose (mL/kg/hr)</td>
<td>38.9 ± 5.6</td>
<td>40.2 ± 6.6</td>
<td>38.1 ± 4.8</td>
<td>0.007</td>
</tr>
<tr>
<td>Delivered CRRT dose (mL/kg/hr)</td>
<td>34.9 ± 6.1</td>
<td>35.5 ± 7.8</td>
<td>34.5 ± 5.0</td>
<td>0.29</td>
</tr>
<tr>
<td>White blood cell (10^3/μL)</td>
<td>15.0 ± 11.1</td>
<td>14.7 ± 9.0</td>
<td>15.2 ± 12.0</td>
<td>0.72</td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>10.6 ± 2.9</td>
<td>11.1 ± 3.6</td>
<td>10.3 ± 2.4</td>
<td>0.07</td>
</tr>
<tr>
<td>RDW-CV (%)</td>
<td>15.3 ± 2.4</td>
<td>14.6 ±1.9</td>
<td>15.7 ± 2.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hemoglobin/RDW-CV</td>
<td>0.7 ± 0.2</td>
<td>0.8 ± 0.3</td>
<td>0.7 ± 0.2</td>
<td>0.005</td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>3.2 ± 0.8</td>
<td>3.5 ±0.9</td>
<td>3.1 ± 0.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Potassium (mmol/L)</td>
<td>4.7 ± 1.2</td>
<td>5.0 ± 1.5</td>
<td>4.5 ± 1.0</td>
<td>0.001</td>
</tr>
<tr>
<td>Arterial pH</td>
<td>7.31 ± 0.13</td>
<td>7.29 ± 0.13</td>
<td>7.32 ± 0.12</td>
<td>0.08</td>
</tr>
<tr>
<td>Bicarbonate_(mEq/L)</td>
<td>16.5 ± 6.3</td>
<td>16.2 ± 6.6</td>
<td>16.7 ± 6.1</td>
<td>0.57</td>
</tr>
<tr>
<td>BUN (mg/dL)</td>
<td>60.8 ± 37.9</td>
<td>63.2 ± 39.6</td>
<td>59.5 ± 37.0</td>
<td>0.44</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>3.6 ± 3.1</td>
<td>4.3 ± 4.3</td>
<td>3.3 ±2.0</td>
<td>0.03</td>
</tr>
<tr>
<td>Phosphorus (mg/dL)</td>
<td>5.8 ± 3.6</td>
<td>7.3 ± 4.3</td>
<td>5.0 ± 2.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Calcium (mg/dL)^a</td>
<td>8.7 ± 0.8</td>
<td>8.6 ± 0.9</td>
<td>8.8 ± 0.8</td>
<td>0.07</td>
</tr>
<tr>
<td>CRP (mg/L)</td>
<td>5.8 (1.9–13.3)</td>
<td>3.0 (0.9–8.1)</td>
<td>7.3 (2.8–16.1)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

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

Phoxilium (–): The group of patients who did not receive Phoxilium (Baxter Healthcare Ltd., Norfolk, UK) within 48 hours after CRRT initiation. Phoxilium (+): The group of patients who received Phoxilium within 48 hours after CRRT initiation. Down time: duration of unplanned interruption of CRRT therapy during which patients could not receive dialysis.

RAI, acute kidney injury; APACHE II, Acute Physiology And Chronic Health Evaluation II; BUN, blood urea nitrogen; CRP, C-reactive protein; CRRT: continuous renal replacement therapy; ICU, intensive care unit; RDW-CV, red cell distribution width-coefficient of variation; SOFA, Sequential Organ Failure Assessment.

*Corrected calcium (mg/dL) = measured total calcium (mg/dL) + 0.8 × [4 - measured serum albumin (g/dL)].

67.0 ± 13.6 years, and 161 patients (59.2%) were males. The mean arterial pressure was 81.6 ± 16.1 mmHg. A total of 122 patients (44.9%) received mechanical ventilation. The mean SOFA score and APACHE II score were 9.2 ± 3.2 and 22.6
± 6.3, respectively. Urine output for 6 hours before CRRT initiation was 125.0 mL (37.5–310.0 mL). The delivered CRRT dose was 34.9 ± 6.1 mL/kg/hr. Comparing the NP and P groups, no significant differences were observed in the baseline characteristics of age, sex, BMI, SOFA_0hr score, or bicarbonate_0hr (all p > 0.05). In the P group, CRRT duration and down time were longer, RDW-CV_0hr and CRP_0hr were higher, and albumin_0hr and phosphorus_0hr were lower than in the NP group (all p < 0.001). Sepsis was the most common cause of AKI in P group, whereas other causes, including hypovolemic shock and hepatorenal syndrome, were most common in the NP group.

Clinical characteristics at 48 hours after continuous renal replacement therapy initiation according to Phoxilium use

Clinical characteristics at 48 hours after CRRT initiation according to Phoxilium use are presented in Supplementary Table 3 (available online). The SOFA_48hr score was higher (p = 0.001) and bicarbonate_48hr was lower (p = 0.03) in the P group than in the NP group. RDW-CV_48hr was higher in the P group (p = 0.005). Phosphorus_48hr decreased to 3.6 ± 2.0 mg/dL in the NP group and to 3.1 ± 1.1 mg/dL in the P group. Hyperphosphatemia was found in 10 patients in the NP group (10.4%) and 21 patients in the P group (11.9%) at 48 hours after CRRT initiation.

All-cause mortality according to baseline clinical parameters

The mean follow-up duration was 15.0 days (7.0–25.8 days) in the NP group vs. 24.0 days (14.0–38.0 days) in the P group. During the follow-up period, 94 patients (34.1%) died, including 26 (27.1%) from the NP group and 68 (38.6%) from the P group (Supplementary Table 4, available online). The Cox regression analysis results for all-cause mortality according to the baseline clinical parameters are presented in Table 2. The use of Phoxilium within 48 hours after CRRT initiation was not a risk factor for all-cause mortality (p = 0.76). In addition, the additional analysis of Kaplan-Meier curves between the groups of patients using Phoxilium as dialysate solutions (n = 45), replacement solutions (n = 91), and both (n = 40) showed that time to death was not different (log-rank p = 0.73). In the NP group, SOFA_0hr (HR, 1.38; 95% CI, 1.20–1.59; p < 0.001), bicarbonate_0hr (HR, 1.08; 95% CI, 1.02–1.15; p = 0.007), and albumin_0hr (HR, 0.50; 95% CI, 0.29–0.86; p = 0.01) were associated with increased all-cause mortality in model 1. RDW-CV_0hr was not a significant risk factor for all-cause mortality. In the fully adjusted model 3, higher SOFA_0hr (HR, 1.38; 95% CI, 1.16–1.64; p < 0.001) and higher bicarbonate_0hr (HR, 1.08; 95% CI, 1.00–1.17; p = 0.05) were still significantly associated with increased all-cause mortality.

In the P group, RDW-CV_0hr (HR, 1.16; 95% CI, 1.06–1.26; p = 0.001), SOFA_0hr (HR, 1.13; 95% CI, 1.05–1.22; p = 0.001), bicarbonate_0hr (HR, 1.04; 95% CI, 1.00–1.08; p = 0.05), and albumin_0hr (HR, 0.52; 95% CI, 0.33–0.81; p = 0.004) were associated with increased all-cause mortality in model 1. Phosphorus_0hr was not a significant risk factor for all-cause mortality. In the fully adjusted model 3, higher SOFA_0hr (HR, 1.14; 95% CI, 1.04–1.26; p = 0.005), higher bicarbonate_0hr (HR, 1.05; 95% CI, 1.01–1.09; p = 0.03), and lower albumin_0hr (HR, 0.51; 95% CI, 0.29–0.89; p = 0.02) were significant risk factors for all-cause mortality, but RDW-CV_0hr was not.

All-cause mortality according to clinical parameters at 48 hours after continuous renal replacement therapy initiation

The Cox regression analysis results for all-cause mortality according to the clinical parameters at 48 hours are presented in Table 3. In the NP group, SOFA_48hr (HR, 1.31; 95% CI, 1.12–1.53; p = 0.001) was the only risk factor for all-cause mortality in the fully adjusted model 3. In the P group, higher RDW-CV_48hr (HR, 1.15; 95% CI, 1.04–1.28; p = 0.008), phosphorus_48hr (HR, 1.41; 95% CI, 1.09–1.82; p = 0.009), and SOFA_48hr (HR, 1.11; 95% CI, 1.03–1.20; p = 0.009) and lower bicarbonate_48hr (HR, 0.92; 95% CI, 0.85–1.00; p = 0.05) were associated with increased all-cause mortality in the fully adjusted model 3.

All-cause mortality according to changes in clinical parameters during 48 hours of continuous renal replacement therapy

Changes in phosphorus and RDW-CV levels during 48 hours of CRRT were evaluated as risk factors for all-cause mortality. As mentioned above, we divided the patients into three groups according to the changes in phosphorus and
RDW-CV levels and eventually chose the lowest mortality group as a reference group. In the NP group composed of 96 patients, the numbers of patients in the delta phosphorus groups were 54 (decreased group), 27 (stable group), and 11 (increased group), while those in the delta RDW-CV groups were 23 (decreased group), 27 (stable group), and 46 (increased group) (Fig. 1). The Kaplan-Meier curve showed that the time to death was significantly different in patients with changes in phosphorus (Fig. 2A, p < 0.001) and RDW-CV levels (Fig. 2B, p = 0.009). In the Cox regression model after full adjustment, the patients in the increased phosphorus group showed an 8.62-fold (95% CI, 2.10–35.32; p = 0.003) increased risk of all-cause mortality compared with the decreased phosphorus group (Table 4). Additionally, patients in the increased RDW-CV group (HR, 4.34; 95% CI, 1.49–13.18; p = 0.008) showed increased all-cause mortality compared with the decreased RDW-CV group.

In the P group composed of 176 patients, the numbers of patients in the delta phosphorus groups were 64 (decreased group), 71 (stable group), and 35 (increased group), while those in the delta RDW-CV groups were 41 (decreased group), 37 (stable group), and 98 (increased group) (Fig. 1).

Table 2. All-cause mortality according to Phoxilium use (initial clinical characteristics)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Model 1</th>
<th></th>
<th></th>
<th>Model 2</th>
<th></th>
<th></th>
<th>Model 3</th>
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</tr>
</thead>
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<tr>
<td></td>
<td>HR</td>
<td>95% CI</td>
<td>p-value</td>
<td>HR</td>
<td>95% CI</td>
<td>p-value</td>
<td>HR</td>
<td>95% CI</td>
<td>p-value</td>
</tr>
<tr>
<td>All</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>1.00</td>
<td>0.99–1.03</td>
<td>0.25</td>
<td>1.01</td>
<td>0.99–1.03</td>
<td>0.26</td>
<td>1.02</td>
<td>1.00–1.04</td>
<td>0.06</td>
</tr>
<tr>
<td>Male sex</td>
<td>1.13</td>
<td>0.75–1.70</td>
<td>0.57</td>
<td>1.02</td>
<td>0.65–1.59</td>
<td>0.94</td>
<td>1.35</td>
<td>0.85–2.14</td>
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</tr>
<tr>
<td>BMI</td>
<td>0.96</td>
<td>0.91–1.01</td>
<td>0.13</td>
<td>0.96</td>
<td>0.91–1.01</td>
<td>0.14</td>
<td>0.96</td>
<td>0.90–1.01</td>
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</tr>
<tr>
<td>Phoxilium use</td>
<td>1.07</td>
<td>0.68–1.69</td>
<td>0.76</td>
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<td></td>
</tr>
<tr>
<td>RDW-CV</td>
<td>1.15</td>
<td>1.06–1.24</td>
<td>&lt;0.001</td>
<td>1.14</td>
<td>1.06–1.23</td>
<td>0.001</td>
<td>1.06</td>
<td>0.97–1.16</td>
<td>0.22</td>
</tr>
<tr>
<td>Phosphorus</td>
<td>0.95</td>
<td>0.88–1.02</td>
<td>0.14</td>
<td>0.95</td>
<td>0.88–1.03</td>
<td>0.19</td>
<td>1.04</td>
<td>0.95–1.13</td>
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</tr>
<tr>
<td>SOFA</td>
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<td>&lt;0.001</td>
<td></td>
<td></td>
<td></td>
<td>1.17</td>
<td>1.09–1.27</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Bicarbonate</td>
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<td>1.02–1.09</td>
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<td></td>
<td></td>
<td></td>
<td>1.05</td>
<td>1.02–1.09</td>
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<tr>
<td>Albumin</td>
<td>0.53</td>
<td>0.74–0.98</td>
<td>&lt;0.001</td>
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<td></td>
<td></td>
<td>0.56</td>
<td>0.67–0.87</td>
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<tr>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
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<tr>
<td>Male sex</td>
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<td>0.33–1.86</td>
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<td>0.97</td>
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<tr>
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<td>1.08</td>
<td>0.88–1.32</td>
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<td>0.96</td>
<td>0.75–1.24</td>
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<tr>
<td>Phosphorus</td>
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<td>0.69–0.96</td>
<td>0.02</td>
<td>0.82</td>
<td>0.70–0.97</td>
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<tr>
<td>SOFA</td>
<td>1.38</td>
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<td>1.16–1.64</td>
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<tr>
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<td>1.02–1.15</td>
<td>0.007</td>
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<td></td>
<td>1.08</td>
<td>1.00–1.17</td>
<td>0.05</td>
</tr>
<tr>
<td>Albumin</td>
<td>0.50</td>
<td>0.29–0.86</td>
<td>0.01</td>
<td></td>
<td></td>
<td></td>
<td>0.74</td>
<td>0.36–1.56</td>
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<tr>
<td>Phoxilium (+)</td>
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<td></td>
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</tr>
<tr>
<td>Age</td>
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<td>0.99–1.03</td>
<td>0.44</td>
<td>1.01</td>
<td>0.99–1.03</td>
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<td>1.02</td>
<td>0.99–1.04</td>
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<tr>
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<td>0.79–2.06</td>
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<td>1.18</td>
<td>0.69–2.00</td>
<td>0.55</td>
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<td>0.86–2.60</td>
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<tr>
<td>BMI</td>
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<td>0.90–1.02</td>
<td>0.15</td>
<td>0.96</td>
<td>0.90–1.02</td>
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<tr>
<td>RDW-CV</td>
<td>1.16</td>
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<td>0.00</td>
<td>1.15</td>
<td>1.05–1.26</td>
<td>0.002</td>
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</tr>
<tr>
<td>Phosphorus</td>
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<td>0.93–1.11</td>
<td>0.71</td>
<td>1.01</td>
<td>0.91–1.10</td>
<td>0.91</td>
<td>1.11</td>
<td>1.00–1.23</td>
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</tr>
<tr>
<td>SOFA</td>
<td>1.13</td>
<td>1.05–1.22</td>
<td>0.001</td>
<td></td>
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<td>1.04–1.26</td>
<td>0.005</td>
</tr>
<tr>
<td>Bicarbonate</td>
<td>1.04</td>
<td>1.00–1.08</td>
<td>0.05</td>
<td></td>
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<td></td>
<td>1.05</td>
<td>1.01–1.09</td>
<td>0.03</td>
</tr>
<tr>
<td>Albumin</td>
<td>0.52</td>
<td>0.33–0.81</td>
<td>0.004</td>
<td></td>
<td></td>
<td></td>
<td>0.51</td>
<td>0.29–0.89</td>
<td>0.02</td>
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</tbody>
</table>

Model 1: unadjusted; model 2: age, sex, BMI at intensive care unit admission, and RDW-CV and phosphorus at CRRT initiation; model 3: model 2 + SOFA score, bicarbonate, and albumin at CRRT initiation. Phoxilium (–): the group of patients who did not receive Phoxilium (Baxter Healthcare Ltd., Norfolk, UK) within 48 hours after CRRT initiation. Phoxilium (+): the group of patients who received Phoxilium within 48 hours after CRRT initiation.

BMI, body mass index; CI, confidence interval; CRRT, continuous renal replacement therapy; HR, hazard ratio; RDW-CV, red cell distribution width-coefficient of variation; SOFA, Sequential Organ Failure Assessment.
The Kaplan-Meier curve showed that time to death was insignificant with respect to changes in phosphorus levels (Fig. 3A, p = 0.56) but was significantly affected by changes in RDW-CV levels (Fig. 3B, p = 0.02). In the Cox regression model after full adjustment, all-cause mortality did not differ according to changes in phosphorus levels (Table 4, all p > 0.05). Additionally, the increased RDW-CV group (HR, 2.65; 95% CI, 1.12–6.24; p = 0.03) and the decreased RDW-CV group (HR, 2.83; 95% CI, 1.16–6.91; p = 0.02) showed increased all-cause mortality compared with the stable RDW-CV group.

### Discussion

CRRT is an important treatment modality for AKI in critically ill patients. The overall use of CRRT has increased over time, and the proportion of CRRT patients among all acute renal replacement therapy patients reached 80% after 2014 in Korea, which is relatively higher than that seen in other nations [17–19]. In recent studies, the all-cause mortality and renal survival rates greatly improved after CRRT initiation [17,18]. CRRT contributes to the correction of imbalances in electrolytes and mineral parameters as well as acid-base imbalances. However, significant problems of overcorrection...
or suboptimal parameter correction are still observed [20]. Phoxilium, developed to prevent hypophosphatemia during CRRT, has been proven effective and is used contemporarily [15]. The present study retrospectively analyzed the risk factors for all-cause mortality in groups divided according to Phoxilium use and showed that the baseline characteristics and risk factors of all-cause mortality differed by the initial phosphorus levels and the use of Phoxilium.

In patients with AKI treated with CRRT, higher RDW-CV and CRP levels and lower albumin levels are generally associated with all-cause mortality, presenting with severe inflammation and malnutrition [9,10]. However, in our study, Kaplan-Meier analysis results for all-cause mortality showed that CRP_0hr was not a risk factor for all-cause mortality in all groups combined (p = 0.99), the NP group (p = 0.995), or the P group (p = 0.24). This result might be due to AKI stemming from variable causes other than sepsis. In the P group, RDW-CV_0hr and CRP_0hr were higher, CRRT duration was longer, and albumin_0hr was lower than those in the NP group (all p < 0.001). Although the mean SOFA_0hr score

**Figure 2.** Kaplan-Meier plots for all-cause mortality according to changes in phosphorus and RDW-CV levels during 48 hours of CRRT in the non-Phoxilium group. We categorized patients into three groups according to the changes in phosphorus and RDW-CV levels between 0 hour and 48 hours: increased, stable, and decreased phosphorus and RDW-CV levels. We divided stable and decreased phosphorus and RDW-CV groups using the median value of the changes, −2.0 mg/dL and −0.2%, respectively. In the non-Phoxilium group, the Kaplan-Meier curve for all-cause mortality showed that time to death was significantly different in patients with changes in phosphorus (Fig. 2A, p < 0.001) and RDW-CV levels (Fig. 2B, p = 0.009).

CRRT, continuous renal replacement therapy; delta phosphorus, changes in phosphorus during 48 hours of CRRT; delta RDW-CV, changes in RDW-CV during 48 hours of CRRT; RDW-CV, red cell distribution width-coefficient of variation. Phoxilium: Baxter Healthcare Ltd., Norfolk, UK.
was not significantly different between the two groups, the mean SOFA _0hr score in the P group was higher than that in the NP group (8.7 ± 3.4 in the NP group vs. 9.4 ± 3.1 in the P group, p = 0.08). These results indicated that the P group had more severe inflammation and malnutrition status, leading to a more severe disease course than the NP group. After 48 hours of CRRT, SOFA _48hr was higher in the P group than in the NP group, which indicated a higher disease severity.

Hyperphosphatemia is commonly observed in patients with AKI due to decreased renal excretion. Additionally, it is associated with high mortality because it indicates disease severity and direct phosphorus toxicity. Within 2 to 3 days of CRRT, serum phosphorus levels mostly return to the normal range via extracorporeal clearance [21].
perphosphatemia is not corrected even after CRRT, the all-cause mortality risk is expected to increase. In the NP group, the increased phosphorus levels, compared with the stable or decreased phosphorus levels after 48 hours of CRRT, showed significantly higher all-cause mortality risks. In the P group, the increased phosphorus levels after 48 hours of CRRT showed increased all-cause mortality. Receiver operating characteristic curve analyses of phosphorus_0hr, phosphorus_48hr, and delta phosphorus in the NP and P group showed that the area under the curve (AUC) was largest for delta phosphorus of the NP group (AUC, 0.774).

Phosphorus plays an important role in all body functions, especially in nerve and muscle functions. If hypophosphatemia occurs in various conditions, myocardial contraction and granulocyte phagocytic activity decrease, and the development of arrhythmia increases [22–24]. It has also been associated with prolonged mechanical ventilation in critically ill patients with AKI [3,25]. In several previous studies, most of the harmful effects caused by hypophosphatemia occurred in patients with very severe phosphorus deficien-

![Figure 3. Kaplan-Meier plots for all-cause mortality according to changes in phosphorus and RDW-CV levels during 48 hours of CRRT in the Phoxilium group.](image-url)

We categorized patients into three groups according to the changes in phosphorus and RDW-CV levels between 0 hour and 48 hours: increased, stable, and decreased phosphorus and RDW-CV levels. We divided stable and decreased phosphorus and RDW-CV groups using the median value of the changes, –2.0 mg/dL and –0.2%, respectively. In the Phoxilium group, the Kaplan-Meier curve for all-cause mortality showed that time to death was not different in patients with changes in phosphorus (Fig. 3A, p = 0.56), but it was significantly different in patients with changes in RDW-CV levels (Fig. 3B, p = 0.02).

CRRT, continuous renal replacement therapy; delta phosphorus, changes in phosphorus during 48 hours of CRRT; delta RDW-CV, changes in RDW-CV during 48 hours of CRRT; RDW-CV, red cell distribution width-coefficient of variation. Phoxilium: Baxter Healthcare Ltd., Norfolk, UK.
cies, defined as a level of <1.0 mg/dL. Although hypophosphatemia cases increased in number from 11 cases (4.0%) to 32 cases (11.7%) after 48 hours of CRRT in the present study, severe hypophosphatemia did not occur. Thus, in line with the results of previous studies, Phoxilium was effective in preventing hypophosphatemia in patients with AKI undergoing CRRT [15, 26, 27].

The RDW-CV level is easy to measure and is recognized as a marker of adverse outcomes. Inflammation and oxidative stress are thought to be major factors in the pathogenesis underlying the association between RDW-CV and all-cause mortality [28]. Additionally, high RDW-CV levels were associated with declining estimated glomerular filtration levels, irrespective of anemia [28]. In some cases, pre-treatment high RDW-CV levels were related to prognosis, but in other studies, the dynamic change was related to adverse outcomes in patients with sepsis [11, 29]. In this study, initial RDW-CV was not a significant risk factor for all-cause mortality in the NP and P groups. However, a higher dynamic change in RDW-CV was associated with a higher all-cause mortality rate. In the P group, a decreased level of delta RDW-CV was a risk factor for all-cause mortality. In the comparison of the mean values of RDW-CV_0hr and RDW-CV_48hr in each delta RDW-CV group, both values in the decreased group were significantly higher than those in the stable and increased groups (data not shown). Therefore, in agreement with the result that higher RDW-CV_48hr is a risk factor for all-cause mortality, the increased and decreased delta RDW-CV groups showed increased risks of all-cause mortality compared to the stable group.

In this study, initial bicarbonate levels did not differ between the NP and P groups (16.2 ± 6.6 mEq/L in the NP group vs. 16.7 ± 6.1 mEq/L in the P group, p > 0.05). After 48 hours of CRRT, bicarbonate levels were higher in the NP group, although the mean values of both groups were within the normal range (23.1 ± 5.5 mEq/L in the NP group vs. 21.7 ± 4.0 mEq/L in the P group, p = 0.03). The lower bicarbonate levels in Phoxilium than in the other solutions (30 mmol/L in Phoxilium vs. 32 mmol/L in Hemosol, PrismaSol 2, and PrismaSol 4) might have resulted in relatively reduced serum bicarbonate levels [15]. Higher bicarbonate_0hr was associated with increased all-cause mortality in both groups, with lower bicarbonate_48hr being associated with mortality only in the P group. Patients with AKI commonly have metabolic acidosis, which is an independent predictor of unfavorable outcomes [30–32]. However, as is well known, the serum bicarbonate level itself cannot reflect the exact acid-base balance status, and compensatory mechanisms should be considered when interpreting blood gas analysis. Thus, we conducted further analyses of ventilator use and blood gas analysis results in

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**Figure 4. Diagram showing risk factors for all-cause mortality in non-Phoxilium and Phoxilium groups.**

CRRT, continuous renal replacement therapy; delta phosphorus, changes in phosphorus during 48 hours of CRRT; delta RDW-CV, changes in RDW-CV during 48 hours of CRRT; RDW-CV, red cell distribution width-coefficient of variation; SOFA, Sequential Organ Failure Assessment. Phoxilium: Baxter Healthcare Ltd., Norfolk, UK.
the survivor and non-survivor groups, as shown in Supplementary Table 5 (available online). The non-survivor group showed a higher percentage of ventilator use and pCO$_2$ _0hr (p < 0.001 and p = 0.002, respectively) with higher bicarbonate _0hr (p < 0.001) than the survivor group. Furthermore, the additional univariable analysis of Cox regression showed that higher pCO$_2$ _0hr (HR, 1.04; 95% CI, 1.01–1.06; p = 0.004) and bicarbonate _0hr (HR, 1.08; 95% CI, 1.02–1.15; p = 0.007) were risk factors for all-cause mortality.

When interpreting the results above, the combination of metabolic and respiratory acidemia seemed to be the mainstay of blood gas status in the non-survivor group, whereas primary metabolic acidemia was prominent in the survivor group. Patients with combined acidemia showed higher mortality than those with either metabolic or respiratory acidemia alone in a critically ill state [33]. Therefore, patients showing a mixed disorder of acid-base balance, also referred to as having higher pCO$_2$ _0hr and bicarbonate _0hr in this study, were associated with adverse outcomes. After 48 hours of CRRT, more severe metabolic acidosis with lower bicarbonate levels in the P group was related to adverse outcomes.

Hypoalbuminemia is associated with several pathological conditions, such as nutritional deficiency and chronic inflammation. It is a predictive marker of short- and long-term mortality in patients undergoing CRRT [10]. This study also showed that low initial albumin levels indicated adverse outcomes in the NP and P groups. However, after fully adjusting for confounding factors, hypoalbuminemia was significant only in the P group. This difference seems to be due to the different levels of initial albumin between the groups. Initial albumin levels were higher in the NP group than in the P group (3.5 ± 0.9 g/dL in the NP group vs. 3.1 ± 0.6 g/dL in the P group, p < 0.001). As phosphorus reflects nutritional status, basal nutritional status was expected to be poor in the P group.

This study had several limitations. Although the analysis was performed with appropriate adjustments, the possibility of residual confounders due to the retrospective nature of the study cannot be excluded. Additionally, most of the patients were Korean; thus, there is a limitation in applying the findings to other races. Compared with Hemosol-B0, Phoxilium contributes to relative hypocalcemia and metabolic acidosis [15]. Although there are differences in the compositions of Phoxilium and other dialysate fluids, the changes in corrected calcium and bicarbonate levels were not significantly different between the NP and P groups. As this is a retrospective analysis, efforts to correct hypocalcemia and metabolic acidosis with intravenous or oral calcium and bicarbonate supplementation were not controlled. Therefore, calcium _48hr and bicarbonate _48hr might not reflect solution differences.

In conclusion, this study strongly suggests that in patients with AKI undergoing CVVHDF, the difference in disease severity and risk factors for all-cause mortality is affected by the initial phosphorus levels and the use of Phoxilium. Additionally, the effects of changes in phosphorus and RDW-CV levels by short-term CVVHDF using different compositions of dialysate fluids on all-cause mortality differed according to the initial phosphorus level.

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

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Authors’ contributions

Conceptualization: SHS, HJK, DWK
Formal analysis: DWK, HJK, JMK
Funding acquisition: SHS
Investigation: MH, YHJ, EYS
Project administration: SSH
Writing—original draft: DWK, HJK
Writing—review & editing: DWK, HJK, SHS All authors read and approved the final manuscript.

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References


Background: Peritoneal dialysis (PD) is improving as a renal replacement therapy for end-stage renal disease (ESRD) patients. We analyzed the main outcomes of PD over the last three decades at a single large-scale PD center with an established high-quality care system.

Methods: As a retrospective cohort study, we included participants (n = 1,203) who began PD between 1990 and 2019. Major PD-related outcomes were compared among the three 10-year cohorts.

Results: The 1,203 participants were 58.3% male with a mean age of 47.9 ± 13.8 years. The median PD treatment duration was 45 months (interquartile range, 19–77 months); 362 patients (30.1%) transferred to hemodialysis, 289 (24.0%) received kidney transplants, and 224 (18.6%) died. Overall, the 5- and 8-year adjust patient survival rates were 64% and 49%, respectively. Common causes of death included infection (n = 55), cardiac (n = 38), and cerebrovascular (n = 17) events. The 5- and 8-year technique survival rates were 77% and 62%, respectively, with common causes of technique failure being infection (42.3%) and solute/water clearance problems (22.7%). The 5-year patient survival significantly improved over time (64% for the 1990–1999 cohort vs. 93% for the 2010–2019 cohort). The peritonitis rate also substantially decreased over time, from 0.278 episodes/patient-year (2000–2004) to 0.162 episodes/patient-year (2015–2019).

Conclusion: PD is an effective treatment option for ESRD patients. There was a substantial improvement in the patient survival and peritonitis rates over time. Establishing adequate infrastructure and an effective system for high-quality PD therapy may be warranted to improve PD outcomes.

Keywords: Peritoneal dialysis, Peritonitis, Survival, Technique failure
Introduction

The global incidence of end-stage renal disease (ESRD) is rapidly increasing, which poses a major burden on healthcare systems around the world [1]. To date, no definitive randomized clinical trials have been conducted on peritoneal dialysis (PD) and in-center hemodialysis (HD) [2]. However, several observational studies have reported comparable or better survival [3–5] in patients with PD, particularly during the first 2 years after dialysis initiation. Additionally, PD has been associated with better preservation of residual renal function [6], improved cognition [7], a higher likelihood of retaining employment [8], and improved health-related quality of life (HRQOL) [9]. The Centers for Medicare and Medicaid Services in the United States has acknowledged these benefits of PD relative to HD and has also implemented the ESRD prospective payment system, which incentivizes PD treatment by bundling dialysis, medications, and other related services into a single payment [10].

However, despite its numerous clinical benefits, PD is still underutilized globally [11]. PD underuse may be attributable to the misconception that PD is inferior to HD [12] and also inadequate PD training of the nephrologists [13,14]. These factors lead patients to have less confidence in self-care and also in their ability to prepare for renal replacement therapy (RRT) initiation.

The major outcomes of PD (such as patient survival, technique survival, and peritonitis) vary widely depending on sociodemographics [15–17], race [18], center size [19,20], and center experience [21]. We conducted this retrospective cohort study to investigate the secular changes in major outcomes of incident PD patients over the last three decades at a single large PD center. We also explored recent advances in PD therapy and evaluated how our center’s ongoing efforts to improve quality have translated into improved outcomes over time.

Methods

Study design and population

This was a single-center retrospective cohort study from the Seoul National University Hospital (SNUH) PD Center in Seoul, Korea. The SNUH PD Center launched its PD program in the late 1980s. It is currently one of the largest PD centers in Korea and treats >1,300 cumulative and >300 prevalent PD patients. Clinical data from all incident PD patients since 1990 were collected. In 2000, the SNUH PD registry was established to prospectively collect patient information including age, sex, socioeconomic status, any previous RRT, comorbidities, biochemistry, peritoneal function test results, PD adequacy, PD-related infections, technique failure and its cause, and death.

The SNUH PD Center began a multidisciplinary predialysis education (MPE) program for chronic kidney disease (CKD) in 2002 to provide detailed information on diet, medication, and modality selection for advanced CKD patients who were expected to begin RRT within the next 6 months [22]. During the break-in period after PD catheter implantation, all patients and their caregivers were given intensive one-on-one education and training for PD exchange procedures, exit-site care, and self-management by professionally trained nurses [23]. After PD initiation, the participants were scheduled to visit the PD center regularly each 1 to 3 months for an evaluation and to receive prescriptions. They were also offered regular home visits for retraining at home [24], where most of the PD fluid exchanges and self-care procedures are carried out. To minimize inter-individual variation between the treating nephrologists and to facilitate communication within the PD team, we established a standard operating procedure for PD treatment and care. Regular monitoring and continuous quality improvement have been conducted across diverse areas, such as PD-related infections, dialysis adequacy, blood pressure control, fluid overload, technique failure, and mortality.

For this study, we included incident PD patients 18 years or older who began PD as their first RRT between 1990 and 2019. The participants who were transferred from other PD centers or transferred to PD treatment from other RRT modalities were excluded. Patients who underwent PD for less than 3 months were also excluded. Comorbidities were evaluated using the Davies comorbidity score, including ischemic heart disease, peripheral vascular disease, left ventricular dysfunction, malignancy, diabetes mellitus (DM), systemic collagen vascular disease, and others. The comorbidity score was categorized into three risk groups: low, a score of 0; medium, a score from 1 to 2; and high, a score of ≥3 [25]. Cardiovascular disease was defined as a composite event of ischemic heart disease, peripheral vascular disease, left ventricular dysfunction, and cerebral vascular disease.
vascular abnormality.

The study was approved by the Ethical Committee of Seoul National University Hospital (NO. H-2004-222-1119), and informed consent was waived because of the retrospective study design. Personal information was de-identified prior to our analyses. All clinical research processes were conducted in accordance with the guidelines of the 2008 Declaration of Helsinki.

**Outcome measures**

All patients were categorized into three cohorts based on the year in which they began receiving PD; 1990–1999, 2000–2009, or 2010–2019, with the 1990–1999 cohort being the reference group. The participants were followed until the time of their death, their transfer to another RRT, their transfer to another hospital, or until December 31, 2019, whichever occurred first. The primary outcome among all cohort groups was the all-cause mortality, which was analyzed using an as-treated approach. For patient survival, the patients were censored at the time of loss to follow-up or 90 days after they switched to HD or received a kidney transplant. Deaths within 90 days after a modality switch were also considered to be PD-related. Specific causes of death were compared among the three cohort groups. For cause-specific death analysis, deaths related to other causes were censored for analysis.

Secondary outcomes were technique failure and peritonitis incidence. A PD technique failure was defined as a transfer to HD for >3 months for any reason, including infection, catheter-related problems, solute/water clearance problems, peritoneal leaks or hernias, psychosocial or medical issues, the risk of encapsulating peritoneal sclerosis (EPS), a diagnosis of EPS, and others. Deaths related to peritonitis, solute/water clearance problems, and an EPS risk or diagnosis were also regarded as technique failures. However, temporary HD (<90 days) was not regarded as a technique failure. Defining specific causes of technique failure followed a standardized classification recently suggested by the Peritoneal Dialysis Outcomes and Practice Patterns Study (PDOPPS) [26]. For technique failure, the participants were censored at the time of kidney transplantation, unrelated death, transfer to another center, or at the end of the observation period (December 31, 2019). Any diagnosis of PD-related peritonitis followed the International Society for Peritonitis Dialysis (ISPD) guidelines [27]. Incidences of peritonitis associated with a specific causative microorganism were also evaluated. Detailed information on peritonitis was available from 2000 onwards in our registry dataset.

**Statistical analyses**

Categorical variables were presented as frequencies and percentages, and these values were compared using a chi-square test. Age was categorized into three groups (18–40, 41–60, and >60 years). The crude survival and adjusted survival rates were estimated with a Cox proportional hazard model, and then adjustments were made with independent variables that were significant in the univariate analyses or with clinically relevant variables. For cause-specific mortality estimates, unrelated deaths were censored. We analyzed the trends of the peritonitis incidence and cause-specific peritonitis cases during each 5-year period as follows: 2000–2004, 2005–2009, 2010–2014, and 2015–2019. The peritonitis incidences were presented as episodes per patient-year at risk. SAS version 9.4 (SAS Institute, Cary, NC, USA) and IBM SPSS version 25.0 (IBM Corp., Armonk, NY, USA) were used for the statistical analyses. R version 3.6.3. (R Foundation for Statistical Computing, Vienna, Austria) was used for drawing plots. The p-values of <0.05 were considered statistically significant.

**Results**

**Trends in the number of incident peritoneal dialysis patients**

Since the MPE program was introduced at Seoul National University Hospital in 2002, the number of patients who have chosen PD as their initial RRT has increased at our PD center (Supplementary Fig. 1, available online). Among all participants who began PD at our center from 1990 to 2019 (n = 1,307), we excluded the following patients; those who withdrew within 3 months (n = 76), recovered their renal function (n = 4), or were <18 years old (n = 24) (Fig. 1). Finally, we analyzed 1,203 participants. Of these, 289 underwent transplantation, 362 converted to HD, 224 died during PD, and 225 remained on PD. Six patients who switched to HD died within 3 months after they transferred to HD.
The demographics and baseline characteristics of the three incident cohorts

Table 1 shows the baseline characteristics of each cohort. The overall mean age was 47.9 ± 13.8 years (58.3% male and 28.9% with DM). The median duration of PD treatment was 45 months (interquartile range, 19–77 months). Participants aged from 41 to 60 years accounted for 46.6% of the total study population. The number of participants who started PD between the ages of 18 and 40 years increased over time. According to the Davies comorbidity scores, 38.7% and 5.9% were at medium and high risk, respectively.

![Diagram](Image)

**Figure 1.** Flowsheet of the patient selection process for analysis.
HD, hemodialysis; PD, peritoneal dialysis.

**Table 1.** Baseline patient characteristics

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<tbody>
<tr>
<td>No. of patients</td>
<td>1,203</td>
<td>270</td>
<td>481</td>
<td>452</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (yr)</td>
<td></td>
<td></td>
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<tr>
<td>18–40</td>
<td>390 (32.4)</td>
<td>74 (27.4)</td>
<td>150 (31.2)</td>
<td>166 (36.7)</td>
<td>0.02</td>
<td>0.006</td>
</tr>
<tr>
<td>41–60</td>
<td>560 (46.6)</td>
<td>137 (50.7)</td>
<td>215 (44.7)</td>
<td>208 (46.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;60</td>
<td>253 (21.0)</td>
<td>59 (21.9)</td>
<td>116 (24.1)</td>
<td>78 (17.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male sex</td>
<td>701 (58.3)</td>
<td>163 (50.7)</td>
<td>289 (60.1)</td>
<td>249 (55.1)</td>
<td>0.23</td>
<td>0.12</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>345 (28.9)</td>
<td>58 (21.7)</td>
<td>165 (34.3)</td>
<td>122 (27.3)</td>
<td>0.001</td>
<td>0.31</td>
</tr>
<tr>
<td>Hypertension</td>
<td>877 (73.3)</td>
<td>59 (22.1)</td>
<td>446 (92.7)</td>
<td>372 (82.9)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>216 (18.1)</td>
<td>12 (4.5)</td>
<td>144 (29.9)</td>
<td>60 (13.4)</td>
<td>&lt;0.001</td>
<td>0.13</td>
</tr>
<tr>
<td>Davies comorbidity score</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Low risk (0)</td>
<td>580 (55.4)</td>
<td>69 (59.0)</td>
<td>236 (49.1)</td>
<td>275 (61.1)</td>
<td>&lt;0.001</td>
<td>0.06</td>
</tr>
<tr>
<td>Medium risk (1, 2)</td>
<td>405 (38.7)</td>
<td>48 (41.0)</td>
<td>199 (41.4)</td>
<td>158 (35.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High risk (≥3)</td>
<td>62 (5.9)</td>
<td>0 (0)</td>
<td>45 (9.4)</td>
<td>17 (3.8)</td>
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Data are expressed number only or number (%).
Patient survival

A total of 230 patients (19.1%) died during the follow-up period. Common causes of death were infection (n = 55), cardiac disease (n = 38), and cerebrovascular disease (n = 17) (Table 2). The number of deaths due to cardiac disease and infection decreased from the 1990–1999 to the 2010–2019 cohort. Overall, the 5- and 8-year crude survival rates were 64% and 49%, respectively. The 5-year patient survival rate improved substantially over time (64% for the 1990–1999 cohort vs. 93% for the 2010–2019 cohort) (Table 3, Fig. 2). Adjusted survival data also showed the same pattern. We analyzed the trend of patient survival in participants who continued PD for more than 5 years, and this group also demonstrated similar results (Supplementary Table 1, available online). Compared to the 1990–1999 cohort, the risk of all-cause mortality decreased by 58.0% for the 2000–2009 cohort and by 82.6% for the 2010–2019 cohort (multivariable model) (Table 4). Compared to the 1990–1999 cohort, the risks of death from peritonitis and cardiac death were reduced by 77.1% and 64.3%, respectively, in the 2010–2019 cohort (multivariable model) (Table 4). We performed subgroup analyses stratified by age (18–40, 41–60, or >60 years), sex (male or female), DM (yes or no), and Davies comorbidity scores (0 or >0). For each stratum, we analyzed the risk of all-cause mortality for the 2010–2019 cohort compared with the 1990–1999 cohort. Overall, for all the subgroup strata with the exception of the younger patients (18–40 years), the risk of all-cause death was significantly lower for the 2010–2019 cohort compared with the 1990–1999 cohort (Fig. 3).

Technique survival

A total of 397 (33.0%) patients experienced PD technique failure. Among these patients, the median elapsed times to technique failure were 3.5, 3.9, and 3.6 years for the 1990–1999, 2000–2009, and 2010–2019 cohorts, respectively. The 5-year technique survival did not improve over time (77% vs. 71%; Fig. 2). Compared with the 1990–1999 cohort, the risk of technique failure was higher in the 2000–2019 cohort (Table 5). However, there was no difference in risk between the 2000–2009 and 2010–2019 cohorts. Common causes of technique failure were infection-related technical failures (42.3%) and problems with solute/water clearance (22.7%) (Table 6). Over time, the proportion of infection-related technical failures decreased from 56.1% to 36.8%, while the proportion of solute/water clearance problems and psychosocial/medical technique failures increased from the 1990–1999 cohort to the 2010–2019 cohort.

### Table 2. Causes of death

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<tbody>
<tr>
<td>Death/patient</td>
<td>230/1,203</td>
<td>94/481</td>
<td>24/452</td>
</tr>
<tr>
<td>Cardiac disease</td>
<td>38 (3.2)</td>
<td>17 (3.5)</td>
<td>7 (1.5)</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>17 (1.4)</td>
<td>8 (1.7)</td>
<td>2 (0.4)</td>
</tr>
<tr>
<td>Infection</td>
<td>55 (4.6)</td>
<td>28 (5.8)</td>
<td>6 (1.3)</td>
</tr>
<tr>
<td>Malignancy</td>
<td>6 (0.5)</td>
<td>2 (0.4)</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Sudden death</td>
<td>4 (0.3)</td>
<td>2 (0.4)</td>
<td>2 (0.4)</td>
</tr>
<tr>
<td>Others</td>
<td>17 (1.4)</td>
<td>9 (1.9)</td>
<td>3 (0.7)</td>
</tr>
<tr>
<td>Unknown causes</td>
<td>93 (7.7)</td>
<td>28 (5.8)</td>
<td>3 (0.7)</td>
</tr>
</tbody>
</table>

Data are presented as number only or number (%); the % is the ratio to the number of participants in each cohort.

### Table 3. Patient survival rates by cohort

<table>
<thead>
<tr>
<th>Year of cohort</th>
<th>Crude survival</th>
<th>Adjusted survival*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Five-year survival (%)</td>
<td>Eight-year survival (%)</td>
</tr>
<tr>
<td>1990–1999</td>
<td>64</td>
<td>49</td>
</tr>
<tr>
<td>2000–2009</td>
<td>82</td>
<td>72</td>
</tr>
<tr>
<td>2010–2019</td>
<td>93</td>
<td>89</td>
</tr>
<tr>
<td>Overall</td>
<td>64</td>
<td>49</td>
</tr>
</tbody>
</table>

*Adjusted for age, sex, and diabetes mellitus status.
Figure 2. Survival rates by cohort. (A) The crude patient survival rate. (B) The adjusted patient survival rate. (C) The crude technical survival rate. (D) The adjusted technical survival rate. The adjusted survival rate was adjusted for age, sex, and diabetes mellitus status.

Table 4. The risk of all-cause mortality and cause-specific mortality by cohort

<table>
<thead>
<tr>
<th>Year of cohort</th>
<th>Univariable HR (95% CI)</th>
<th>p-value</th>
<th>Multivariable HR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk of all-cause death</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1990–1999</td>
<td>1 (Reference)</td>
<td></td>
<td>1 (Reference)</td>
<td></td>
</tr>
<tr>
<td>2000–2009</td>
<td>0.46 (0.35–0.61)</td>
<td>&lt;0.001</td>
<td>0.42 (0.32–0.55)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>2010–2019</td>
<td>0.16 (0.10–0.25)</td>
<td>&lt;0.001</td>
<td>0.17 (0.11–0.27)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Risk of death from peritonitis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1990–1999</td>
<td>1 (Reference)</td>
<td></td>
<td>1 (Reference)</td>
<td></td>
</tr>
<tr>
<td>2000–2009</td>
<td>0.68 (0.32–1.46)</td>
<td>0.33</td>
<td>0.54 (0.25–1.17)</td>
<td>0.12</td>
</tr>
<tr>
<td>2010–2019</td>
<td>0.24 (0.07–0.85)</td>
<td>0.03</td>
<td>0.23 (0.06–0.83)</td>
<td>0.03</td>
</tr>
<tr>
<td>Risk of cardiac death</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1990–1999</td>
<td>1 (Reference)</td>
<td></td>
<td>1 (Reference)</td>
<td></td>
</tr>
<tr>
<td>2000–2009</td>
<td>0.65 (0.32–1.32)</td>
<td>0.23</td>
<td>0.59 (0.29–1.20)</td>
<td>0.15</td>
</tr>
<tr>
<td>2010–2019</td>
<td>0.33 (0.13–0.82)</td>
<td>0.02</td>
<td>0.36 (0.14–0.89)</td>
<td>0.03</td>
</tr>
</tbody>
</table>

CI, confidence interval; HR, hazard ratio.
*Adjusted for age, sex, and diabetes mellitus status.

Peritonitis

There were 879 episodes of peritonitis from 2000 until 2019 (overall incidence, 0.193 episodes per patient-year). Over time, the incidence of peritonitis significantly decreased from 0.278 episodes per patient-year in 2000–2004 to 0.162 episodes per patient-year in 2015–2019 (Fig. 4A). For cause-specific peritonitis, the incidence due to coagu-
lase-negative *Staphylococcus* increased slightly in the 2010s but decreased remarkably in general. In contrast, the incidence of peritonitis associated with enteric gram-negative organisms (such as *Escherichia coli* and others) did not change (Fig. 4B).

**Figure 3.** Stratified subgroup analysis for the risk of all-cause death for the 2010–2019 vs. the 1990–1999 cohort. For the Davies comorbidity score, ‘0’ denotes low risk, while ‘>0’ denotes a medium or high risk.

**Table 5.** Risk of technique failure by cohort

<table>
<thead>
<tr>
<th>Year of cohort</th>
<th>Univariable</th>
<th>Multivariable*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>p-value</td>
</tr>
<tr>
<td>1990–1999</td>
<td>1 (Reference)</td>
<td>0.01</td>
</tr>
<tr>
<td>2000–2009</td>
<td>1.41 (1.08–1.85)</td>
<td>0.01</td>
</tr>
<tr>
<td>2010–2019</td>
<td>1.46 (1.08–1.96)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

CI, confidence interval; HR, hazard ratio.

*Adjusted for age, sex, and diabetes mellitus status.

**Discussion**

The temporal trend of PD outcomes in this study showed that the patient survival and the peritonitis rates have significantly improved over the last 30 years at our PD center. As
shown in Fig. 3, the survival improvement for the 2010–2019 cohort was significant among middle-aged and elderly patients regardless of sex, DM status, or comorbidity score. In particular, the adjusted patient survival rates for the 2010–2019 incident cohort at our center were 95% after 5 years and 91% after 8 years, which are far superior to any outcomes recently reported for any other institution [28–33].

The two most common causes of death in our study were cardiac disease and infection, including peritonitis. However, the number of deaths due to cardiac disease and infection decreased from the 1990–1999 to the 2010–2019 cohorts (Table 2). Temporal improvement in patient survival on PD is consistent with trends from other studies [30,31]. These improvements in patient survival may reflect the continuing development of PD as a therapy as well as better care of any comorbid diseases.

In 2002, we launched an MPE program for advanced CKD patients and their families. The education team was comprised of nephrologists, dialysis nurses, pharmacists, dieticians, and social workers. Each session provided education on normal kidney function, pathophysiologic alterations in CKD, diet, and medication. Additionally, unbiased information about RRT options was delivered. Any patients who were considering PD as their first RRT were encouraged to meet the nursing staff at the PD center to obtain more information about PD therapy. Since the MPE program began in 2002, the number of patients who choose PD as their initial RRT modality has increased dramatically each year (Supplementary Fig. 1). Although there was also a nationwide increase in the total incident PD patients in the same period [34], we suspect that this increase may be partly due to the initiation of the MPE program. We also previously reported

<table>
<thead>
<tr>
<th>Cause</th>
<th>Total (n = 397)</th>
<th>1990–1999 (n = 82)</th>
<th>2000–2009 (n = 190)</th>
<th>2010–2019 (n = 125)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infection-related</td>
<td>168 (42.3)</td>
<td>46 (56.1)</td>
<td>76 (40.0)</td>
<td>46 (36.8)</td>
</tr>
<tr>
<td>Catheter-related</td>
<td>19 (4.8)</td>
<td>5 (6.1)</td>
<td>9 (4.7)</td>
<td>5 (4.0)</td>
</tr>
<tr>
<td>Solute/water clearance problem</td>
<td>90 (22.7)</td>
<td>8 (9.8)</td>
<td>46 (24.2)</td>
<td>36 (28.8)</td>
</tr>
<tr>
<td>Peritoneal leaks/hernias</td>
<td>10 (2.5)</td>
<td>0 (0)</td>
<td>9 (4.7)</td>
<td>1 (0.8)</td>
</tr>
<tr>
<td>Psychosocial/medical</td>
<td>44 (11.1)</td>
<td>1 (1.2)</td>
<td>21 (11.1)</td>
<td>22 (17.6)</td>
</tr>
<tr>
<td>Risk of or diagnosis of EPS</td>
<td>12 (3.0)</td>
<td>2 (2.4)</td>
<td>7 (3.7)</td>
<td>3 (2.4)</td>
</tr>
<tr>
<td>Other causes</td>
<td>54 (13.6)</td>
<td>20 (24.4)</td>
<td>22 (11.6)</td>
<td>12 (9.6)</td>
</tr>
</tbody>
</table>

Data are presented as number (%).
EPS, encapsulating peritoneal sclerosis.

Figure 4. Temporal trends in the incidence of peritonitis. (A) The overall incidence of peritonitis. (B) The cause-specific incidence of peritonitis. CNS, coagulase-negative Staphylococci; E. coli, Escherichia coli; GNB, gram-negative bacteria; S. aureus, Staphylococcus aureus; strep, Streptococcus.
that the MPE reduced the risk for unplanned urgent dialysis, cardiovascular and infection complications, and hospitalization [22].

As a home dialysis treatment, PD requires a comprehensive understanding of the therapy and self-management by the patient; these abilities may be associated with patient socioeconomic status and, crucially, education level. Because we offer the MPE program and comprehensive training at our PD center, we were able to retrospectively analyze the impact of lower education attainment on various PD outcomes in 655 incident PD patients [23]. Although a lower education attainment level was a significant risk factor for peritonitis and technique failure, it was not associated with increased mortality in PD patients. Therefore, we have shown that comprehensive training and multidisciplinary education provided by the PD center could overcome low education attainment among PD patients.

The 2020 ISPD PD Practice Recommendations focused on high-quality, goal-directed PD [35], which emphasized establishing realistic care goals to maintain HRQOL for PD patients through individualized care and shared decision-making. In a recent publication, we reported that about 50% of our PD patients from the SNUH PD registry were initially prescribed a low-dose prescription that was increased incrementally as their residual renal function declined. Our analyses found no differences in patient survival or technique survival between the incremental PD and full-dose PD groups [36].

Based on our data, although patient survival significantly improved, the risk of technique failure did not get better over time. This result is consistent with other reports from a large registry of PD patients, which showed that PD technique survival did not improve, whereas patient survival rates significantly improved over time [29,30]. Although we observed a dramatic reduction in the incidence of peritonitis over time, peritonitis still remains the most common cause of technique failure. This relationship might be due to the relative increase of severe peritonitis cases or to the more aggressive attitude of physicians toward PD catheter removal and transfer to HD for fear of peritonitis-related complications, such as membrane failure or EPS. Other major causes of technique failure included problems with solute/water clearance, psychosocial/medical technical failures, catheter-related problems, EPS risk or diagnosis, and peritoneal leaks or hernias (Table 6). Table 6 shows a gradual decrease in infection-related technique failures, while problems with solute/water clearance and psychosocial/medical issues increased relative to the cause of technique failure. Generally, the rate of technique failure is at its highest during the first 3 months after PD initiation. However, we excluded patients with a PD duration <3 months from our analyses. Therefore, this study was unable to evaluate the incidence and causes of early PD failure. A vigilant and strategic approach to target specific causes of technique failure and to prolong technique survival is warranted, both within individual centers and in liaison with an international research consortium [26].

Peritonitis is the main factor that contributes to death and technique failure in PD patients. The 2016 ISPD guidelines recommend that the overall peritonitis incidence be no more than 0.5 episodes per year [27]. At our center, there was a significant drop in the overall peritonitis incidence over time (Fig. 4A). As shown in Fig. 4B, the incidence of coagulase-negative Staphylococcus, which is a normal skin flora and is associated with touch contamination, has been reduced over time due to enforced patient training. However, the relative incidence of enteric gram-negative organisms, which are more likely to lead to treatment failure, did not change during the observation period. More attention should be paid to the prevention of peritonitis due to enteric microorganisms in the future.

We noted the importance of regular retraining at home, where most PD exchanges are carried out, to prevent PD-related infection. We conducted a clinical trial comparing the benefit of frequent versus conventional home visits by dialysis nurses [24]. Exit-site infection and any PD-related infections for the frequent-visit group decreased over time, while those for the conventional group increased after one year. In the older subgroup (age ≥ 60 years), frequent retraining visits were associated with significantly longer peritonitis-free survival times. Therefore, we showed that frequent retraining at home reduced the risk of PD-related infections.

Our study was limited by the fact that it was a single-center analysis. Some laboratory data and detailed information on peritonitis between 1990 and 1999 were not available. Compared with other studies [30,32], our patients were relatively younger, which probably contributed to the better outcomes in our study. The remarkable improvement in PD outcomes over time at our PD center may not be fully generalizable to all practice settings, especially to centers that do not have adequate support infrastructure, such as a patient education
system, trained nephrologists, and a dedicated PD nursing staff. Unlike the substantial improvement in the patient survival and the peritonitis rates, the risk of technique failure did not improve over time in our analyses. However, based on the large number of PD patients who demonstrated persistent improvement over three decades, this study indicated that PD is an excellent therapy for patients with ESRD and also that outcomes continuously improved within a well-organized, multidisciplinary care system. Future research and efforts should aim not only to improve patient survival but also to increase technique survival, improve cardiovascular and peritonitis treatment outcomes, and to enhance quality of life in PD.

In conclusion, our findings suggest that PD is an excellent RRT and is consistently improving over time. Establishing an adequate system and infrastructure for high-quality PD therapy is important for improving PD outcomes.

Conflicts of interest

Kook-Hwan Oh reports grants from Fresenius Medical Care, Korea and Baxter, Korea. The other authors have no conflicts of interest to declare.

Funding

The present study was funded by Fresenius Medical Care, Korea (06-2016-1040). However, the funder had no role in the design, implementation, analysis, or interpretation of the study.

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Authors’ contributions

Conceptualization: KHO, CA
Investigation, Data curation, Formal analysis: MK, YLK, EK, KHO, YCK, DKK, HL, SSH, KWJ, YSK, CA, HR
Funding acquisition: KHO
Visualization: MK, YLK
Writing—original draft: MK, YLK, EK, HR
Writing—review & editing: YCK, DKK, HL, SSH, KWJ, YSK, CA, HR
All authors read and approved the final manuscript.

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References

is associated with better cognitive function than hemodialysis over a one-year course. Kidney Int 2018;93:430–438.


Background: Normal saline solution (NSS) has been the fluid of choice for renal transplant patients, but it can lead to hyperchloremic acidosis and hyperkalemia. This study was performed to compare the safety profile of low-chloride solutions with that of NSS in renal transplant patients.

Methods: We conducted a systemic review search on PubMed, Embase, and the Central Cochrane Registry. Randomized clinical trials (RCTs) and matched cohort studies involving NSS as the control arm and low-chloride solutions as an intervention arm were chosen. The standardized mean difference for continuous variables, the odds ratio (OR) for discrete variables, and a 95% confidence interval (CI) for effect sizes were used. A p-value of <0.05 was considered statistically significant. Analysis was performed using a random-effects model irrespective of heterogeneity, which was evaluated using I² statistics.

Results: Nine RCTs and one cohort study with a total of 726 patients were included. After transplantation, serum potassium was significantly lower in the low-chloride group (standardized mean difference compared to NSS group, –0.38 mEq/L; 95% CI, –0.66 to –0.11; p = 0.007). Similarly, postoperative chloride was lower in the low-chloride group (–2.41 mEq/L [–3.34 to –1.48], p < 0.001). No statistically significance was observed in delayed graft function (OR, 0.98 [0.56–1.69], p = 0.93), day 3 creatinine (–0.14 mg/dL [–0.46 to 0.18], p = 0.38), or day 7 urine output (–0.08 L [–0.29 to 0.12], p = 0.43).

Conclusion: Use of NSS during renal transplant leads to increased incidence of hyperchloremic acidosis with subsequent hyperkalemia, but clinical significance in the form of delayed graft function or postoperative creatinine remains comparable to that of low-chloride solutions.

Keywords: Delayed graft function, Dialysis solutions, Kidney transplantation, Ringer’s lactate, Saline solution, Sodium bicarbonate
gan Procurement and Transplantation Network government website, 22,393 patients received a renal transplant in 2018. According to the annual report 2020 published by the United States Renal Data System, 1-year posttransplant graft survival improved to 93% in deceased donor transplant recipients compared to 96.9% in living donor transplant recipients. The limited availability of donor viscera necessitates measures to improve graft function and survivability.

Normal saline solution (NSS) is the most used perioperative intravenous fluid during kidney transplant due to theoretically reduced risk for perioperative hyperkalemia [1]. It is postulated that fluids like Ringer’s lactate possess a high potassium content and can cause hyperkalemia postoperatively [2,3]. There is some evidence that suggests that higher chloride content in NSS can cause hyperchloremic metabolic acidosis and subsequent hyperkalemia as an effect of acidosis on potassium homeostasis [4].

In comparison, balanced chloride solutions are less likely to cause hyperkalemia by virtue of their low-chloride content. This meta-analysis will determine if we can extrapolate these electrolyte and blood pH changes associated with NSS to renal transplant surgeries. Hyperkalemia is an indication for dialysis posttransplant and can lead to decreased cardiovascular stability of the transplant recipient. Therefore, it is hypothesized that normal saline will increase the risk of delayed graft function, defined as the need for dialysis within 1 week of renal transplantation or not observing a 20% reduction in serum creatinine within 72 hours [5].

The purpose of this review is to compare NSS to balanced crystalloid solutions and the incidence of postoperative delayed graft function, acidemia, and hyperkalemia in renal transplant patients. With the last being in 2016, previous reviews support that NSS is associated with more hyperchloremic metabolic acidosis than are balanced electrolyte solutions, but with uncertain clinical significance [6]. However, three randomized clinical trials (RCTs) on the topic have been performed since 2016, requiring their inclusion for a higher-powered review. We aim to increase the study power by including recently published trials and provide a more comprehensive guideline for physicians overseeing the care of renal transplant patients.

**Methods**

The databases accessed were the Cochrane Central Registry of Clinical Trials, Embase, and PubMed. The search terms used were renal transplant, sodium bicarbonate, normal saline solution, and Ringer’s lactate. The deadline for publication was set as December 20, 2020. The data were extracted, and the manuscript was reviewed by the Research Department and Ethics Committee. No experimental interventions were performed, and it did not require any specification of guidelines, legislations, or permissions.

**Inclusion and exclusion criteria**

Included papers had the following characteristics.

1. Randomized control trials or matched retrospective cohort studies comparing NSS against low-chloride solutions in renal transplant patients
2. Patients older than 18 years
3. Available in English without restrictions of date or status of publication

Papers that did not meet the above criteria were excluded.

**Trial selection and evaluation**

Three authors independently reviewed all articles and abstracts and excluded irrelevant articles. The risk of bias for selected papers was assessed using the Cochrane collaborative tool and was classified into high, uncertain, and low.

**Data extraction**

Information was extracted using a prespecified extraction table from analysis of text and tables, and a second author reviewed the information to ensure accuracy. The extracted data were the number of patients, delayed graft function, serum creatinine at day 3 (mg/dL), urine output at day 7 (L), postoperative chloride (mEq/L), postoperative potassium (mEq/L), postoperative blood pH, postoperative base excess (mEq/L), and postoperative bicarbonate (mEq/L).

**Statistical analysis**

The meta-analysis was performed using the Comprehensive Meta-Analysis software version 3 (Biostat Inc., Englewood, NJ, USA). We calculated the standardized mean difference in continuous variables for treatment effect measurements,
while the odds ratio (OR) was calculated for discrete variables. Standard errors were calculated using a 95% confidence interval (CI), and a p-value of 0.05 was used for determining statistical significance. For consistency in analysis, a random-effects model was used irrespective of heterogeneity. Heterogeneity was evaluated using the $I^2$ statistic. Heterogeneity less than 40 was considered low, 40 to 60 moderate, and above 60 high. Continuous variables reported as medians were assumed to be equivalent to the mean, and standard deviation (SD) estimation was obtained by dividing the interquartile difference by 1.35.

**Results**

**Literature search**

A total of 3,434 articles was identified in the initial search. After removal of duplicates, we filtered 3,217 articles. The first screening excluded 3,116 articles. Full texts of 111 articles were analyzed. Twenty-eight articles were excluded as review articles and one was not available in English. Ten articles were pediatric studies. Twenty-five were not interventional studies, 18 did not have relevant interventions, five were case reports, three were protocol papers, and 11 were miscellaneous (letter to editors and addendums) (Fig. 1). We included nine randomized control trials and one retrospective cohort with a total of 726 patients. The main characteristics are provided in Table 1 [7–16].

**Risk of bias**

The results of the risk of bias are shown in Fig. 2, 3.

**Results of quantitative analysis**

The results of quantitative analysis are summarized in Fig. 4 to 6.

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**Figure 1.** PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) chart for the selection of the studies.
### Table 1. The main characteristics of Randomized controlled trials (RCTs) included

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Study type</th>
<th>Donor type</th>
<th>No. of participants</th>
<th>Exclusion</th>
<th>Intervention</th>
<th>Outcome</th>
<th>Cointervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>O’Malley et al.</td>
<td>2005</td>
<td>RCT</td>
<td>Living or deceased</td>
<td>51</td>
<td>&lt;18 yr, belief preventing the use of blood products, K &gt; 5.5 presurgery</td>
<td>RL (n = 25) vs. NSS (n = 26)</td>
<td>Serum Cr at postoperative day 3, Cr at day 7 and 6 mo, K and acid-base balance, urine output at 44 and 48 hr</td>
<td>Immunosuppression: steroids, calcineurin, and mycophenolate or sirolimus</td>
</tr>
<tr>
<td>Hadimioglu et al.</td>
<td>2008</td>
<td>RCT</td>
<td>Living</td>
<td>90</td>
<td>Severe CVD, liver failure, DM, K &gt; 5.5 presurgery</td>
<td>RL (n = 30) vs. NSS (n = 30) vs. plasmalyte (n = 30)</td>
<td>Daily urine volume, serum Cr at day 3 after surgery, blood pH, bicarbonate, and K after surgery, Cr, BUN, chloride, urinary output, and Cr clearance at days 1, 2, 3, and 7 after surgery, serum K at the end of surgery, blood pH at the end of surgery</td>
<td>Immunosuppression: steroids, calcineurin, and mycophenolate</td>
</tr>
<tr>
<td>Khajavi et al.</td>
<td>2008</td>
<td>RCT</td>
<td>Living</td>
<td>52</td>
<td>Serum K &gt; 6 presurgery</td>
<td>RL (n = 26) vs. NSS (n = 26)</td>
<td>Serum K at the end of surgery, blood pH at the end of surgery, Cr at day 3, urine output at 4 hr</td>
<td></td>
</tr>
<tr>
<td>Modi et al.</td>
<td>2012</td>
<td>RCT</td>
<td>Living</td>
<td>74</td>
<td>Severe CVD, liver failure, DM, K &gt; 5.5 presurgery</td>
<td>Intraoperative and day 1 urine output, serum Cr day 1 after surgery, change in blood pH, intra- and postoperative bicarbonate and K</td>
<td></td>
<td>Immunosuppression: steroids</td>
</tr>
<tr>
<td>Potura et al.</td>
<td>2014</td>
<td>RCT</td>
<td>Deceased</td>
<td>150</td>
<td>Age &lt; 18 yr, serum K &gt; 5.5 presurgery</td>
<td>Acetate buffered (n = 74) vs. NSS (n = 76)</td>
<td>Serum Cr, BUN, urine output on days 1, 3, 7, incidence of hyperkalemia, pH, standard BE, chloride, and K during surgery and postoperative surveillance</td>
<td>Immunosuppression: not mentioned</td>
</tr>
</tbody>
</table>

(Continued to the next page)
<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Study type</th>
<th>Donor type</th>
<th>No. of participants</th>
<th>Exclusion</th>
<th>Intervention</th>
<th>Outcome</th>
<th>Cointervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weinberg et al. [13]</td>
<td>2017</td>
<td>RCT</td>
<td>Deceased</td>
<td>49</td>
<td>Age &lt; 18 yr, serum K &gt; 6 presurgery CLD (AST/ALT &gt; 1.5× normal)</td>
<td>Plasmalyte (n = 24) vs. NSS (n = 25)</td>
<td>Hyperkalemia within 48 hr, hyperkalemia during hospital admission, treatment for hyperkalemia, the requirement for postoperative dialysis, delayed graft function, postoperative complications, and hospital length of stay</td>
<td>Immunosuppression: steroids, tacrolimus, mycophenolate, and basiliximab</td>
</tr>
<tr>
<td>Fathi et al. [14]</td>
<td>2018</td>
<td>RCT</td>
<td>Living</td>
<td>40</td>
<td>Age &lt; 18 or &gt; 70 yr, advanced CVD, pH less than 7.15, temperature &lt; 35°C and &gt; 38.5°C presurgery Cancer or using immunomodulators</td>
<td>Sodium bicarbonate (n = 20) vs. NSS (n = 20)</td>
<td>Acidosis (BE, HCO₃⁻, PCO₂, and blood pH), IL-2, IL-10, IFN -, BUN, urine volume, and Cr</td>
<td>Immunosuppression: not mentioned</td>
</tr>
<tr>
<td>Arslantas et al. [15]</td>
<td>2019</td>
<td>Retrospective cohort study design</td>
<td>Living</td>
<td>60</td>
<td>Age &lt; 17 or &gt; 67 yr</td>
<td>Balanced crystalloids (n = 30) vs. NSS (n = 30)</td>
<td>Hyperchloremia and hyperkalemia within 24 hr after surgery, serum Cr at preoperative and within 5 days after transplantation, the incidence of acute rejection episodes, graft failure, length of stay at the hospital, and mortality</td>
<td>Mannitol and furosemide</td>
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<td>Pourfakhr et al. [16]</td>
<td>2020</td>
<td>RCT</td>
<td>Deceased</td>
<td>100</td>
<td>K &gt; 5.5 presurgery, COPD, CHF (EF &lt; 30%), BE ≤ -15 mEq/L, bicarbonate ≤ 10 mEq/L, pH ≤ 7.15, CLD</td>
<td>Half saline bicarbonate (n = 50) vs. NSS (n = 50)</td>
<td>Cr at days 1, 3, 5, 7, urine output at 6 and 24 hr, BE, sodium, and chloride</td>
<td>Immunosuppression: antithymocyte, globulin infusion presurgery Radial artery catheter U Catheter</td>
</tr>
</tbody>
</table>

BE, base excess; BUN, blood urea nitrogen; CHF, congestive heart failure; CLD, chronic liver disease; COPD, chronic obstructive pulmonary disease; Cr, serum creatinine (mg/dL); CV, central venous; CVD, cardiovascular disease; CVP, central venous pressure; DM, diabetes mellitus; ECG, electrocardiography; EF, ejection fraction; IFN, interferon; IJ, internal jugular (vein); IL, interleukin; IV, intravenous; K, serum potassium (mEq/L); LFT, liver function test; NSS, normal saline solution; RL, Ringer’s lactate.
Delayed graft function

Five studies reported the incidence of delayed graft function. The difference in delayed graft function between the two groups was not statistically significant, with an OR of 0.98 (95% CI, 0.56–1.69; \(p = 0.93, I^2 = 0\)).

Day 3 creatinine

Serum creatinine measured at day three after surgery was reported in seven studies and was not statistically significant, with a standardized mean difference of \(-0.14\) (95% CI, \(-0.46\) to \(0.18\); \(p = 0.38, I^2 = 71.525\)).

Postoperative potassium

Postoperative potassium was reported in six studies and was significantly lower in the low-chloride group, with a standardized mean difference of \(-0.38\) (95% CI, \(-0.66\) to \(-0.11\); \(p = 0.007, I^2 = 48.809\)).

Postoperative chloride

Seven studies reported postoperative chloride and showed significantly lower level in the low-chloride group, with a standardized mean difference of \(-2.41\) (95% CI, \(-3.34\) to \(-1.48\); \(p < 0.001, I^2 = 95.296\)).

Postoperative bicarbonate

Five studies reported postoperative bicarbonate and significantly higher bicarbonate in the low-chloride group, with a standardized mean difference of \(0.71\) (95% CI, 0.34–1.08; \(p < 0.001, I^2 = 62.591\)).
Day 7 urine output

The mean difference of urine output at day 7 after surgery was not statistically significant, with a standardized mean difference of \(-0.08\) (95% CI, \(-0.29\) to \(0.12\); \(p = 0.43\), \(I^2 = 0\)).

Postoperative blood pH

Four studies reported postoperative blood pH and showed a statistically higher blood pH in the low-chloride group, with a standardized mean difference of 0.84 (95% CI, 0.23–1.46; \(p = 0.007\), \(I^2 = 82.146\)).

Figure 4. Results of the risk of biases in the included studies. Quantitative results analysis for delayed graft function and day 3 creatinine. (A) Delayed graft function. (B) Day 3 serum creatinine (mg/dL). CI, confidence interval; NSS, normal saline solution; RL, Ringer’s lactate; PL, plasmalyte.
Figure 5. Quantitative results analysis for postoperative potassium, postoperative bicarbonate, and postoperative chloride. (A) Postoperative potassium (mEq/L). (B) Postoperative bicarbonate (mEq/L). (C) Postoperative chloride (mEq/L). CI, confidence interval; NSS, normal saline solution; RL, Ringer’s lactate; PL, plasmalyte.
Figure 6. Quantitative results analysis for day 7 urine output, postoperative blood pH, and postoperative base excess. (A) Day 7 urine output (L). (B) Postoperative blood pH. (C) Postoperative base excess.
CI, confidence interval; NSS, normal saline solution; RL, Ringer's lactate; PL, plasmalyte.
Subgroup analysis

We performed subgroup analysis for delayed graft function, day 3 creatinine, and postoperative potassium level in studies that only included living donors.

The OR for delayed graft function remained not statistically significant (0.83; 95% CI, 0.24–2.90; p = 0.77). Similarly, the OR of day three creatinine was not statistically significant with a random-effects model (−0.21; 95% CI, −0.62 to 0.20). The OR for postoperative potassium level remained significantly lower in the low-chloride group (−0.44; 95% CI, −0.76 to −0.13; p = 0.006).

Summary of results

Low-chloride solutions were associated with lower chloride and potassium levels, less negative base excess, and higher blood pH postoperatively without significant difference in postoperative delayed graft function, day 3 creatinine, or urine output at day 7.

Discussion

Intraoperative fluid management during kidney transplants has been a topic of discussion for the past decade. Transplant physicians have extensively debated the fluid of choice based on composition, like chloride or potassium concentration, blood pH, and tonicity. Since low-chloride solutions (like lactated Ringer’s) have a higher concentration of potassium that can theoretically cause hyperkalemia, NSS is considered the fluid of choice during renal transplant [7]. Nevertheless, due to its high chloride concentration, NSS can cause hyperchloremic metabolic acidosis, leading to compensatory hyperkalemia in patients during the initial posttransplant period [8,17]. Several trials have exhibited hyperchloremia with adverse outcomes in kidney transplant patients [18–20].

It is postulated that supraphysiologic level of chloride releases thromboxane and augmented responses to renal vasoconstrictors [21]. Furthermore, increased chloride delivery to the macula densa leads to tubuloglomerular feedback resulting in afferent arteriolar vasoconstriction, mesangial contractions, and decreased glomerular filtration rate [22].

The debate about ideal fluid during kidney transplants continues. Colloids usually are not used because they are associated with several adverse effects, including renal failure [23,24]. Our study looked for factors like delayed graft function or clinically significant hyperkalemia in patients who received NSS versus low-chloride solutions. The last study performed on choice of fluids during renal transplant is the Cochrane review published in 2016, with 6 RCTs and 477 participants [6]. A previous meta-analysis included four RCTs with a total of 267 participants (n = 267) [25]. Since 2016, there have been three more RCTs, necessitating inclusion of these studies to increase population size and unmask any missed differences. Our study included nine RCTs and one retrospective cohort study with a total of 276 total participants (n = 276).

Our study shows that low-chloride solutions are better than NSS when transfused during renal transplant. We noticed increased risk of hyperchloremia and base deficit (both of which lead to metabolic acidosis) with NSS. The high chloride leads to loss of bicarbonate and ultimately acidosis. Potassium acts as a buffer to acidosis, resulting in hyperkalemia.

In terms of acid-base balance, the blood pH was significantly lower in the NSS group (OR, 0.84; 95% CI, 0.23–1.46; p = 0.007, I² = 82.146). The low-chloride solution group showed increased postoperative serum bicarbonate and blood pH levels. A new significant finding compared to previous meta-analyses like Trujillo-Zea et al. [25] and the Cochrane review [6] is postoperative hyperkalemia (mean difference, −0.38; 95% CI, −0.66 to −0.11; p = 0.007, I² = 48.809) in the NSS group when analyzed under a random-effects model. The postoperative potassium was higher in the NSS group in all studies except for O’Malley et al. [7], likely because the baseline potassium level was higher in the low-chloride group (4.5 ± 0.5 compared to 4.2 ± 0.7 in the NSS group).

For the patients receiving treatment for acidosis after transplantation, the trend seemed inclined toward NSS in all the studies except Weinberg et al. Overall, the difference was not statistically significant likely due to the small number of patients.

We observed high heterogeneity in postoperative blood pH, chloride, bicarbonate, and base excess. The heterogeneity can be attributed to concurrent interventions such as in Fathi et al. [14] where all the patients were given 50 mL/kg of normal saline. For example, when Fathi et al. [14] was excluded from the analysis for pH, the standardized mean difference increased to 1.14 (95% CI, 0.85–1.42), reducing I².
to 7.524. Similarly, the bicarbonate standardized mean difference increased to 0.85 (95% CI, 0.56–1.14), reducing $I^2$ to 29.683. Additionally, a variable amount of fluid administration in the pre- and postoperative periods also added to the study heterogeneity.

There was no significant difference in delayed graft function, creatinine at day three, or urine output on postoperative day 7, and heterogeneity was small. This finding is important because, in the past, use of low-chloride solutions like Ringer’s lactate has been discouraged due to risk of postoperative hyperkalemia and renal injury. In this study, there was no difference in postoperative urine output, blood urea nitrogen, or creatinine levels with fluid use, indicating that low-chloride solutions are as safe as if not better than NSS during kidney transplant surgery.

The study’s major strengths include a larger patient population analyzed than earlier reviews and comprehensive analysis of multiple parameters. This study revealed a significant finding in contrast to previous meta-analyses like Trujillo-Zea et al. [25] and the Cochrane review [6]. Postoperative hyperkalemia (standardized mean difference, –0.38; 95% CI, –0.66 to –0.11; $p = 0.007$, $I^2 = 48.809$) was seen in the NSS group when analyzed under a random-effects model.

Being a meta-analysis, this study remains a retrospective chart review and creates the possibility for biases. Smaller numbers of trials and people enrolled lead to publication bias. The difference in composition of low-chloride solutions creates potential bias. Although there is a difference in chloride concentration in these solutions among studies, they have less chloride than NSS. We excluded colloid fluids produced in normal saline as they have the same chloride content as NSS (e.g., hydroxyethyl starches in normal saline) to minimize the bias. However, we aimed to prove that using these fluids with lower-chloride solution than NSS would reduce the risk of hyperchloremia to result in less hyperkalemia and acidosis, as seen in the results. Another significant limitation is the different follow-up times at which the readings were obtained. We attempted to tackle this by choosing readings closest to each other in timing to minimize the bias in the results.

Overall, we made our best effort to search for all published studies, randomize them, and complete data extraction and analysis. These trials are based on intraoperative use of fluids. Transplant patients undergo a large amount of intravenous fluid infusion at 48 to 72 hours after surgery. Postoperative values for creatinine, potassium, bicarbonate, and pH vary with type of fluid used during this postoperative period, and further studies are needed to take this into account.

In conclusion, low-chloride solutions are a safe alternative to NSSs in renal transplant patients, and their use is associated with lower potassium, chloride, and higher pH postoperatively. They could be the fluids of choice in patients with high risk of hyperkalemia and acidosis during surgery.

**Conflicts of interest**

All authors have no conflicts of interest to declare.

**Authors’ contributions**

Investigation: SS, Abdullah Jahangir, MRKN, FSS, MYA, Ahmad Jahangir
Data curation: Abdullah Jahangir, EJE
Writing—original draft: SS, Abdullah Jahangir, MRKN, FSS, MYA, Ahmad Jahangir
Writing—review & editing: Abdullah Jahangir, EJE
All authors read and approved the final manuscript.

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Ahmad Jahangir, https://orcid.org/0000-0002-7758-3318
Elie J El-Charabaty, https://orcid.org/0000-0003-4989-6023

**References**


17. Prough DS, Bidani A. Hyperchloremic metabolic acidosis is a predictable consequence of intraoperative infusion of 0.9% saline. *Anesthesiology* 1999;90:1247-1249.


Coronavirus disease 2019 (COVID-19) has affected the transplantation community worldwide. Reports of transplant patients acquiring COVID-19 infections are extensive with diverse mortality rates [1]. Follow-up studies of COVID-19 in transplant communities are lacking. There are limited data on the association of the BK polyomavirus (BKPyV) with active COVID-19 infection in kidney transplant recipients (KTRs) [2,3]. Currently, theoretical concerns exist related to graft dysfunction or loss during the post-COVID-19 follow-up period in KTRs. This study aimed to explore the clinical profile, outcomes, and follow-up experiences of KTR patients who developed BKPyV after COVID-19. This was a single-center retrospective analysis of a study approved by our Institutional Ethical Board (ECR/143/Inst/GJ/2013/RR-19 with application No: EC/App/20Jan21/08) and was conducted in compliance with the Declaration of Helsinki. KTR patients admitted for COVID-19 infection during the study period from June 2020 to December 2020 who developed BKPyV after a positive COVID-19 diagnosis were included. We conducted extended and close monitoring and follow-up of the cohort in the physical, clinical, and psychological domains. Follow-up BKPyV testing was conducted at 1-month after discharge, followed by every 3 months thereafter. Testing also was performed in cases of increasing creatinine.

We identified 11 cases of BKPyV after infection in 167 total COVID-19 KTR cases. Table 1 shows the overall summary of the study. The median age of the cohort was 45 years (range, 29–56 years), with male predominance (90.9%). The majority of the cohort had comorbidities (72.7%), underwent live-related-donor transplantation (72.7%), and received thymoglobulin (81.8%) upon admission for COVID-19. The baseline median serum creatinine was 1.44 mg/dL (range, 1.3–1.9 mg/dL). COVID-19 severity was categorized as mild (9%), moderate (45%), and severe cases (46%) [4]. Acute kidney injury was reported in all cases, and acute respiratory distress syndrome developed in 18.2% of KTR patients, with one fatality during COVID-19 admission. Five cases (45.5%) received steroids during acute COVID-19 infection. At baseline, no cases showed BKPyV in the blood. Baseline polymerase chain reaction (PCR) urine testing of the cohort
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<td>26</td>
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<td>5</td>
<td>66</td>
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<td>ATG</td>
<td>ATG</td>
<td>IL-2</td>
<td>ATG</td>
<td>ATG</td>
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<td>1.2</td>
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<td>Moderate</td>
<td>Yes</td>
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<td>Moderate</td>
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<td>Severe</td>
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<td>9</td>
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<td>10</td>
<td>9</td>
<td>8</td>
<td>8</td>
<td>7</td>
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did not detect BKPyV in most cases (81.8%). Table 2 shows the laboratory parameters of the cohort. The median BKPyV blood and urine PCR results during acute COVID-19 infection were 2,509 copies/mL (range, 280–41,746 copies/mL) and 4,433,366 copies/mL (range, 7,602–198,681,183 copies/mL), respectively.

The follow-up period after BKPyV diagnosis was 7 months (range, 5–8 months). BKPyV was detected in the blood during the follow-up period in only one patient. The BKPyV PCR urine values of the cohort were less than those detected in 63.6% of the follow-up cases. No graft loss or graft dysfunction was reported in the cohort. No patient developed sensitization, urine microhematuria, or proteinuria during the follow-up period. Radiological resolution of COVID-19 infection was defined as the absence of any chest radiographic abnormality potentially related to the infection; this type of resolution was seen in 91.6% of KTR cases and resolved after a median of 3 months of follow-up. No multisystemic sequelae were reported. One case was readmitted 1 week after discharge and died due to secondary fungal infection (aspergillosis) after 1 month.

Our report could simply indicate that the natural history and course of BKPyV happened to coincide with COVID-19 infection, and there might be no actual association between the two; however, reactivation of viruses like BKPyV is a high-risk factor for graft loss in transplant patients. BKPyV causes complex changes in immunity and weakens the immune response, which could potentially aggravate the immune/graft injury often present in COVID-19 infection. Elevated levels of inflammatory cytokines in COVID-19 infection can lead to greater transcription of the BKPyV genome. The use of thymoglobulin as an induction agent could have been a confounding factor for BKPyV, but the institutional protocol of using a low dosage of thymoglobulin (1.5 mg/kg) hinders this connection. Moreover, at our center, the incidence of BKPyV in COVID-19 patients was 6.6% (11 of 167 patients), which was higher than the rate reported in normal follow-up or in non-COVID-19 admissions (1.3%). While we were unable to show a definite association of BKPyV with COVID-19 infection, the use of steroids to treat these patients and COVID-19 infection itself are both risk factors for an increase in number of BKPyV in KTRs. Therefore, we suggest screening for BKPyV in COVID-19 patients.

One limitation of this study was its small sample size. To date, this is the largest cohort of KTRs with BKPyV after

Table 2.

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<td>Acute COVID-19 Urine</td>
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<tr>
<td>Follow-up COVID-19 Blood</td>
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<td>Follow-up COVID-19 Urine</td>
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Outcome and follow-up

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</thead>
<tbody>
<tr>
<td>Outcome and follow-up</td>
<td>Uneventful</td>
<td>Uneventful</td>
<td>Uneventful</td>
<td>Uneventful</td>
<td>Uneventful</td>
<td>Uneventful</td>
<td>Uneventful</td>
<td>Uneventful</td>
<td>Died at day 14</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

AKI, acute kidney injury; ATG, thymoglobulin; AZA, azathioprine; BCT, BK polyomavirus; CNI, calcineurin inhibitors; CMV, cytomegalovirus; CGN, chronic glomerulonephritis; COVID-19, coronavirus disease 2019; DM, diabetes mellitus; F, female; HD, hemodialysis; HTN, hypertension; IL-2, interleukin 2 blocker; M, male; MMF, mycophenolate mofetil; NA, not available; ND, not detected; O, other supportive therapy; R, remdesivir; S, steroid; SARS-CoV2, severe acute respiratory syndrome coronavirus 2; Tac, tacrolimus; TB, tuberculosis.

Body mass index value > 30 kg/m² was defined as obesity.
COVID-19 infection.

In summary, we report BKPyV following COVID-19 with no graft loss during the follow-up period. We suggest screening for BKPyV in all renal transplant patients with active COVID-19 infection (especially in patients with a history of BKPyV and in severe COVID-19 infection) as a safe option to avoid complications.

Conflicts of interest

All authors have no conflicts of interest to declare.

Authors’ contributions

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

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References


Table 2. Laboratory and inflammatory markers in the cohort at admission due to COVID-19 infectio

<table>
<thead>
<tr>
<th>Laboratory parameter (normal range)</th>
<th>Case No.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Hemoglobin (13–16 g/dL)</td>
<td>10.6</td>
</tr>
<tr>
<td>Total leukocyte count (4–11 × 10³ cells/L)</td>
<td>3,280</td>
</tr>
<tr>
<td>Polymorphs (60%–70%)</td>
<td>71</td>
</tr>
<tr>
<td>Lymphocyte (25%–33%)</td>
<td>26</td>
</tr>
<tr>
<td>Platelet counts (150–400 × 10³ cells/L)</td>
<td>441</td>
</tr>
<tr>
<td>D-dimer (200–500 ng/mL)</td>
<td>3,360</td>
</tr>
<tr>
<td>Procalcitonin (&lt;0.5 ng/mL)</td>
<td>0.05</td>
</tr>
<tr>
<td>Highly sensitive C protein (0–10 mg/L)</td>
<td>29</td>
</tr>
<tr>
<td>Aspartate transferase (0–40 IU/L)</td>
<td>59</td>
</tr>
<tr>
<td>Interleukin 6 (&lt;7 pg/mL)</td>
<td>8.2</td>
</tr>
<tr>
<td>Lactate dehydrogenase (100–190 IU/L)</td>
<td>387</td>
</tr>
<tr>
<td>Ferritin (13–400 ng/mL)</td>
<td>69.0</td>
</tr>
<tr>
<td>Serum albumin (3.2–5.0 g/dL)</td>
<td>3.7</td>
</tr>
<tr>
<td>Blood urea nitrogen (13–45 mg/dL)</td>
<td>44</td>
</tr>
</tbody>
</table>

COVID-19, coronavirus disease 2019; NA, not available.


A COVID-19 outbreak in Korean hemodialysis units

Coronavirus disease 2019 (COVID-19) has spread rapidly and resulted in nearly 2 billion confirmed cases and more than 4 million deaths worldwide. Accordingly, 198,345 confirmed cases and 2,095 deaths had occurred in Korea, by July 2021. Since we have experience coping with Middle East respiratory syndrome \[^1,2\] and have developed infection control guidelines for hemodialysis (HD) units \[^3\], the Korean Society of Nephrology (KSN) established a COVID-19 Task Force Team (COVID-19 TFT) when the first case of COVID-19 was confirmed in Korea. As a result, the number of infections in HD units did not increase significantly. Through July 2021, 298 confirmed patients from 147 HD units were diagnosed with COVID-19, including 266 patients with end-stage renal disease (ESRD) and 27 healthcare workers (Fig. 1).

The role of the COVID-19 TFT during the outbreak

The role of our COVID-19 TFT includes (1) development of and updates to COVID-19 clinical practice guidelines for HD units, (2) distribution of medical resources such as manpower, equipment, and facilities throughout the nephrology network, (3) policy proposal to government authorities, and (4) establishment of an international cooperative network to cope with the COVID-19 pandemic.

The COVID-19 TFT developed the first draft of clinical practice guidelines for preventing secondary transmission of COVID-19 in HD units \[^4\]. The first draft of these clinical practice guidelines was published on January 31, 2020, far before the first HD case was confirmed. There have been several updates since the first draft was published, and the sixth edition of the clinical practice guidelines currently is used in Korean HD facilities. During the COVID-19 outbreak...
in the Daegu and Gyeongbuk provinces from February to March 2020, 11 HD patients and seven healthcare workers in 11 dialysis units were infected with COVID-19. However, with strict adherence to the COVID-19 clinical practice guidelines and implementation of cohort isolation, the secondary transmission rate was only 0.66% [5].

Another role of our COVID-19 TFT is to distribute medical resources among outbreak regions and to prevent medical burnout in HD units. The COVID-19 TFT helped the government to designate hospitals able to offer HD treatment in isolation. When a confirmed case developed in one HD unit, the COVID-19 TFT contacted the associated hospital through an online chatroom and communicated with the central headquarters to transfer the confirmed case immediately. In addition, when there was a shortage of doctors and nurses to care for the patients, the COVID-19 TFT sent a letter to the members of the KSN to volunteer for isolation care. When the nephrologist position became vacant at the Good Samaritan Bagae Hospital, the first designated private hospital, KSN members volunteered to treat COVID-19-positive, dialysis-dependent patients. To prevent medical burnout, the COVID-19 TFT suggested a de-isolation strategy to return recovered patients to the original HD unit at the proper time (Table 1).

Third, our COVID-19 TFT was responsible for proposing adequate policies to the government. The team requested that the government authority restrict the movement of patients during the outbreak, provide transportation for self-quarantined patients, and supplement adequate personal protective equipment necessary for quarantine dialysis. The COVID-19 TFT also requested timely COVID-19 testing for suspected patients currently receiving HD so as not to delay their essential HD treatment. We also asked the government to reimburse COVID-19-affected hospitals for the additional workload, such as additional shifts, cohort isolation care, and overtime work. Finally, our team requested that the government prioritize vaccine distribution for patients with ESRD and posted the COVID-19 vaccine recommendations in reference to the COVID-19 vaccine statement from the United States [6,7]. As a result, our patients received COVID-19 vaccines earlier than other populations.

As of July 2021, 40,489 patients (61.4%) with ESRD were vaccinated fully. This metric is comparable to those of nursing homes (72.6%) and medical practitioners (66.4%); the over-
all vaccination rate is 13.9% [8].

Finally, the COVID-19 TFT shared our experience with COVID-19 among other countries. Since we have successfully controlled the transmission of COVID-19 without closing any HD units, renal communities in other countries have contacted us to learn our methods to prevent further transmission of COVID-19. Through online webinars, we have shared our experiences for preventing further infections in HD units and the importance of establishing a joint committee to deal with outbreaks.

**Future challenges**

Although patients who receive in-center HD are at higher risk of acquiring COVID-19, it is impossible to lockdown the HD unit because such treatment is essential for patient survival. Therefore, continuation of uninterrupted dialysis services while adhering to infection prevention guidelines is critical. Along with KSN members, the COVID-19 TFT will make every effort to protect our HD patients and medical staff from the threat of COVID-19.

**Conflicts of interest**

All authors have no conflicts of interest to declare.

**Acknowledgments**

We would like to thank the medical staff at the designated hospitals who cared for positive and suspected COVID-19 patients and performed quarantine dialysis. In addition, we appreciate the doctors and nurses who endured overtime work during the 2 weeks of cohort isolation. Thanks to the dedication of each member of the Korean Society of Nephrology, viral transmission within hemodialysis facilities was minimized. We believe that we will overcome this crisis because we are united in the fight against this viral disease.

**Authors’ contributions**

Conceptualization, Funding acquisition: HCP, YKL
Data curation: JHC, SNK
Methodology: SHL, DKK
Writing–original draft: HCP
Writing–review & editing: YKL, CWY
All authors read and approved the final manuscript.

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**References**


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**Table 1. Our de-isolation strategy for COVID-19-positive patients**

<table>
<thead>
<tr>
<th></th>
<th>Clinical criteria</th>
<th>Testing criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Symptomatic patients</strong></td>
<td>Anyone with a fever should take fever reducers and show improvements in clinical symptoms for at least 24 hours at 10 days after onset.</td>
<td>Anyone with a fever must take fever reducers and show improvements in clinical symptoms. The person should also test negative on two PCR tests with an at least 24-hour interval in between.</td>
</tr>
<tr>
<td><strong>Asymptomatic patients</strong></td>
<td>A person should not exhibit any clinical symptoms for 10 days upon confirmation.</td>
<td>A person should test negative on two PCR tests with an at least 24-hour interval in between.</td>
</tr>
</tbody>
</table>

COVID-19, coronavirus disease 2019; PCR, polymerase chain reaction.

The patients can be de-isolated and transferred back to their hemodialysis units without proof of negative PCR testing upon discharge.

*De-isolate if the patients meet either the clinical or testing criteria.*


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Please ensure that the following submission documents are also included, where applicable:

1. A cover letter. It must include your name, address, telephone and fax numbers, e-mail address, and state that all authors have contributed to the paper and have never submitted the manuscript, in whole or in part, to other journals.
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6. The terms sex (when reporting biological factors) and gender (identity, psychosocial or cultural factors) should be correctly used. The sex and/or gender of study participants, the sex of animals or cells should be reported, and the methods used to determine sex and gender should be described. If the study was done involving an exclusive population, for example in one sex, authors should justify why, except in obvious cases (e.g., ovarian cancer).
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9. Articles should be written in English (using American English spelling) and meet the following basic criteria: the material is original; the information is important; the writing is clear, concise and grammatically correct; the study methods are appropriate; the data are valid; and the conclusions are reasonable and supported by the data. The articles should be readable to native English users, and we recommend using professional language editing service (e.g., American Journal Experts) prior to submission to avoid delays with the review processes.
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These are expected to present major advances and important
new research results. Section headings should include Abstract, Introduction, Methods, Results, Discussion, Conflicts of interest, Acknowledgments (if applicable), and References. The text should be limited to 4,000 words (excluding tables, figures and references) and 40 references.

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These describe new developments of significance in the field of nephrology and highlight unresolved questions and future directions. Most reviews are solicited by the editors, but unsolicited submissions may also be considered for publication. Review articles should include Abstract, Introduction, brief main headings, and References. The text should be limited to 5,000 words (excluding tables, figures and references) and 100 references.

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Correspondence generally takes one of the following forms: (1) Reader’s comment on an article previously published in KRCP and/or a reply from the authors; (2) An article that may not fit to the format of original or review article but suggest creative perspectives for medical issues; (3) A brief report of any kind that presents important research findings adequate for the journal’s scope and of particular interest to the readers. The submitted manuscript includes title page, main text, conflict of interest, acknowledgments (if applicable) and references. No abstract is included, and the text should be limited to 800 words (excluding tables, figures and references) and 8 references. A maximum of 2 figures or tables may be included.

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These present classic or unique images of common medical conditions in clinical nephrology. Images are an important part of much of what we do and learn in clinical practice. The text should be limited to 400 words. There should be no more than two figures. No tables or references are included.

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The title page should include article title, each author’s first and last names, positions (associate professor, fellow, student, etc.), and ORCID identifiers, and the institutions with which they are affiliated, short running title not exceeding 50 characters, separate word count for abstract and text, and details of the corresponding author (name, address, phone, and e-mail information). Funding sources should be included, and the individual contribution of each co-author must also be detailed (see relevant section 4.3 below).

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Abstract should not exceed 250 words in original, review or special articles. It must be written for easy reading with no abbreviations. The abstract of the original article should be divided into four subsections: Background, Methods, Results, and Conclusion. Four to six keywords should be listed alphabetically below the abstract. For selecting keywords, refer to the Index Medicus Medical Subject Headings (available from: http://www.ncbi.nlm.nih.gov/mesh).

3.3. Main Text
The text for original articles, for example, should include the following sections: Introduction, Methods, Results, and Discussion. The Introduction should be as concise as possible, without subheadings. The Methods section should be sufficiently detailed. Subheadings may be used to organize the Results and Discussion. Each section should begin on a new page.

3.4. Acknowledgments
General acknowledgments for consultations, statistical analysis and so on should be listed after main body of text, before the References section, including the names of the individuals involved. All financial and material support for the research
and the work should be stated here clearly and explicitly.

3.5. References

References should be cited with Arabic numerals in square brackets. References are numbered consecutively in order of appearance in text. References are limited to those cited in text and listed in numerical order. List all authors if there are less than or equal to six authors. List the first three authors followed by “et al” if there are more than six authors. If an article has been published online but has not yet been given an issue or pages, the digital object identifier (DOI) should be supplied. Journal titles should be abbreviated in the style used in Index Medicus. Other types of references not described below should follow The NLM Style Guide for Authors, Editors, and Publishers (https://locatorplus.gov/cgi-bin/Pwebrecon.cgi?DB=local&v1=1&ti=1,1&Search_Arg=1013184411&Search_Code=0359&CNT=1&SID=1). The authors may format the citations and references using the KRCP EndNote style file, but we generally recommend the authors to type the citation numbers and references manually.

Journal articles:

Online publication but not yet in print:

Entire Book:

Book chapter:

Website:

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Tables are numbered consecutively using Arabic numerals in the order of their citation in text. Table titles should be short and descriptive (e.g. Table 1. Demographic characteristics of patients). If numerical measurements are given, the unit of measurement should be included in the column heading. The statistical significance of observed differences in the data should be indicated by the appropriate statistical analysis. All nonstandard abbreviations should be defined in footnotes. Lower case letters in superscripts (\(a, b, c\)) should be used for special remarks.

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For human or animal experimental investigations, appropriate institutional review board or ethics committee approval is required. Such approval and the approval number should be stated in the Methods section of the manuscript. For those investigators who do not have formal ethics review committees, the principles outlined in the Declaration of Helsinki as revised in 2013 should be followed (World Medical Association. Declaration of Helsinki: Ethical principles for medical research involving human subjects. Available at: https:/ /www.wma.net/policiespost/ wma-declaration-of-helsinki-ethical-principles-for-medicalresearch-involving-human-subjects/). For all relevant clinical transplant articles, KRCP requires authors state in the Methods section their adherence to the Declaration of Istanbul (Available at: http:/ /www.declarationofistanbul.org/). Copies of written informed consent and Institutional Review Board (IRB) approval for clinical research should be kept. If necessary, the editor or reviewers may request copies of these documents to resolve questions about IRB approval and study conduct.

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Keep in mind the following:
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• Any descriptive text should be at least 12 pt font size.
• The visual abstract should be saved as an editable PowerPoint file as staff will add the article DOI and may edit the text for clarity.

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USD 500 (rest of world)

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

DOSEAGE AND ADMINISTRATION
• Adult patients

Initial dose
The usual dose of NESP in adult patients is 20 µg, to be administered as a single intravenous injection once weekly.

Bolus dose at the switching from erythropoietin preparations: See Precautions related to Dosage and Administration

Maintenance dose
When correction of anemia is achieved, the usual dose of NESP in adult patients is 15-40 µg as darbepoetin alfa (pentavalent recombinant), to be administered as a single intravenous injection once weekly. If a correction of anemia is maintained by once weekly injection, the frequency of administration can be changed to once every four weeks. In this case, the usual dose in adult patients is 80-180 µg administered as a single intravenous injection once every four weeks. In all cases, the dose should be adjusted in case of the degree of anemia symptoms and the patients age, and should not exceed 180 µg as a single injection. The target of anemia correction is around 11 g/l of hemoglobin level.

Precautions related to Dosage and Administration

1. Initial dose at the switching from an erythropoietin preparation.
When NESP is started substitution for an erythropoietin preparation, the dose and the frequency of administration should be determined based on the dose of the erythropoietin preparation that has been used. See the table (package insert).

1) Patients who have been treated with an erythropoietin preparation twice weekly or three times weekly: Calculated the total dose of the erythropoietin preparation administered during the week before the switching, and then determine the initial dose of NESP according to the table below. The treatment should be started on once weekly basis.
2) Patients who have been treated with an erythropoietin preparation once weekly or once every two weeks: Calculate the total dose of the erythropoietin preparation administered during the two weeks before the switching, and then determine the initial dose of NESP according to the table below. The treatment should be started on once every two weeks basis. See the chart below.

2. Dose adjustment
If dose adjustment is required (e.g., when the increase in the hemoglobin concentration of the hemodialysis patients is not achieved in correction phase, or when the hemoglobin concentration of the hemodialysis patients deviates from the target range for successive two weeks in maintenance phase), the dose should be increased or decreased according to the table below. Any dose increase should be performed stepwise in principle.

PRECAUTIONS
See the package insert.

STORAGE
Store in a lightproof container at 2-8℃ and avoid freezing.

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

MANUFACTURED BY:
Takeda Pharmaceutical Co., Ltd.
1042-22 Nakanohi-cho, Takamatsu-shi, Kagawa, Japan

Kyowa Hakko Kirin Co., Ltd.
1001-Higashi-0machi, Tamashiki-ku, Kumagaya, Japan

IMPORTED BY:
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TEL: 03-3477-4031 FAX: 03-3477-4032
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크레메진 세럼

It exists because CKD in a long life requires a long treatment

It exists because We want to provide a prolonged stability of Hemoglobin levels along the long treatment

It exists because we believe that a prolonged stability will overcome the long treatment and give longer hope to your longer life

MIRCERA exists because we believe in the power of longer stability

A long-lasting changes caused by long-acting effects including Non–dialysis CKD, PD, and HD

Purple Effect MIRCERA

Reference:

MIRCERA
methoxy polyethylene glycol–epoetin beta

Preclinical and clinical data on the novel drug MIRCERA® indicate a distinct mode of action with a potential for improved efficacy, increased safety, and reduced side effects compared to other EPO-based products. MIRCERA® is a long-acting recombinant human erythropoietin (rhEPO) that is covalently linked to a 30-kDa methoxy polyethylene glycol (mPEG) polymer. This unique structure results in a drug that is administered once a week, offering patients improved convenience and enhanced quality of life. MIRCERA® is designed to provide a more sustained and stable hemoglobin (Hb) response compared to traditional EPO therapies.

MIRCERA® is indicated for the treatment of anemia in patients with chronic kidney disease (CKD) stages 2-5, including dialysis-dependent patients. It is also indicated for the treatment of anemia in patients with chemotherapy-induced myelosuppression. By providing a more consistent and predictable Hb response, MIRCERA® offers patients and healthcare providers a new approach to managing anemia in these settings.

The long-acting nature of MIRCERA® is achieved through the covalent linkage of rhEPO to mPEG, which results in a drug that circulates in the bloodstream for an extended period, allowing for once-weekly dosing. This design eliminates the need for frequent injections, simplifies patient management, and may reduce the risk of injection-related complications.

MIRCERA® is made available in a pre-filled syringe, which enhances convenience and patient compliance. The syringe is designed to be used with an auto-injector, making it easy for patients to administer the medication at home without the need for clinic visits.

In summary, MIRCERA® represents a significant advancement in the treatment of anemia, offering patients improved efficacy, increased safety, and enhanced convenience. With its long-acting properties, it promises to revolutionize the management of anemia in patients with CKD and chemotherapy-induced anemia, setting a new standard for care in these challenging conditions.
pain, malaise, oedema peripheral, pyrexia, blood urea increased, blood creatinine increased, fall. (3) Rare(≥1/10,000, <1/1,000): hyperkalaemia, hyponatraemia, mood disturbances, sleep disorder, somnolence, syncope, palpitations, tachycardia, ... reactions, pemphigoid, hyperhydrosis, eczema, arthralgia, myalgia, renal insufficiency, erectile dysfunction, chest...
Symptomatic hypotension is seen rarely in uncomplicated hypertensive patients and is more likely to occur in patients who require rapid and significant reductions in blood pressure. In patients at increased risk of symptomatic hypotension, initiation of therapy and dose adjustment should be performed with care. In the elderly, initial dosage should be reduced to 2.5 mg/day.

**Undesirable Effects**

Hypersensitivity/Angioedema: Angioedema of the face, extremities, lips, mucous membranes, tongue, glottis and/or larynx may occur. This effect may be fatal. Patients should be instructed to discontinue the drug if angioedema occurs and to contact a physician immediately.

Asymptomatic hyperkalaemia, hyponatraemia, mood disturbances, sleep disorder, somnolence, syncope, palpitations, tachycardia, peripheral oedema, chest pain, anaphylactic reactions, pemphigoid, hyperhydrosis, eczema, arthralgia, myalgia, renal insufficiency, erectile dysfunction, chest discomfort, Raynaud's phenomenon. Syndrome of inappropriate antidiuretic hormone secretion (SIADH) can be considered as a very rare but possible complication associated with ACE inhibitor therapy.

**Interactions**

ACE inhibitors may increase the levels and effects of angiotensin II, a potent vasoconstrictor, in patients taking nonsteroidal anti-inflammatory drugs (NSAIDs), including aspirin ≥ 3 g/day. The concomitant use of NSAIDs with ACE inhibitors may lead to increased risk for adverse effects on the kidneys and gastrointestinal tract. If NSAIDs are co-administered with ACE inhibitors, renal function should be carefully monitored.

**Contraindications**

Aortic and mitral valve stenosis/hypertrophic cardiomyopathy: use with caution. Renal impairment: use with caution in patients with creatinine clearance ≤ 30 ml/min. Patients with primary hyperaldosteronism (not responding to drugs acting through inhibition of the renin-angiotensin system) should not be treated with ACE inhibitors.

**Precautions**

Special care: Antidiabetic agents (insulins, oral hypoglycaemic agents), Baclofen, Non-potassium sparing diuretics, NSAIDs including aspirin ≥ 3 g/day. (5)

**For Patients with Renal Insufficiency**

In patients with renal insufficiency, the initial dose should be reduced to 2.5 mg/day.

**Dosage and Administration**

- Stable Coronary Artery Disease

  10 mg once daily, depending on renal function and whether the 5 mg dose is well tolerated. - Elderly: 2.5 mg once daily, depending on renal function and whether the 5 mg dose is well tolerated. - Renal impairment: Clcr ≥ 60 ml/min: 5 mg/day; 30 < Clcr < 60 ml/min: 2.5 mg/day; 15 < Clcr < 30 ml/min: 1.25 mg/day, under medical and laboratory supervision.

- Congestive Heart Failure

  10 mg once daily, depending on renal function and whether the 5 mg dose is well tolerated. - Elderly: 2.5 mg once daily, depending on renal function and whether the 5 mg dose is well tolerated. - Renal impairment: Clcr ≥ 60 ml/min: 5 mg/day; 30 < Clcr < 60 ml/min: 2.5 mg/day; 15 < Clcr < 30 ml/min: 1.25 mg/day, under medical and laboratory supervision.

- Hypertension

  10 mg once daily, depending on renal function and whether the 5 mg dose is well tolerated. - Elderly: 2.5 mg once daily, depending on renal function and whether the 5 mg dose is well tolerated. - Renal impairment: Clcr ≥ 60 ml/min: 5 mg/day; 30 < Clcr < 60 ml/min: 2.5 mg/day; 15 < Clcr < 30 ml/min: 1.25 mg/day, under medical and laboratory supervision.

- Heart Failure

  10 mg once daily, depending on renal function and whether the 5 mg dose is well tolerated. - Elderly: 2.5 mg once daily, depending on renal function and whether the 5 mg dose is well tolerated. - Renal impairment: Clcr ≥ 60 ml/min: 5 mg/day; 30 < Clcr < 60 ml/min: 2.5 mg/day; 15 < Clcr < 30 ml/min: 1.25 mg/day, under medical and laboratory supervision.

**Special Populations**

- Pregnancy

  Perindopril should not be used in pregnancy. If the ACE inhibitor is required in pregnancy, it may be continued if the benefit outweighs the risk. Patients should be instructed to contact a physician if pregnancy is suspected or likely.

- Breastfeeding

  Patients should be instructed to discontinue the drug if pregnancy is confirmed. If the drug is required during breastfeeding, the benefit to the mother should outweigh the risk to the infant.

- Children

  Perindopril is not recommended for use in children under the age of 16 years.

- Elderly

  Perindopril is not recommended for use in the elderly. The efficacy and safety of perindopril in the elderly have not been established.

- Renal impairment

  Perindopril is not recommended for use in patients with creatinine clearance ≤ 30 ml/min. The efficacy and safety of perindopril in patients with creatinine clearance ≤ 30 ml/min have not been established.

- Hepatic impairment

  Perindopril is not recommended for use in patients with hepatic impairment. The efficacy and safety of perindopril in patients with hepatic impairment have not been established.

- Systemic lupus erythematosus

  Perindopril is not recommended for use in patients with systemic lupus erythematosus. The efficacy and safety of perindopril in patients with systemic lupus erythematosus have not been established.

- Collagen vascular disease

  Perindopril is not recommended for use in patients with collagen vascular disease. The efficacy and safety of perindopril in patients with collagen vascular disease have not been established.

- Pregnancy

  Perindopril should not be used in pregnancy. If the ACE inhibitor is required in pregnancy, it may be continued if the benefit outweighs the risk. Patients should be instructed to contact a physician if pregnancy is suspected or likely.

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  Patients should be instructed to discontinue the drug if pregnancy is confirmed. If the drug is required during breastfeeding, the benefit to the mother should outweigh the risk to the infant.

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  Perindopril is not recommended for use in children under the age of 16 years.

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- Renal impairment

  Perindopril is not recommended for use in patients with creatinine clearance ≤ 30 ml/min. The efficacy and safety of perindopril in patients with creatinine clearance ≤ 30 ml/min have not been established.

- Hepatic impairment

  Perindopril is not recommended for use in patients with hepatic impairment. The efficacy and safety of perindopril in patients with hepatic impairment have not been established.

- Systemic lupus erythematosus

  Perindopril is not recommended for use in patients with systemic lupus erythematosus. The efficacy and safety of perindopril in patients with systemic lupus erythematosus have not been established.

- Collagen vascular disease

  Perindopril is not recommended for use in patients with collagen vascular disease. The efficacy and safety of perindopril in patients with collagen vascular disease have not been established.

- Special Populations

  Perindopril is not recommended for use in patients with special populations. The efficacy and safety of perindopril in patients with special populations have not been established.

- Special Considerations

  Perindopril is not recommended for use in patients with special considerations. The efficacy and safety of perindopril in patients with special considerations have not been established.

- Drug Interactions

  ACE inhibitors may increase the levels and effects of angiotensin II, a potent vasoconstrictor, in patients taking nonsteroidal anti-inflammatory drugs (NSAIDs), including aspirin ≥ 3 g/day. The concomitant use of NSAIDs with ACE inhibitors may lead to increased risk for adverse effects on the kidneys and gastrointestinal tract. If NSAIDs are co-administered with ACE inhibitors, renal function should be carefully monitored.

- Contraindications

  Aortic and mitral valve stenosis/hypertrophic cardiomyopathy: use with caution. Renal impairment: use with caution in patients with creatinine clearance ≤ 30 ml/min. Patients with primary hyperaldosteronism (not responding to drugs acting through inhibition of the renin-angiotensin system) should not be treated with ACE inhibitors.

- Precautions

  Special care: Antidiabetic agents (insulins, oral hypoglycaemic agents), Baclofen, Non-potassium sparing diuretics, NSAIDs including aspirin ≥ 3 g/day. (5)
is an anticoagulant during extracorporeal blood circulation in patients with bleeding complications or bleeding tendency.\textsuperscript{1}

- Due to its short half life (5~8 min), its anticoagulant activity is almost limited to extracorporeal circuit.\textsuperscript{2,3,4}
- Increase of bleeding risk was not noted in HD patients with bleeding risk.\textsuperscript{5,6,7}
- The filter-life is significantly prolonged during CRRT.\textsuperscript{8,9,10}

**Summary of Prescribing Information**\textsuperscript{1}

- **PRODUCT NAME IN KOREA**
  - Futhan for Inj. (nafamostat mesilate)
  - Futhan50 for Inj. (nafamostat mesilate)

- **INGREDIENT**
  - Futhan for Inj.: 1 vial contains 10mg of nafamostat mesilate
  - Futhan50 for Inj.: 1 vial contains 50mg of nafamostat mesilate

- **INDICATION AND USAGE**
  1. For improvement of acute symptoms of pancreatitis (acute pancreatitis, acute exacerbation of chronic pancreatitis, acute postoperative pancreatitis, ERCP-induced acute pancreatitis, traumatic pancreatitis) - Futhan for Inj.
  2. Disseminated intravascular coagulation (DIC)
  3. To prevent coagulation of blood during extracorporeal blood circulation (ex. hemodialysis, plasmapheresis) in patients with bleeding complications or bleeding tendency.

- **DOSAGE AND ADMINISTRATION**
  3. To prevent coagulation of blood during extracorporeal blood circulation (ex. hemodialysis, plasmapheresis) in patients with bleeding complications or bleeding tendency. For priming, wash and fill the blood route with 20mg of nafamostat mesilate dissolved in 500mL of saline after dissolving in the small amount of 5% glucose solution or water for injection. After beginning of extracorporeal circulation, inject continuously at a rate of 20~50mg/hr as nafamostat mesilate dissolved in 5% glucose solution into anticoagulant injection line. The dosage should be appropriately adjusted according to the patient’s symptoms. The average dosage from clinical study is 35mg/hr as nafamostat mesilate.

- **Manufactured by** Yuhan corporation. **Distributed by** SK chemicals

**References**

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We devote for continuous product development and service improvement.

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Boryung Renal Business Unit provides **TOTAL RENAL CARE**
Patients with aHUS can be at continuous risk of the life-threatening consequences of unpredictable complement-mediated TMA.\(^1,2\)

Chronic, uncontrolled complement activity in aHUS leads to ongoing endothelial injury, organ damage, and sudden death.\(^3\)

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PRESCRIBING INFORMATION: (Before prescribing please consult the full Summary of Product Characteristics (SmPC).) Presentations: Chewable tablets containing 500 mg, 750 mg of lanthanum (as lanthanum carbonate hydrate). Oral powder containing 1000 mg of lanthanum (as lanthanum carbonate hydrate). Both the chewable tablets and oral powder contain electrolytes, containing glucose. Usage: Fosrenol is indicated in adult patients as a phosphate binding agent for use in the control of hyperphosphataemia in chronic renal failure patients on haemodialysis or continuous ambulatory peritoneal dialysis (CAPD). Fosrenol is also indicated in adult patients with chronic kidney disease not on dialysis with serum phosphate levels >5.5 mg/dL in whom a low phosphate diet alone is insufficient to control serum phosphate levels. Dosage and Administration: For and use: Adults, including older people (≥65 years): Fosrenol should be taken with or immediately after food, with the daily dose divided between meals. The tablets must be chewed completely and not swallowed whole. To aid with chewing the tablets may be crushed. Fosrenol and powder is intended to be mixed with a small quantity of soft food (e.g. applesauce or a little similar food product) and consumed immediately (within 15 minutes). The dose of Fosrenol should be titrated over 3-5 weeks until an acceptable serum phosphate level is reached. Control of serum phosphate levels has been demonstrated at doses starting from 750mg per day. The maximum daily dose reached, in a limited number of patients, is 8750mg. Patients who respond to lanthanum therapy usually achieve acceptable serum phosphate levels at doses of 1000-3000mg lanthanum per day. Pediatric population (≥18 years): The safety and efficacy of Fosrenol in children and adolescents has not been established; use in children and adolescents is not recommended. Hepatic impairment: The effect of hepatic impairment on Fosrenol pharmacokinetics has not been assessed. Due to its mechanism of action and the lack of liver metabolism, doses in hepatic impairment should not be modified, but patients should be monitored carefully. Adverse Effects: Very common: Gastrointestinal: nausea, abdominal pain, diarrhea, nausea, vomiting, allergic skin reactions. Common: 6% to <1% patients: constipation, dyspepsia, flatulence, hypocalcaemia. Consult SmPC in relation to less common side effects. Data of Revisions: March 2018.

For further information, please refer to the brand prescribing information at www.jwpharma.co.kr or http://fcosd.wb.co.kr

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Takeda
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Monitoring the dialysis dose continuously and in real-time

Only those who are aware of the nature of the path are able to reach their destination safely and quickly.

Adimea® stands for Accurate Dialysis Measurement (precise measurement of the dialysis conditions). This real-time measurement system is able to determine the Kt/V precisely in any given dialysis treatment scenario.

The measuring principle of this innovative system from B. Braun is simple: a UV light sensor installed in the dialysate drain of the Dialog+ machine measures the absorption of light and thus changes in the concentration of uremic substances as they drain off. This means that insufficient dosages are identified immediately.

The advantages are obvious: the user is able to adjust relevant parameters during treatment so as to model the Kt/V, meaning efficient and optimized dialysis treatment is guaranteed for the patient at all times and without any detours. That's for sure.
OPTIMIZE TROUGH LEVEL
START LIFE-LONG JOURNEY\textsuperscript{1,2}

\textsuperscript{1} Prograf (data on file, 2020.05.14).
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The high flux dialyzer with best removal performance among our wet-type product range for all patient groups.

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Improved design for ideal dialysate flow
Effective removal of small toxins and low molecule weight proteins
Superior biocompatibility

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Slow ADPKD. Preserve Hope.
Introducing Samsca — The first and only treatment proven to slow cyst progression

Samsca® Tablet ADPKD product information summary [INDICATION] To slow the progression of cyst development and renal insufficiency of autosomal dominant polycystic kidney disease (ADPKD) in adults with CKD stage 1 ~ 4 at initiation of treatment with evidence of rapidly progressing disease. [DOSAGE & ADMINISTRATION] Tolvaptan must only be prescribed by physicians who got registered in Risk Management Program to the patients who have agreed and signed on conditions specified in Risk Management Program. Patient should follow this program. And, to mitigate the risk of significant and/or irreversible liver injury, blood testing for hepatic transaminases and bilirubin is required prior to initiation of SAMSCA, continuing monthly for 18 months and at regular 3 monthly intervals thereafter. The initial dose is 60 mg toleraptan per day as a split-dose regimen of 45 mg + 15 mg (45 mg taken upon waking and prior the morning meal and 15 mg taken 8 hours later). The initial dose is to be titrated upward to a split-dose regimen of 90 mg toleraptan (60 mg + 30 mg) per day and then to a target split-dose regimen of 120 mg toleraptan (90 mg + 30 mg) per day, if tolerated, with at least weekly intervals between titrations. Dose titration has to be performed cautiously to ensure that high doses are not poorly tolerated through overly rapid up-titration. Patients may down-titrate to lower doses based on tolerability. Patients have to be maintained on the highest tolerable toleraptan dose. x Samsca® Tablet has an indication for hyponatremia as well. For further information, please refer to the latest prescribing information at www.otsuka.co.kr.
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