Application of C5 inhibitors in glomerular diseases in 2021

Mayo imaging classification is a good predictor of rapid progress among Korean patients with autosomal dominant polycystic kidney disease: results from the KNOW-CKD study

Efficacy and safety of rapid intermittent bolus compared with slow continuous infusion in patients with severe hypernatremia (SALSA II trial): a study protocol for a randomized controlled trial

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

Parathyroidectomy versus cinacalcet in the treatment of tertiary hyperparathyroidism after kidney transplantation: a retrospective study

Ambulatory blood pressure trajectories and blood pressure variability in kidney transplant recipients: a comparative study against chronic kidney disease 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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The image on the front cover: Lee et al reported the recommendations on controversial issues in diagnosis and management of hyponatremia from Korean Society of Nephrology. They recommended the management of hyponatremia according to the symptom and severity of hyponatremia. Please see the text for more details (pp. 393–411).
Autosomal dominant polycystic kidney disease (ADPKD) is the most common inherited cystic kidney disease, characterized by the development of renal cysts and a variety of extrarenal manifestations [1]. It was a disease that was accepted as a fate even if dialysis treatment was started at a relatively young age. Currently, the treatment goal of ADPKD is not to accept it as a fate, but to delay the time of kidney failure as much as possible through active renal protection.

In 2006, CRISP (Consortium for Radiologic Imaging Studies of Polycystic Kidney Disease) investigators reported that kidney function decreased as the volume of the kidney increased [2]. Based on evidence that vasopressin antagonists could inhibit the progression of kidney volume, tolvaptan has been tested in clinical trials in ADPKD. In the TEMPO (Tolvaptan Efficacy and Safety in Management of ADPKD and Its Outcomes) 3:4 trial, tolvaptan decreased kidney growth by about 49% and slowed the rate of decline in kidney function by about 1.2 mL/min per year [3]. In 2017, the U.S. Food and Drug Administration (FDA) approved the total kidney volume (TKV) as a biomarker of disease progression in ADPKD. In 2018, the U.S. FDA approved tolvaptan as the first drug treatment to slow kidney function decline in adult ADPKD patients who are at risk of rapidly progressive disease.

With the development of disease-modifying drugs for ADPKD, rapid and reliable tools are needed to identify patients who will benefit from an effective therapy. Irazabal et al. [4] have developed a predictive tool that uses the age-adjusted TKV as represented by the Mayo Imaging Classification (MIC). The MIC allows clinicians to estimate each patient's unique rate of kidney growth and also to identify patients with rapidly progressive disease who are likely to benefit from effective therapy [4]. In clinical practice, nephrologists can estimate the TKV growth rate and prognosis of patients by using only one TKV measurement and age. It is commonly used in stratifying and finding rapid progressors with ADPKD in Korean clinics. However, two questions have been raised in the clinical application of MIC findings in Korean ADPKD patients. One is whether the MIC, whose cohort consists mostly of Caucasians, is applicable to Koreans. The second question is whether it is better to apply the Higashihara equation which has...
shown stable results of the height-adjusted TKV (HtTKV) – estimated annual growth rate (% per year, termed eHT-KV-α), is calculated by the equation $[\text{HtTKV at age } t] = K \left(1 + \alpha/100\right)^{t-A}$ over years, instead of the original MIC. In this issue of *Kidney Research and Clinical Practice*, Park et al. [5] validated the MIC for predicting the renal outcome among a Korean ADPKD prospective cohort and evaluated the clinical parameters associated with rapid disease progression. A comparison of Irazabal’s original equation from the MIC (A = 0 and K = 150) and a modified equation from the Higashihara group (A = 0 and K = 130) [6] showed that while the Higashihara equation showed more stable prediction ability over the years, the change in the MIC at an individual level did not differ between the original and modified equations. However, the Higashihara MIC tended to overestimate MIC subclasses compared to the original MIC in this study. Therefore, people classified as slow progressors by the original MIC might actually now be considered rapid progressors. Moreover, the Higashihara equation did not predict the renal outcome according to the MIC. Being a rapid progressor as defined by the original MIC was an independent predictor of the renal outcome (doubling of serum creatinine, 50% decline of estimated glomerular filtration rate (eGFR), initiation of renal replacement therapy, hazard ratio of 4.086) together with the presence of macroalbuminuria and the baseline eGFR. Rapid progressors as defined by the original MIC also demonstrated a greater annual percent change of HtTKVs (mHTKV-α) and a greater annual decline rate of the eGFR (mGFR-α) compared to slow progressors. If the eHTKV-α is stable in untreated patients, then any change in the eHTKV-α from baseline can be used to estimate individual treatment effects on the HtTKV. The Higashihara equation, which shows a more stable eHTKV-α, might be useful for estimating treatment effects. However, it could not be used for predicting renal outcomes or the mHTKV-α of Korean ADPKD patients in this study.

Another characteristic of Korean ADPKD patients in this study was their faster enlargement of the mHTKV-α with a similar mGFR-α according to MIC classes compared with previous studies of the TEMPO 3:4 and HALT-PKD groups [3,7]. The mGFR-α was in rapid progressors (−3.58 mL/min per year in 1C, −3.7 in 1D, and −4.52 in 1E), and the mHTKV-α was in rapid progressors (5.3% per year in 1C, 9.4% in 1D, and 11.7% in 1E). Another study showed that the average age at which Koreans reach kidney failure is seven years later than that of a Caucasian population [8]. These differences are highly likely to be related to ethnicity or a genetic predisposition. There is a need to study whether

**Figure 1. Imaging techniques for measuring kidney volume to predict autosomal dominant polycystic kidney disease progression.**

TKV, total kidney volume.

<table>
<thead>
<tr>
<th>Ellipsoid method</th>
<th>Stereology</th>
<th>Planimetry</th>
<th>Automatic segmentation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Practical tool that allows nephrologist to measure TKV within minutes</td>
<td>Both methods have high accuracy and reproducibility but require trained personnel</td>
<td>A method including a deep learning-based one will be useful in future clinical practice</td>
<td></td>
</tr>
</tbody>
</table>

**Recommend for**

Young patients with borderline risk of progression (1B–1C);
TKV measurement excluding prominent exophytic renal cyst;
Determination of treatment effort based on changes in TKV

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There are differences in the clinical course or prognosis and treatment response using a large number of patients with varying ethnicities. This study showed that MIC classes could change over time in some individuals. In particular, patients whose MIC classes changed overtime were younger than those whose MIC classes were stable. Younger age is also important because it is a risk factor that is associated with rapid progression, along with male sex, high blood pressure, higher body mass index, higher serum uric acid, and lower eGFR. Although this study confirmed a strong correlation of TKV by ellipsoid with TKV by stereology, more accurate methods (such as stereology and planimetry) are needed to measure the TKV in younger patients with borderline 1B/1C classification because even a small miscalculation in the TKV might change the MIC subclass, such as between class 1B and 1C [9]. An expanded imaging classification can recalculate the TKVs by excluding prominent exophytic cysts in both class 2Ae and class 1 patients with prominent exophytic cysts, leading to improved predictions for developing chronic kidney disease (CKD) stage 3 and eGFR trajectories [10]. Volumetry using stereology and planimetry is useful for excluding prominent exophytic cysts. It is also useful for determining treatment effects based on changes in the TKV (Fig. 1).

This study showed that MIC classes could change over time in some individuals. Especially, patients whose MIC classes changed overtime were younger than those whose MIC classes were stationary. Younger age is also important because it is a risk factor along with male sex, high blood pressure, higher body mass index, higher serum uric acid, and lower eGFR associated with rapid progressors. Although this study confirmed the strong correlation of TKV by ellipsoid with TKV by stereology, more accurate volumetry (such as stereology and planimetry) are needed to measure TKV for younger patients with borderline class 1B/1C because even small miscalculation of TKV might change the subclass of MIC such as class 1B and 1C [9]. An expanded imaging classification can recalculate the TKVs by excluding prominent exophytic cysts in both class 2Ae and class 1 patients with prominent exophytic cysts, leading to improved predictions for developing CKD stage 3 and eGFR trajectories [10]. Volumetry using stereology and planimetry is useful for excluding prominent exophytic cysts. It is also useful for determining treatment effects based on changes in TKV (Fig. 1).

In summary, the original MIC can be useful for predicting renal outcomes and effectively defining rapid progressors among Korean ADPKD patients. A nephrologist can easily measure the TKV using the ellipsoid method to determine kidney volume, and the results can be applied to the MIC. More accurate volumetry (such as stereology and planimetry) should also be considered in younger patients, who are at higher risk for rapid progression.

Conflicts of interest
The author has no conflicts of interest to declare.

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9. Chebib FT, Torres VE. Assessing risk of rapid progression in

Korean Society of Nephrology 2022 Recommendations on controversial issues in diagnosis and management of hyponatremia

Yeonhee Lee1, Kyung Don Yoo2, Seon Ha Baek3, Yang Gyun Kim4, Hyo Jin Kim5, Ji Young Ryu3, Jin Hyuk Paek6, Sang Heon Suh7, Se Won Oh8, Jeonghwan Lee9, Jong Hyun Jhee10, Jin-Soon Suh11, Eun Mi Yang12, Young Ho Park13, Yae Lim Kim14, Miyoung Cho15, Kook-Hwan Oh16, Sejoong Kim17; on behalf of the Hyponatremia Guideline Development Group

For further information on the authors’ affiliations, see Additional information.

The Korean Society for Electrolyte and Blood Pressure Research, in collaboration with the Korean Society of Nephrology, has published a clinical practice guideline (CPG) document for hyponatremia treatment. The document is based on an extensive evidence-based review of the diagnosis, evaluation, and treatment of hyponatremia with the multidisciplinary participation of representative experts in hyponatremia with methodologist support for guideline development. This CPG consists of 12 recommendations (two for diagnosis, eight for treatment, and two for special situations) based on eight detailed topics and nine key questions. Each recommendation begins with statements graded by the strength of the recommendations and the quality of the evidence. Each statement is followed by rationale supporting the recommendations. The committee issued conditional recommendations in favor of rapid intermittent bolus administration of hypertonic saline in severe hyponatremia, the use of vasopressin receptor antagonists in heart failure with hypervolemic hyponatremia, and syndrome of inappropriate antidiuresis with moderate to severe hyponatremia, the individualization of desmopressin use, and strong recommendation on the administration of isotonic fluids as maintenance fluid therapy in hospitalized pediatric patients. We hope that this CPG will provide useful recommendations in practice, with the aim of providing clinical support for shared decision-making to improve patient outcomes.

Keywords: Evidence-based practice, GRADE approach, Guideline, Hyponatremia, Recommendation

Introduction

Hyponatremia, defined as serum sodium (SNa) concentration of <135 mmol/L, is the most frequent body fluid and electrolyte balance disturbance encountered in clinical practice. Although several international guidelines for
managing hyponatremia are available, the differential diagnosis of hyponatremia is frequently challenging in patients with complex clinical settings and varying treatment. To assist patients, clinicians, and other healthcare professionals with decisions about the diagnostic approach to and treatment of hyponatremia, a multidisciplinary guideline development committee representing specialists with a genuine interest in hyponatremia was convened by the Korean Society for Electrolyte and Blood Pressure Research in collaboration with the Korean Society of Nephrology clinical practice guideline (CPG) committee.

The development committee has developed the CPG and applied strict management strategies to minimize potential bias. The committee prioritized clinical questions and outcomes according to their importance for clinicians and patients. The committee used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach, including GRADE Evidence-to-Decision frameworks, to assess evidence and make recommendations. The level of evidence for each result is graded as high/moderate/low/very low. The recommendation grade was divided into four levels: strong recommendation (A), conditional recommendation (B), against recommendation (C), and inconclusive (I). Definitions of the evidence levels are shown in Table 1. The key questions that cannot be adapted or developed directly due to the limitations of existing research are expressed as expert consensus (E). In addition to a rigorous approach to methodology and evaluation, this document represents recommended approaches for multiple etiologies of hyponatremia based on both the consensus opinions of experts in hyponatremia and the most recent published data in this field. There is also a link to full-text documents and lists of the most important reports so that the readers can obtain further information (most of which is available online).

### Recommendations on diagnostic procedures

#### Classification of hyponatremia

Hyponatremia is defined by less than 135 mmol/L of SNa\[^1\]. Hyponatremia can be classified based on different parameters, including SNa concentration, timing of development, symptom severity, serum osmolality, and volume status. The criteria are described in Table 2 [1-3]. Because consistency and clarity of classification of hyponatremia are critical for diagnosis and management, we sought to compare the terminology used in the existing two guidelines (European and American guidelines) when discussing the classification of hyponatremia (Table 2).

#### Table 1. Strength of recommendations and quality of evidence

<table>
<thead>
<tr>
<th>Category/grade</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Strength of recommendation</strong></td>
<td></td>
</tr>
<tr>
<td>Strong recommendation (A)</td>
<td>Considering the benefits and risks of the treatment, the level of evidence, values and preferences, and resources, it is strongly recommended in most clinical situations.</td>
</tr>
<tr>
<td>Conditional recommendation (B)</td>
<td>The use of the treatment may vary depending on the clinical situation or patient/social value, so it is recommended to use it selectively or conditionally.</td>
</tr>
<tr>
<td>Against recommendation (C)</td>
<td>The risk of the treatment may outweigh the benefit and, taking into account the clinical situation or patient/social value, implementation is not recommended.</td>
</tr>
<tr>
<td>Inconclusive (I)</td>
<td>Considering the benefits and risks of the treatment, values and preferences, and resources, the level of evidence is too low, the scale of benefit/risk is too uncertain, or the variability is large, so the decision to implement the intervention is not made. This means that we cannot recommend or object to the use of treatment, so the decision is at the clinician’s discretion.</td>
</tr>
<tr>
<td>Expert consensus (E)</td>
<td>Although clinical evidence is insufficient, use is recommended in accordance with clinical experience and expert consensus when considering the benefits and risks of the treatment, the level of evidence, values and preferences, and resources.</td>
</tr>
<tr>
<td><strong>Quality of evidence</strong></td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>We are confident that the estimate of the effect is close to the actual effect.</td>
</tr>
<tr>
<td>Moderate</td>
<td>The estimate of the effect appears to be close to the actual effect, but may vary considerably.</td>
</tr>
<tr>
<td>Low</td>
<td>The confidence in the estimate of the effect is limited. The actual effect may differ significantly from the estimated effect.</td>
</tr>
<tr>
<td>Very low</td>
<td>There is little confidence in the estimate of the effect. The actual effect will differ significantly from the estimated effect.</td>
</tr>
</tbody>
</table>
Differential diagnosis of hyponatremia

A practical diagnostic approach can progress step by step as follows (Fig. 1) [1].

1) Step 1
Check plasma osmolality for differentiating hypoosmolar hyponatremia from other causes of hyponatremia [1,3]. When plasma osmolality is reduced, you may require further steps of differential diagnosis. When plasma osmolality is above 275 mOsm/kg and hyponatremia is present, hyperglycemia should be checked. When serum glucose levels are increased, recheck the corrected sodium level according to the correction formula.

Corrected Na level (Hillier et al. [4]) = Na + 0.024 × (serum glucose [mg/dL] – 100)

Beyond hyperglycemia, hyperproteinemia, hyperlipidemia, and the use of mannitol or radiocontrast media can be a cause of hyper- or iso-osmolar hyponatremia [1-3].

2) Step 2
When hypoosmolar hyponatremia has been confirmed, the severity of clinical hyponatremic symptoms should be evaluated [1]. We have divided symptoms of hyponatremia into ‘asymptomatic-mild,’ ‘moderate,’ and ‘severe’ categories (Table 2). Symptomatic hyponatremia should be corrected immediately with acute management [1]. If acute management has been initiated or there are no symptoms of hyponatremia, go to the next step.

3) Step 3
Check urinary osmolality and discriminate excessive water intake.

When urinary osmolality is below 100 mOsm/kg, discriminate excessive water intake and excessive intake of hypotonic food or fluid (e.g., beer, rice wine, liquid diet) [1-3].

4) Step 4
Check urinary sodium to discriminate excessive renal excretion of sodium. When urinary sodium is above 30

Table 2. Classification of hyponatremia

<table>
<thead>
<tr>
<th>Classification in the Korean Society of Nephrology clinical practice guideline</th>
<th>European guideline</th>
<th>American guideline</th>
</tr>
</thead>
<tbody>
<tr>
<td>SNa concentration</td>
<td>Mild</td>
<td>Mild</td>
</tr>
<tr>
<td></td>
<td>Moderate</td>
<td>125–129 mmol/L</td>
</tr>
<tr>
<td></td>
<td>Severe&lt;sup&gt;a&lt;/sup&gt;</td>
<td>&lt;125 mmol/L</td>
</tr>
<tr>
<td>Severity of clinical symptoms</td>
<td>Asymptomatic-mild</td>
<td>Less pronounced</td>
</tr>
<tr>
<td></td>
<td>Moderate</td>
<td>Nausea without vomiting, confusion, headache, drowsiness, general weakness, myalgia</td>
</tr>
<tr>
<td></td>
<td>Severe&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Vomiting, stupor, seizures, coma (Glasgow Coma Scale ≤ 8)</td>
</tr>
<tr>
<td>Time of development</td>
<td>Acute</td>
<td>&lt;48 hr</td>
</tr>
<tr>
<td></td>
<td>Chronic</td>
<td>≥48 hr</td>
</tr>
<tr>
<td>Serum osmolality</td>
<td>Hypotonic</td>
<td>&lt;275 mOsm/kg</td>
</tr>
<tr>
<td></td>
<td>Isotonic</td>
<td>275–295 mOsm/kg</td>
</tr>
<tr>
<td></td>
<td>Hypertonic</td>
<td>&gt;295 mOsm/kg</td>
</tr>
<tr>
<td>Clinical assessment of volume status</td>
<td>Hypovolemic, euvolemic, hypervolemic</td>
<td>No difference</td>
</tr>
</tbody>
</table>

*The term ‘severe’ is used for both classifications according to concentration and symptoms. We considered replacing ‘severe’ with a new term to avoid confusion, but no other terms seemed appropriate. According to several studies, symptoms become more common when SNa concentration drops below 125 mmol/L [3]. Therefore, the expression ‘severe’ is used interchangeably, but the type of classification is added in parentheses.

SNa, serum sodium.

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mmol/L, discriminate the cause of hyponatremia according to volume status [1,3]. When volume status is decreased, check use of diuretics and cerebral salt wasting (CSW). When volume status is normal, check adrenal insufficiency, hypothyroidism, syndrome of inappropriate antidiuresis (SIAD), and other diseases or drugs that can cause SIAD.

When urinary sodium is below 30 mmol/L, recheck volume status and discriminate the causes. When volume status is decreased, check diarrhea or vomiting. When volume status is increased, discriminate congestive heart failure, liver cirrhosis, and nephrotic syndrome.

Volume status can be assessed through history-taking and physical examination. Symptoms of decreased volume status are usually nonspecific and may include thirst, fatigue, weakness, muscle cramps, and orthostatic dizziness. On physical examination, decreased skin turgor, low jugular vein pressure, orthostatic hypotension or postural tachycardia may appear. When more body fluid is lost, findings suggestive of decreased organ perfusion due to decreased intravascular fluid (low consciousness, oliguria, and peripheral cyanosis) or compensatory mechanisms (tachycardia, tachypnea, and sweating) may appear as symptoms of shock. On laboratory findings, increased urine osmolality, decreased urine sodium (UNa), alkalosis due to decreased volume status, relatively increased hemoglobin and albumin concentration may also be seen. Symptoms of increased volume status may include dyspnea on exercise, orthopnea, and peripheral edema. After underlying causes are evaluated, take further steps for managing them [1,3].

The diagnostic criteria of SIAD are summarized in Table 3 [1,2]. In addition, fractional excretion of uric acid (FEUA) can be used for discrimination of SIAD and use of diuretics.
(Recommendation 1) [3]. Serum copeptin/UNa ratio may also be used for discrimination of volume status. However, practical applications are still limited since copeptin measurement is not widely used (Recommendation 2).

Diagnostic approaches should be performed step by step, including measuring plasma osmolality, urinary osmolality, and urinary sodium levels. Patient history and physical examination are also important to discriminate underlying causes of hyponatremia. Drug history should also be checked, as it can be associated with hyponatremia including SIAD [1].

For example, thiazide diuretics are a common cause in elderly women, and desmopressin in elderly men [5,6]. In patients with chronic pain, NSAID use should be checked. In patients with skin disorders or autoimmune diseases, adrenal insufficiency should be evaluated.

**Table 3. Diagnostic criteria for syndrome of inappropriate antidiuresis [1,2,7]**

<table>
<thead>
<tr>
<th>Essential criteria</th>
<th>Supplemental criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased effective osmolality (serum osmolality of &lt;275 mOsm/kg)</td>
<td>Serum uric acid, &lt;4 mg/dL</td>
</tr>
<tr>
<td>Urine osmolality of &gt;100 mOsm/kg at some level of serum hypoosmolality</td>
<td>Serum urea, &lt;21.6 mg/dL</td>
</tr>
<tr>
<td>Clinical euvolemia, as defined by the absence of signs of volume depletion</td>
<td>Failure to correct hyponatremia after 0.9% saline infusion</td>
</tr>
<tr>
<td>Elevated urine sodium concentration of &gt;30 mmol/L with normal dietary salt and water intake</td>
<td>Correction of hyponatremia through fluid restriction</td>
</tr>
<tr>
<td>Absence of other potential causes of euvolemic hypoosmolality: severe hypothyroidism, adrenal insufficiency</td>
<td>Fractional sodium excretion, &gt;0.5%</td>
</tr>
<tr>
<td>Normal renal function and absence of diuretic intake (especially thiazide diuretics)</td>
<td>Fractional urea excretion, &gt;55%</td>
</tr>
</tbody>
</table>
| FEUA is a supplemental diagnostic criterion for SIAD [7]; in patients using diuretics, FEUA performed best among UNa, fractional excretion of sodium (FENa), fractional urea excretion, and serum uric acid concentration (area under the curve, 0.96; 0.92–1.12) [8]. In the 2013 guideline published by the *American Journal of Medicine*, the measurement of FEUA in patients taking diuretics has been suggested to be helpful when trying to exclude hypovolemia [2]. According to the 2014 European guideline from the European Society of Endocrinology, European Society of Intensive Care Medicine, and European Renal Association European Dialysis and Transplant Association, FEUA using a threshold of >12% was most useful for distinguishing SIAD from non-SIAD-related hyponatremia in patients on diuretics with a sensitivity of 0.86 and specificity of 1.00 [1]. However, the previous guidelines had no evidence derived from high-quality randomized controlled trials (RCTs). Our literature search identified two new observational studies from 2014 when the previous guideline was published.

In an observational study of 298 patients admitted with profound hypoosmolar hyponatremia (Na of <125 mmol/L), FEUA was higher in patients with SIAD compared with other hyponatremia etiologies (p < 0.001) [9]. We identified direct evidence from five observational studies (387 patients) that interpreted FEUA and FENa in hyponatremia patients due to SIAD and on diuretics [8–12]. Of these, one study was conducted with only patients taking thiazide diuretics, and in the other four studies, the group of patients taking
thiazide or loop diuretics was not separated in our meta-analysis. A meta-analysis of studies showed that FEUA was significantly higher in SIAD patients than in patients taking diuretics. Two of five observational studies identified FEUA cutoff values of 10% and 12% (with specificity of 100% and 96%, respectively) [9,10]. Our meta-analysis found no differences in FENa. Since uric acid transporters are mostly located in the proximal tubules of the kidney, in which diuretics do not work primarily, we consider it reasonable that FEUA be used as a diagnostic test for the differential diagnosis of hyponatremia. However, caution is needed in interpreting FEUA. When patients taking diuretics were divided into thiazide and loop diuretics, SIAD-and thiazide-induced hyponatremia showed similar FEUA values in one study [10]. Furthermore, hypouricemia with increased FEUA is also observed in CSW. FEUA can be normalized after correction of hyponatremia in SIAD despite the continued increase in FEUA in CSW [13]. Lastly, concurrent use of drugs such as antihypertensives that alter uric acid excretion may affect FEUA levels [14]. Further evidence is needed to address the role of FEUA in diuretic-induced hyponatremia.

**Recommendation 2.**

There are insufficient data to make a recommendation for using copeptin to UNa ratio to assess patient volume status (I, very low).

**Remarks:**

1. Copeptin levels overlap widely in hyponatremic patients and are affected by non-osmotic stimuli.
2. The ratio of copeptin to UNa was higher in disorders with secondary arginine vasopressin (AVP) release than those with primary AVP secretion such as SIAD.

Assessment of volume status in hyponatremic patients is important, but often challenging. Since the sensitivity and specificity of traditional clinical assessment of patient volume status are low, there have been efforts to identify novel biomarkers. Plasma AVP is a promising marker for the differentiation of volume disorders from a pathophysiological perspective. However, AVP is not routinely measured in clinical practice due to its instability. Copeptin has become a surrogate maker for AVP concentration and has advantages over AVP in aspects of stability and ease of measurement. Both American and European guidelines discussed copeptin briefly [1,2]. The American (2013) and European (2014) guidelines recommend that measurement of the copeptin to UNa ratio could distinguish hypovolemic hyponatremia from SIAD and that copeptin could discriminate euvolemia from hypovolemia and hypervolemia. Both guidelines were developed based on the same observational study [15]. There were no RCTs or meta-analyses exploring the value of copeptin in patients with hyponatremia. In the present guideline, one observational study published after 2015 was added and discussed [16].

Since copeptin levels overlap widely in hyponatremic patients and are affected by nonosmotic stimuli, copeptin to UNa ratio can be useful. In a previous report of 106 German hyponatremia patients, patients were classified into five categories: 1) normal volume with excessive water intake; 2) normal volume with SIAD; 3) decreased volume due to renal sodium loss; 4) decreased or normal volume due to non-renal sodium loss; and 5) increased volume [15]. A recent study of 100 Korean hyponatremic patients also classified patients into five categories: 1) normal volume with adrenal insufficiency; 2) normal volume with SIAD; 3) decreased volume due to renal sodium loss; 4) decreased volume due to non-renal sodium loss; and 5) increased volume [16]. Both observational studies revealed that copeptin to UNa ratio was superior to copeptin level for differentiating patient volume status. The ratio of copeptin to UNa was higher in disorders with secondary AVP release (decreased effective arterial volume) than conditions with primary AVP secretion such as SIAD.

**Recommendations on treatment issues**

The first step treatment evaluation of hyponatremia is identifying clinical symptoms and duration of hyponatremia, as mentioned above [1]. Treatment can be approached step by step as follows (Fig. 2).

1) **Symptomatic acute/chronic hyponatremia**

Hypertonic saline should be administered for symptomatic hyponatremia as moderate or severe symptomatic hyponatremia reflects increased intracranial pressure. In terms of the infusion method of hypertonic saline, rapid intermittent bolus (RIB) regimens are suggested [1,2]. The treatment approach used for hypertonic saline in the American and European guidelines, and in a recent RCT performed
in Korea is as follows (Table 4) [1–3,17]. A comparison of the efficacy and safety of hypertonic saline according to infusion methods (RIB vs. slow continuous infusion [SCI]) is discussed in Recommendation 3.

**Figure 2. Algorithm for the management of hyponatremia.**
RIB, rapid intermittent bolus.

**Table 4. Approach to giving hypertonic saline and re-lowering excessive correction**

<table>
<thead>
<tr>
<th>Variable</th>
<th>American guideline [2,3]</th>
<th>European guideline [1,3]</th>
<th>SALSA trial in Korea [17]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial infusion of hypertonic saline</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Severe symptoms</td>
<td>Bolus: 100 mL over 10 min × 3 as needed</td>
<td>Bolus: 150 mL over 20 min × 2–3 as needed</td>
<td>Bolus: 2 mL/kg over 20 min × 2 as needed</td>
</tr>
<tr>
<td>Moderate symptoms</td>
<td>Continuous infusion: 0.5–2 mL/kg/hr</td>
<td>Bolus: 150 mL over 20 min once</td>
<td>Bolus: 2 mL/kg over 20 min once</td>
</tr>
<tr>
<td>Re-lowering treatment of SNa</td>
<td>5% dextrose solution 3 mL/kg/hr + desmopressin 2–4 µg IV</td>
<td>5% dextrose solution 10 mL/kg over 1 hr + desmopressin 2 µg IV</td>
<td>Continuous infusion: 0.5 m/kg/hr</td>
</tr>
</tbody>
</table>

IV, intravenous; SALSA, Efficacy and Safety of Rapid Intermittent Correction Compared With Slow Continuous Correction With Hypertonic Saline in Patients With Moderately Severe or Severe Symptomatic Severe Hyponatremia; SNa, serum sodium.
Hypertonic saline has been used to treat symptomatic severe hypotonic hyponatremia. Overcorrection from indiscriminate prolonged use of hypertonic saline may result in irreversible neurologic sequelae from ODS, whereas under-correction of hyponatremia may insufficiently improve fatal complications of cerebral edema. Therefore, appropriate correction of SNa is needed. Although the American (2013) and European (2014) guidelines recommend administering hypertonic saline in small, fixed boluses (recommendation grade: expert opinion in the American guidelines, 1D in the European guidelines), they were not based on high-quality RCT evidence [1,2,17]. In order to examine whether RIB therapy of hypertonic saline has any benefit for symptom relief, correction of SNa, complications, and prognosis compared to SCI in patients with symptomatic severe hypotonic hyponatremia, we reviewed a prospective cohort study (24 hours of follow-up after treatment) and a RCT (48 hours of follow-up after treatment) published after the European guideline (2014).

A prospective cohort study reported that the RIB group had more rapid elevation of SNa and greater improvement in the Glasgow Coma Scale (GCS) at 6/12 hours than the SCI group. However, there was no difference between the two groups in GCS improvement at 24 hours [18].

A RCT demonstrated that the RIB group had the higher increment in SNa at 1 hour, a higher proportion meeting the target correction rate (achieving SNa of 5–9 mmol/L within 24 hours and SNa of 10–17 mmol/L or ≥130 mmol/L within 48 hours) at 1 hour, lower SNa at 12 hours, and a lower incidence of re-lowering treatment (5% dextrose infusion 10 mL/kg over 1 hour and/or intravenous desmopressin 2 µg if SNa level increase is ≥10 mmol/L within the first 24 hours or ≥18 mmol/L within 48 hours) than the SCI group [17].

In both studies, the target correction rate, the degree of SNa elevation at 24 hours, and overcorrection (increase in SNa by >12 mmol/L within the first 24 hours or increase in SNa by >18 mmol/L within 48 hours) did not differ between the two groups [17,18]. ODS did not occur in either study [17,18]. Death occurred in five patients in the RCT and four patients in the prospective cohort study, with no significant difference between the two groups [17,18]. Only one RCT for hypertonic saline infusion in symptomatic severe hypotonic hyponatremia has been reported in Korea; thus, additional large-scale RCTs are needed.

In cases of severe symptomatic hyponatremia, RIB regimens of hypertonic saline should be promptly administered to increase SNa by 4 to 6 mmol/L to relieve cerebral edema, and then cause-specific treatment can be planned [1]. In cases of moderate symptomatic hyponatremia, RIB or SCI methods of hypertonic saline can be used and cause-specific treatment can be prioritized without administration of hypertonic saline [1]. We suggest checking SNa concentration 1 hour after first hypertonic saline administration, then rechecking SNa concentration every 6 hours to adjust the administration interval or infusion rate of hypertonic saline [1]. We recommend that the rate of sodium correction be reevaluated when symptoms improve or SNa concentration increases by 5 to 9 mmol/L [1,2]. If symptoms do not improve or SNa concentrations do not reach target correction, infusion of hypertonic saline may be repeated [1,2]. In patients with hypervolemic hyponatremia, hypertonic saline and loop diuretics should be administered at the same time [3].

2) Asymptomatic acute hyponatremia
The absence of moderate or severe symptoms indicates that the clinically significant brain edema has not yet developed.

Therefore, prompt diagnostic assessment of hyponatremia is suggested versus immediate infusion of hypertonic saline. Nonessential fluids and medications that can contribute to or provoke hyponatremia should be stopped. If the acute decrease in SNa concentration exceeds 10 mmol/L,
we suggest administering the same amount of hypertonic saline as in patients with moderate symptoms to prevent a further drop in SNa concentration [1].

3) Asymptomatic chronic hyponatremia
Asymptomatic chronic hyponatremia does not require prompt correction but may lead to localized neurologic impairment and increased mortality compared to normonatremia. Even patients with mild hyponatremia have a higher mortality rate compared to patients with normonatremia.

**Recommendation 4.**
We recommend rigorously evaluating the causes of mild hyponatremia and to managing causative diseases to improve clinical outcomes (E).

**Remarks:***
1. Mild hyponatremia increases the risk of mortality compared with those with normonatremia.
2. There is no clear evidence that correcting hyponatremia itself improves patient-important outcomes.
3. There are insufficient data to make a recommendation regarding treating mild hyponatremia with hypertonic saline or oral sodium chloride solely to increase SNa concentration.

In the case of mild hyponatremia, it is often unnoticed in clinical practice because it rarely presents with specific symptoms. Moreover, there is lack of evidence from RCTs that treatment of mild hyponatremia with fluid therapy or medication with the sole aim of correction to normal SNa concentration improves patient outcomes. The European guideline (2014) recommends against treatment simply to increase SNa concentration (grade of recommendation 2C). However, several observational studies have shown that mild hyponatremia increases the risk of mortality both in short-term and long-term follow-up. Waikar et al. [19] reported that hospitalized patients with mild hyponatremia defined as a SNa concentration of 130 to 134 mEq/L showed increased in-hospital mortality risk compared with those with normonatremia. Doshi et al. [20] found that hospitalized cancer patients with mild hyponatremia showed two-fold increased risk of morality compared to those with normonatremia. Furthermore, Kovesdy et al. [21] observed that mild hyponatremia defined as 130 to 135.9 mEq/L increased the risk of relatively long-term mortality (median follow-up duration, 5.5 years) in patients with chronic kidney disease with estimated glomerular filtration rate less than 60 mL/min/1.73 m². From a meta-analysis including above studies that compared the short-term (less than 90 days or in-hospital mortality) and long-term (more than 5 years mortality) mortality risk, mild hyponatremia increased both short-term (odds ratio [OR], 2.09; 95% confidence interval [CI], 1.90–2.30; p < 0.001) and long-term (OR, 1.46; 95% CI, 1.44–1.48; p < 0.001) mortality risk compared with normonatremia.

In a domestic retrospective study [22], improved SNa concentration at discharge had the strongest association with long-term mortality in acute myocardial infarction patients with hyponatremia. However, because mild hyponatremia patients were not distinguished from other study patients, and interventions such as hypertonic saline were not addressed in this study, these findings were not included in the rationale under the consensus of the Development Committee. Although there is insufficient data that the correction of mild hyponatremia with the sole aim of correcting SNa concentration has clinical benefit, it is reasonable to rigorously evaluate the causes of mild hyponatremia and to manage the diseases because mild hyponatremia increases the risk of mortality.

(1) Hypervolemic hyponatremia is commonly seen in heart failure or liver cirrhosis. Restriction of sodium and free water intake (approximately <800–1,000 mL/day) is the first-line treatment. Additional pharmacologic therapies including loop diuretics and vasopressin receptor antagonists (‘vaptans’) can be used to increase renal free water excretion [1–3]. The possibility of using vaptans in patients with heart failure or liver cirrhosis is discussed greater detail in Recommendation 5. Fluid intake should not be restricted to prevent overcorrection when using vaptans [2].

**Recommendation 5.**
1. We suggest vaptan use in heart failure with hypervolemic hyponatremia in terms of rapid sodium correction (B, moderate).
2. We make no recommendation on the use of vaptans in liver cirrhosis with hypervolemic hyponatremia (E).
Although vaptans have shown effectiveness for correcting SNAs in SIAD, heart failure, and liver cirrhosis, the U.S. Food and Drug Administration (FDA) limited the use of vaptans in liver cirrhosis in 2013 due to hepatic toxicity concerns. The European guideline recommended against treating vaptans in hypervolemic hyponatremia (grade of recommendation 1C). Therefore, we accepted the previous guideline in hyponatremia in liver cirrhosis and did not seek further evidence. We reviewed only patients with heart failure, excluding studies on liver cirrhosis patients.

Including 11 RCTs, one observational study, and two systematic reviews (SRs), the guideline found no clinical benefit to the use of vaptans in hypervolemic hyponatremia. However, the quality of the studies varied, the characteristics of enrolled patients were not similar, and most of the RCTs did not distinguish patients with hypervolemia from those with normal volume status. Also, two studies only included patients with liver cirrhosis, and three studies only enrolled patients with heart failure. Thus, it is difficult to conclude that vaptans are superior to loop diuretics. Although vaptans showed a clinical benefit compared with placebo in the two SRs, there was no comparison of vaptans with loop diuretics as a basic therapeutic agent in hypervolemic hyponatremia. Since 2015, various studies have investigated whether additional use of vaptans with loop diuretics could lead to clinical benefit in hyponatremia with heart failure. Only one study compared vaptans and loop diuretics [23], and nearly all studies sought to clarify the effectiveness of additional vaptan use on loop diuretics. Recent studies showed the efficacy of vaptans in patients with chronic kidney disease and heart failure [24,25].

Therefore, this guideline focused on the benefit of additional vaptan use with loop diuretics in hypervolemic hyponatremia with heart failure in terms of survival gain, sodium correction, and conservation of renal function. We reviewed nine RCTs [23–31], five SRs, and several observational studies. All RCTs were conducted in patients with hyponatremic heart failure prescribed tolvaptan 7.5 to 30 mg per day, and allowed furosemide intravenous or oral use. There was no survival benefit of adding tolvaptan on furosemide [23,25,26,29,31]. Renal function decline, which was defined as the increase of serum creatinine more than 0.3 mg/dL per week, was not different between the tolvaptan-added group and furosemide-alone group [23,26,27,30]. Sodium correction for 24 hours was higher when tolvaptan was added to furosemide [25–27].

2. The addition of vaptans to loop diuretics is more effective to elevate SNa concentration compared with loop diuretics alone.
3. The addition of vaptans to loop diuretics does not worsen renal function compared with loop diuretics alone.
4. The addition of vaptans to loop diuretics does not show survival benefit compared with loop diuretics alone.
5. The addition of vaptans has the potential to lead to hepatotoxicity in patients with liver cirrhosis.

**Remarks:**
1. We evaluated the efficacy of adding vaptans to loop diuretics since few studies compared vaptans versus loop diuretics in heart failure with hypervolemic hyponatremia.
2. The addition of vaptans to loop diuretics is more effective to elevate SNa concentration compared with loop diuretics alone.
3. The addition of vaptans to loop diuretics does not worsen renal function compared with loop diuretics alone.
4. The addition of vaptans to loop diuretics does not show survival benefit compared with loop diuretics alone.
5. The addition of vaptans has the potential to lead to hepatotoxicity in patients with liver cirrhosis.

**Recommendation 6.**
We suggest treatment with vaptans in SIAD patients with moderate to severe hyponatremia (B, low).
Vaptans correct hyponatremia, effectively causing urinary excretion of free water without increased sodium excretion [34]. However, the European guideline recommends against vasopressin receptor antagonists in SIAD patients without severe or moderately severe symptoms. They emphasized that the safety of vaptans should be considered. First, vaptans can lead to overcorrection of SNa concentration, especially in patients with severe hyponatremia. Second, hepatotoxicity was reported in autosomal dominant polycystic kidney disease patients on high doses of tolvaptan [1].

Previous studies focused on short-term outcomes such as normalization of SNa or overcorrection. Few studies evaluated the effect of vaptans stratified by volume status: hypervolemia or euvoelmia [35,36]. Aggravation of hyponatremia can cause severe symptoms such as poor oral intake, general weakness or altered consciousness, leading to hospitalization. Long-term outcomes were worse in patients who developed repeated symptoms of hyponatremia [19,37].

Placebo or water restriction was used as a control group for vaptans, as there were no studies comparing vaptans with loop diuretics in the previous guidelines or our literature search. Therefore, we reviewed 12 RCTs evaluating the effect of vaptans on sodium correction, survival or complications compared with water restriction or placebo [3,38–48]. All RCTs included euvolemic hyponatremia patients: three included only euvolemic hyponatremia, nine included euvolemic or hypervolemia patients. In our meta-analysis, vaptans effectively normalized SNa in euvolemic hyponatremia. Vaptans did not decrease mortality in euvolemic hyponatremia. Although data on complications of vaptans are insufficient, vaptans did not increase the risk of overcorrection of hyponatremia compared with water restriction or placebo. There were few data regarding hepatotoxicity in euvolemic hyponatremia. In conclusion, vaptans can effectively normalize SNa concentration without increased risk of overcorrection or death.

The evidence was low quality and grade (B) in this recommendation because the included participants were not clearly defined as having SIAD, but instead as hyposmolar hyponatremia with euvoelmia or hypervolemia in the included RCTs. However, most euvolemic hyponatremia is SIAD and the diagnostic criteria for SIAD are not clearly defined [49]. Experts agreed that most of included participants might have SIAD. Therefore, we suggest using vaptans in SIAD patients with moderate to severe hyponatremia.

3) In patients with hypovolemic hyponatremia, restoring extracellular fluid volume with intravenous isotonic fluid (0.9% saline) or balanced crystalloid will suppress vasopressin secretion causing electrolyte-free water excretion to increase [1–3]. After a 0.5 to 1.0 L infusion of isotonic fluid or balanced crystalloid, hyponatremia will begin to be corrected without signs of volume overload in patients with hypovolemic hyponatremia [2].

4) Overcorrection and re-lowering treatment of serum sodium

Target correction is achieving a SNa increase of 5 to 9 mmol/L/10 to 17 mmol/L within the first 24/48 hours or reaching a SNa of 130 mmol/L [1]. SNa concentration should not be corrected by ≥10 mmol/L per day, with a more stringent limit of >8 mmol/L per day for patients at high risk of ODS (SNa concentration of ≤105 mmol/L, hypokalemia, alcoholism, malnutrition, and advanced liver disease) [2]. Overcorrection (defined as an increase in the SNa level by >12/18 mmol/L within 24/48 hours) may result in ODS [1–3]. ODS has no specific treatment and has a poor prognosis. Therefore, caution is required when correcting hyponatremia [1]. We recommend discontinuing ongoing treatment and prompt intervention to re-lower SNa concentration based on electrolyte-free water (5% dextrose solutions) and/or desmopressin if overcorrection occurs (Table 4) [1–3]. Desmopressin use as a re-lowering treatment for SNa is discussed in Recommendation 7. Diuresis as a result of antagonizing vasopressin-mediated free water retention by volume repletion or discontinuing hyponatremia induc-
ing medications often occurs when correcting hyponatremia and is a common reason for overcorrection. Therefore, urine output should be monitored during treatment.

**Recommendation 7.**

We suggest that desmopressin should be applied individually according to risk factors affecting overcorrection, hypertonic saline therapeutic regimen, and whether to administer dextrose solution during overcorrection in patients with hyponatremia (B, very low).

**Remarks:**
1. There is no evidence that administration of desmopressin as a proactive or reactive strategy is effective for preventing overcorrection.
2. Administration of desmopressin in patients with hyponatremia has the potential to increase the incidence of ODS compared to no administration, but drawing a valid conclusion is difficult due to the low level of evidence.
3. Administration of desmopressin for the prevention of overcorrection in hyponatremic patients has the potential to improve survival compared to non-administration, but drawing a valid conclusion is difficult due to the low level of evidence.

Desmopressin is an antidiuretic hormone that binds to the V2 receptor in the collecting duct and increases the expression of aquaporin channels to increase water reabsorption of urine passing through the collecting duct. A number of studies found that administration of desmopressin can prevent rapid correction of hyponatremia or stabilize SNa correction rate through water reabsorption if it has already been rapidly corrected. The European guideline recommended that 2 µg of intravenous desmopressin be given at intervals of 8 hours or more to prevent rapid correction (grade of recommendation 1D). In addition, they also recommend injecting 10 mL/kg of electrolyte-free water (dextrose solution) for 1 hour in consideration of urine volume and fluid balance (grade of recommendation 1D). However, there have been no prospective studies on this recommendation. In two retrospective observational studies cited in the guidelines, SNa concentration was corrected using desmopressin or electrolyte-free water to the target of 12 mmol/L within 24 hours and less than 18 mmol/L within 48 hours when overcorrection occurred [51]. However, the quality of the studies included in the guidelines varied, the criteria for classification of hyponatremia among the study subjects varied, and there was no comparative study in which patients not using desmopressin were included as a control group. Eighty patients using desmopressin were classified into three strategies in one SR of desmopressin use for hyponatremia in 2015 [52]. The proactive strategy was based on initial SNa concentration, with desmopressin administered before concentration changes of SNa. In the reactive strategy, desmopressin was administered according to an increase in the concentration of SNa or urine output. In the rescue strategy, desmopressin was administrated to re-lower SNa concentration in case of overcorrection. However, final conclusions could not be drawn on the optimal strategy for administration of desmopressin for hyponatremia due to limitations of the study design and sample size.

In this guideline, we evaluated one SR study and three observational studies on whether the administration of desmopressin for hyponatremia has additional benefit in the prevention of overcorrection, complications (ODS), and prognosis (survival to discharge) compared to the non-administered group [50,52-54]. As a result of our analysis, overcorrection prevention did not differ significantly when comparing the group with and without use of desmopressin (proactive and reactive strategies). When the desmopressin use group and the non-desmopressin group were compared, including proactive, reactive, and rescue therapy, the incidence of ODS was higher in the group using desmopressin, but ODS occurred in only one or two cases, and there was a possibility of selection bias. When comparing the survival to discharge of the groups administered and not administered desmopressin (proactive, reactive and rescue strategies), survival rate was significantly higher in the desmopressin use group. However, a larger sample size and prospective studies are needed to determine the optimal strategy for desmopressin administration in hyponatremia.
5) Special situations 1. Treatment of hyponatremia in patients with brain lesions

**Recommendation 8.**
We consider it reasonable that treatment with hypertonic or isotonic saline infusion, oral sodium chloride, or fludrocortisone for the correction of hypoosmolar hyponatremia should be individualized among patients with cerebral diseases (E).

**Remarks:**
1. The causes of hypoosmolar hyponatremia among patients with cerebral diseases are diverse, and include SIAD, CSW, and insufficient cortisol secretion.
2. There is insufficient evidence that hypoosmolar hyponatremia in patients with cerebral diseases can be effectively corrected with a crystalloid solution, including normal saline.

Hyponatremia occurs very frequently in patients with various cerebral diseases such as traumatic brain injury, intracranial or subarachnoid hemorrhage, brain tumor, brain surgery, cerebral infarction, and meningitis. The incidence of hyponatremia in traumatic brain injury patients has been reported to be 27% to 51% [55,56], 40% to 45% in cerebral infarction patients [57], 14% to 63% in subarachnoid hemorrhage [57,58], and 15% to 20% of brain tumor patients [59]. Various factors such as SIAD, CSW, and insufficient secretion of cortisol are major causes of hyponatremia in cerebral diseases. The most common cause of hyponatremia in patients with cerebral disease is SIAD, accounting for approximately 62%, and volume deficit or CSW accounted for about 30% [59].

Concomitant hyponatremia in patients with cerebral disease is closely related to the deterioration of patient condition. Therefore, appropriate treatment depending on the cause of hyponatremia is highly recommended [2]. However, in a clinical setting, it is not easy to accurately determine the cause based on patient volume status and it may require several hours or days to complete diagnostic tests and evaluations to determine the cause. Therefore, the CPG Committee sought to suggest appropriate treatment guidelines for hypoosmolar hyponatremia in patients with various cerebral diseases. We searched Ovid MEDLINE, Embase, Cochrane Library, and KMbase, and found a total of 72 research papers through additional manual searches. We selected 66 documents excluding duplicates and reviewed 13 original texts. We could not find any documents that suitably addressed this key question. Therefore, an expert consensus was made by organizing the results of related research with the existing CPGs.

The American guideline suggested that in the case of hyponatremia in patients with cerebral disease, treatment such as normal saline, oral salt supplementation, hypertonic saline, and fludrocortisone may be considered [2]. In general, treatment guidelines recommend water restriction or hypertonic saline depending on the severity of hyponatremia in SIAD. In addition, volume depletion is common in patients with various cerebral diseases [60]. In particular, volume deficit (body fluid deficiency) accompanying CSW can result in hyponatremia. The occurrence of cerebral infarction and other neurological complications increases when water restriction is implemented in patients with cerebral disease [61,62]. Therefore, in the case of hyponatremia accompanying these cerebral diseases, clinicians should avoid volume depletion through water restriction [63].

Hyponatremia accompanied by neurological symptoms related to hyponatremia can be corrected through hypertonic saline to prevent the progression of neurological complications. However, it should be treated cautiously by controlling the rate of correction to avoid overcorrection in accordance with the general principles of hyponatremia correction rate. Asymptomatic hypoosmolar hyponatremia occurring in patients with cerebral diseases can be initially corrected by preferentially using isotonic crystalloid solution including normal saline, unless volume depletion is clearly excluded by clinical judgment. In the case of asymptomatic hypoosmolar hyponatremia that does not improve despite administering isotonic crystalloid solution such as normal saline, evaluation and tests for differential diagnosis may be performed, and concomitant salt supplementation such as hypertonic saline or oral salt may be considered. In the case of CSW, hyponatremia can be corrected with a mineralocorticoid such as fludrocortisone. Hasan et al. [64] demonstrated the effectiveness of fludrocortisone treatment for the prevention of renal salt excretion and volume status decrease in 91 patients with subarachnoid hemorrhage, which is commonly accompanied by CSW, through a RCT. Misra et al. [65] conducted a RCT on 38 hyponatremic patients with tuberculous meningitis due to CSW and showed that fludrocortisone treat-
ment can correct hyponatremia earlier than normal saline. Further evidence is needed for specific recommendations in hyponatremia patients with cerebral diseases.

6) Special situations 2. Selection of maintenance fluid to prevent hyponatremia in children aged ≤18 years

**Recommendation 9.**

1. To prevent hyponatremia, we recommend the administration of isotonic fluids as maintenance fluid therapy in hospitalized pediatric patients over 1 month and under 18 years of age (A, high).
2. There are insufficient data to make a recommendation regarding administering isotonic fluids as maintenance fluid therapy to prevent hyponatremia in neonates because of the risk of hypernatremia (I, moderate).

**Remarks:**

1. In maintenance fluid therapy for children and adolescents over 1 month and under 18 years of age, the administration of isotonic fluid is effective for preventing the development of hyponatremia and has similar risk of hypernatremia compared to the administration of hypotonic fluids.
2. In maintenance fluid therapy for neonates less than 1 month old, the administration of isotonic fluid is effective for preventing the development of hyponatremia and leads to a higher risk of developing hypernatremia compared to the administration of hypotonic fluids.

Traditionally, hypotonic solutions based on the Holliday-Segar formula have been used as maintenance fluids in hospitalized pediatric patients under the age of 18 years. However, the development of hyponatremia associated with hypotonic solution administration and related neurologic complications and death have been continuously reported. In addition, children are more likely to develop severe symptoms associated with hyponatremia because the brain is relatively large compared to the skull in children. Consequently, there has been controversy over the composition of optimal maintenance fluid. In 2018, the American Academy of Pediatrics recommended an isotonic solution as a maintenance fluid for pediatric patients over 1 month old by integrating evidence from 17 RCTs and seven SRs (grade of recommendation 1A) [66]. In the 2020 revised NICE (National Institute for Health and Care Excellence) guidelines, isotonic solutions were recommended as maintenance fluids in children, including term neonates 8 days of age or older [67]. However, RCT studies have shown inconsistent results.

In this guideline, we performed a meta-analysis by synthesizing 18 RCTs (16 RCTs for children over 1 month and two RCTs for newborns) [68–85] and seven SRs [86–88]. We sought to examine whether the administration of isotonic fluid compared to hypotonic fluids reduced the incidence of hyponatremia without increasing the risk of hypernatremia during maintenance fluid therapy in pediatric patients including newborns. In 18 RCTs, normal saline or Ringer’s lactate solution as an isotonic solution and 0.20% to 0.45% saline as a hypotonic solution were administered to hospitalized pediatric patients. In most studies, 5% dextrose solution was added to the maintenance fluid. A total of 3,231 patients were included in 16 RCT studies of children 1 month and older, including patients who were hospitalized for surgery or were admitted to the intensive care unit, and those who were hospitalized for pneumonia or central nervous system infection. Of these, isotonic solutions were used in 1,608 patients and hypotonic solutions were used in 1,623 patients as maintenance fluid. The incidence of hyponatremia in patients using isotonic solution as maintenance treatment was significantly lower than in the group using hypotonic solution as maintenance treatment (OR, 0.32; 95% CI, 0.24–0.43; p < 0.001). Although hypernatremia was increased in patients administered isotonic solutions in some studies [68–71,74,78], there was no significant difference in a meta-analysis between isotonic fluid and hypotonic fluid (OR, 1.67; 95% CI, 0.92–3.04; p = 0.09). In two non-RCTs, the incidence of hyponatremia had a tendency to be low in patients administered isotonic fluids; however, this was not statistically significant (OR, 0.54; 95% CI, 0.28–1.02; p = 0.05), and the incidence of hypernatremia in patients receiving isotonic fluids was not significantly different from that in patients receiving hypotonic fluids (OR, 1.25; 95% CI, 0.73–2.13; p = 0.58). Two RCTs enrolled a total of 144 neonates, including premature babies aged 34 weeks or older and full-term neonates. Of these, 73 patients received isotonic fluid and 71 received 0.15% to 0.20% hypotonic fluid. These studies reported a significantly lower incidence of hyponatremia in patients receiving isotonic fluids (OR, 0.11; 95% CI, 0.03–0.35; p < 0.001) than in patients receiving hypotonic fluids. However, the incidence of hypernatremia was significantly higher in patients receiving isotonic fluids than in patients receiving hypotonic fluids (OR, 8.24; 95% CI, 1.84–36.91; p < 0.001) [73,77].
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Access to the full-text version

The full-text version of this clinical practice guideline is available on the Korean Society of Nephrology website (https://doi.org/10.23876/j.krcp.33.666).

Conflict of interest

All authors have no conflicts of interest to declare.

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vs. hypotonic (0.18%) saline as maintenance intravenous fluids in children: a randomized controlled trial. *Indian Pediatr* 2014;51:969–974.


Application of C5 inhibitors in glomerular diseases in 2021

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The complement pathway is an essential mechanism in innate immunity, but it is also involved in multiple pathologies. For kidney diseases, strong evidence of a dysregulation in the alternative pathway in atypical hemolytic uremic syndrome (aHUS) led to the use of eculizumab, the first anti-C5 inhibitor available in clinical practice. Intensive fundamental research resulted in the development of subsequent new drugs, such as long-acting C5 inhibitors, oral medications, or antagonists of C5aR, the receptor for C5a. New data in the domain of C5-inhibition in glomerular diseases are still limited and mainly focus on 1) the efficacy of ravulizumab, a long-acting C5 inhibitor in aHUS, and 2) the use of avacopan, a C5aR antagonist, in antineutrophil cytoplasmic antibody vasculitis. Several new studies ongoing or planned for the next few years will evaluate the efficacy of C5 inhibition in secondary thrombotic microangiopathy, C3 glomerulopathy, membranous nephropathy, or immunoglobulin A nephropathy.

Keywords: ANCA associated vasculitis, Complement inhibitors, C5 inhibitors, Hemolytic uremic syndrome, Kidney diseases, Thrombotic microangiopathies

Introduction

Anticomplement therapies were first developed to treat paroxysmal nocturnal hemoglobinuria (PNH), a clonal hematopoietic stem cell disorder, which results in the absence of CD59, a regulator of the complement system, on the surfaces of affected red blood cells. Patients with PNH experience a complement-dependent intravascular hemolysis that is mostly resolved with the administration of eculizumab, a humanized anti-C5 antibody [1]. This was the first major breakthrough indication for this drug.

The second breakthrough occurred when eculizumab was introduced in the field of nephrology. After it was shown that there is a dysregulation of the alternative pathway in atypical hemolytic uremic syndrome (aHUS), eculizumab was used to treat the disease. It showed impressive results, with a reduction in end-stage kidney disease from 50% at 1 year in historical cohorts to 6%–15% after treatment [2–5].

By blocking the terminal part of the complement system, the innate immunity is partially inactivated, especially against encapsulated bacteria. Although these therapies are then a risk factor for invasive meningococcal infections, infection can be efficiently prevented by vaccination and prophylactic antibiotherapy.

This review will focus on the most recent findings con-
Concerning the use of anti-C5 drugs in glomerular disease. Several other complement inhibitors (inhibitors of the lectin pathway, factor B, etc.) have been developed and are currently being evaluated—or will be assessed in the future—for glomerular diseases. However, these will not be discussed in the present review.

**Complement system: basics**

The complement system can be activated through three pathways: the classical pathway, the mannose-binding lectin pathway, and the alternative pathway (Fig. 1). Of these, the classical pathway is activated after recognition of immune complexes by C1q, and the lectin pathway is activated mainly by microbial surfaces, whereas the alternative pathway is spontaneously activated by the phenomenon of “tick-over.” The alternative pathway amplifies the response of the first two pathways or can be activated by properdin.

These pathways lead to the formation of a C3 convertase (C4bC2a for the classical and lectin pathways or C3bBb for the alternative pathway) that cleaves C3 into C3a and C3b. C3b is then incorporated to form a C5 convertase (C4bC2aC3b for the classical and lectin pathways or C3bBbC3b for the alternative pathway) that cleaves C5 into C5a and C5b. C3a and C5a, called anaphylatoxins, are proinflammatory molecules that, following ligation to their inflammatory cell receptors, trigger a release of proinflammatory cytokines and vasoactive agents. Meanwhile, C3b itself promotes opsonization. Together with C6, C7, C8, and C9, C5b leads to the formation of the membrane attack complex, resulting in cell lysis (endothelial cells, bacteria, etc.) [6].

The complement system, particularly the spontaneous tick-over, requires tight control, which is assumed by inhibitors such as factor H, factor I, monocyte chemotactic

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**Figure 1. Complement system: a brief summary.** The complement system can be activated through three pathways: the classical pathway, the mannose-binding lectin pathway, and the alternative pathway. The classical pathway is activated following recognition of immune complexes, and the lectin pathway is activated mainly by microbial surfaces, whereas the alternative pathway is spontaneously activated by the phenomenon of “tick-over.” The alternative pathway amplifies the response of the first two pathways. These pathways lead to the formation of a C3 convertase, which cleaves C3 into C3a and C3b. C3b is then incorporated to form a C5 convertase, which cleaves C5 into C5a and C5b. C3a and C5a are proinflammatory molecules. C5b, together with C6, C7, C8, and C9, leads to the formation of the membrane attack complex (MAC), which results in cell lysis.
protein (MCP), and CD55. These proteins are involved at multiple checkpoints to contain the reaction [6].

Glomerular deposition of the membrane attack complex has been reported in a large proportion of patients with various kidney diseases but is located variably depending upon the disease, such as along the capillary wall in membranous nephropathy and lupus; in the mesangium in immunoglobulin A (IgA) nephropathy and lupus; or throughout the glomerulus in C3 glomerulopathy (C3G), aHUS, and antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis. It is tempting to test the efficacy of anti-C5 therapies in these conditions, but the causal role of the complement system remains unclear in a majority of these diseases (Table 1) [7].

Most of the therapies developed thus far to target C5 inhibit the cleavage of C5 into C5a and C5b, but other drugs have a different mechanism of action—for example, avacopan blocks the C5a receptor and cemdisiran inhibits C5 production in hepatocytes. The properties of these C5 inhibitor drugs are shown in Fig. 2.

**Atypical hemolytic uremic syndrome**

For almost 10 years, anti-C5 therapy for aHUS has produced impressive results, with a significant decline in the number of patients on chronic dialysis after aHUS, a simultaneous increase in the number of patients with preserved renal function, and a similar increase in the number of patients with functioning grafts after transplantation for aHUS [8]. In 2021, new data became available regarding the safety profile, consequences of discontinuation, and benefits of ravulizumab, a new anti-C5 inhibitor.

Concerning the safety of eculizumab, a 5-year safety analysis from a registry cohort of 865 patients (535 adults and 330 children) treated with ≥1 dose of eculizumab for the indication of aHUS has been reported [9]. This group was compared to 456 aHUS patients that had never been treated (307 adults and 149 children). Meningococcal infection occurred in one child and two adults, which represents 0.11 and 0.17 events, respectively, per 100 patient-years. Of the three patients with invasive meningococcal diseases, two had not received antibiotic prophylaxis. Other patients were also at risk of serious infection (e.g., aspergillus infections or infections due to encapsulated bacteria such as Neisseria gonorrhoea, Streptococcus pneumoniae, and Haemophilus influenzae), with a rate of 7.48 events per 100 patient-years in adults and 5.15 events per 100 patient-years in children. In comparison, the control group had 6.17 and 1.12 events, respectively, per 100 patient-years. Death occurred in 4.7% of treated adults and 1.8% of treated children. Infection remained the main cause of death, being responsible for 33% of cases. In the treated cohort, death was less frequent in the group of untreated adults (9.9%) but more frequent than in untreated children (0%). This difference could be explained by the hypothetical frailty of untreated adult patients and by less severe disease in the pediatric setting [9].

The significant information about invasive meningococcal infections has been confirmed in a registry study including PNH and aHUS patients [10] and those with neuromyelitis optica [11]. It was reported respectively as 0.25 and 0.54 events per 100 patient-years. Due to systematic vaccination against the different serotypes of meningococcus, ACYW and B, and to the use of penicillin prophylaxis, the rate of infection has routinely decreased since 2010 and the mortality rate has remained very low.

In view of the risk of infection and the cost of treatment, eculizumab discontinuation must be discussed and weighed against the risk of aHUS recurrence. A recent prospective study [12] including 55 patients (both pediatric and adult) with a history of aHUS treated by eculizumab studied the outcome after drug discontinuation. Among these patients, 51% had a complement gene variant associated with aHUS. Of patients without genetic variants, only

**Table 1. Summary of existing or planned glomerular disease studies designed to test the efficacy of C5 inhibition**

<table>
<thead>
<tr>
<th>Proven efficacy</th>
<th>Areas of uncertainty</th>
<th>Not (yet) studied</th>
</tr>
</thead>
<tbody>
<tr>
<td>aHUS: prospective cohorts</td>
<td>Secondary TMAs: prospective, uncontrolled studies</td>
<td>IgA nephropathy</td>
</tr>
<tr>
<td>ANCA vasculitis: RCT, compared to corticosteroid</td>
<td>C3 glomerulopathy: prospective uncontrolled studies, low number</td>
<td>Lupus nephritis</td>
</tr>
<tr>
<td>IC-MPGN: prospective uncontrolled studies, low number</td>
<td>Membranous nephropathy</td>
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</tbody>
</table>

aHUS, atypical hemolytic uremic syndrome; ANCA, antineutrophil cytoplasmic antibody; IC-MPGN, immune complex-mediated membranoproliferative glomerulonephritis; IgA, immunoglobulin A; RCT, randomized controlled trial; TMA, thrombotic microangiopathy.
one experienced relapse. This unique case was reclassified after the study as congenital thrombotic thrombocytopenic purpura (ADAMTS13 activity at 5% and a pathogenic variant in the ADAMTS13 gene). Among patients who have a variant in complement genes, relapses were more frequent (12 of 28 patients, 42.9%). These relapses occurred mainly during or after an infection. Patients should, therefore, be carefully monitored, especially around infectious episodes. The rate of relapse could be overestimated because 16% of the patients had already experienced ≥1 relapse before inclusion [13]. Multivariate analysis showed an increased risk of relapse for the patients treated with eculizumab with a plasma-soluble C5b9 of ≥300 ng/mL at the start of the study. These relapses were treated with eculizumab, and 11 of 13 patients regained their baseline creatinine levels. During the whole study, eculizumab was not administered for a median of 24 months, and the cost savings were estimated at €32,000,000 [12].

Ravulizumab, another humanized monoclonal antibody that targets the same epitope on the C5 protein as eculizumab, has shown promising results in aHUS [14]. This drug was engineered from eculizumab to have a longer half-life, resulting in an infusion rate of every 8 weeks instead of every 2 weeks with eculizumab. This phase III study (ALXN1210-aHUS-311) showed that ravulizumab could induce a complete thrombotic microangiopathy (TMA) response in 53.6% of patients within 26 weeks. An improvement in renal function was observed in 68% of patients, and dialysis weaning was possible in 58% of patients on dialysis at baseline. This study was a single-arm trial and was not designed to compare ravulizumab and eculizumab. In the C10-004 study evaluating the effect of eculizumab in aHUS, the following results were obtained [2]: a complete TMA response was achieved in 56% of patients, any improvement of renal function in 54% of the patients and among those dialyzed at the baseline, 83% could be

<table>
<thead>
<tr>
<th>Name</th>
<th>Molecule</th>
<th>Administration</th>
<th>Route</th>
<th>Indication</th>
<th>In study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eculizumab</td>
<td>MAb</td>
<td>1x/wk during 1 mo</td>
<td>IV</td>
<td>aHUS</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>then 1x/14 days</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Ravulizumab</td>
<td>MAb</td>
<td>At 1x/2 wk</td>
<td>IV</td>
<td>aHUS</td>
<td>Secondary TMAs</td>
</tr>
<tr>
<td>ALXN1210</td>
<td></td>
<td>during 2 wk</td>
<td></td>
<td></td>
<td>IgAN and lupus nephritis</td>
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<tr>
<td></td>
<td></td>
<td>then 1x/2 mo</td>
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<td></td>
<td></td>
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<tr>
<td>Avacopan</td>
<td>C5aR antag. small</td>
<td>2x/day</td>
<td>Oral</td>
<td>ANCA</td>
<td>IgAN</td>
</tr>
<tr>
<td>CCX168</td>
<td>protein</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crovalimab</td>
<td>MAb</td>
<td>1x/wk during 1 mo</td>
<td>IV</td>
<td>aHUS</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>then 1x/1 mo</td>
<td>dose</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>then SC</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Nomacopan</td>
<td>Recombinant small</td>
<td>1x/day</td>
<td>SC, (IV)</td>
<td>Hematopoietic stem cell transplantation TMA</td>
<td></td>
</tr>
<tr>
<td>Coversin rVA576</td>
<td>protein</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Cemdisiran</td>
<td>RNAi</td>
<td>?</td>
<td>SC</td>
<td>IgAN</td>
<td>aHUS (withdrawn)</td>
</tr>
<tr>
<td>ALN-CC5</td>
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</table>

Figure 2. Anti-C5 therapies. (A) A summary of the different mechanisms of inhibition of the terminal pathway. Cemdisiran, an RNA inhibitor, blocks the production of C5 in hepatocytes. Eculizumab, ravulizumab, crovalimab, and nomacopan inhibit the cleavage of C5 into C5a and C5b. Avacopan is an antagonist of the C5a receptor involved in inflammation pathways. (B) A summary of the different characteristics of anti-C5 therapies in kidney diseases.
weaned of this technique. However, the difference in rates of dialysis weaning between ravulizumab and eculizumab (58% vs. 83%) raised concerns [15]. This could be explained by the different definitions and populations included in the two studies. Populations differed with the inclusion of 1) Asian centers with a significantly less-complete renal response and 2) fewer patients with a pathogenic variant in complement-related genes (57% in the eculizumab group vs. 31% in the ravulizumab group) [16]. The median time to achieve a complete TMA response was also increased among patients treated by ravulizumab (86 days vs. 57 days). Within the extension period of the ALXN1210-aHUS-311 study [16], four more patients attained complete TMA responses, increasing the treatment-response group to 61% of the total number of patients, and the renal response was long-lasting. The safety profile of ravulizumab is similar to eculizumab in the initial and extended studies but still requires confirmation in larger cohorts. Ravulizumab has also been studied in children and adolescents and appears safe and effective in a prospective uncontrolled study including 18 patients who have not previously received complement inhibitors [17].

The single-molecule crovalimab will be examined in a phase III study (COMMUTE-a and -p) for the indication of aHUS in adults or pediatric patients. Crovalimab is a long-acting C5 inhibitor that could be administered subcutaneously.

The conclusion is as follows.

- Anti-C5 therapies carry a risk of infectious complications in the real-life setting, but the risk of invasive meningococcal infection can be modulated with appropriate vaccinations and antibiotic prophylaxis.
- Eculizumab can be discontinued in aHUS patients, leading to a relapse rate of <5% in aHUS patients without a pathogenic variant in complement genes and with a relapse rate of approximately 50% in aHUS patients with a pathogenic variant. When a discontinuation is proposed, careful follow-up should occur, especially during or after an infectious event.
- Ravulizumab, another anti-C5 therapy, with a longer half-life, is effective in aHUS, but its noninferiority compared to eculizumab has not been established thus far in comparative trials.

### Other thrombotic microangiopathies

Whereas the causal role of the alternative pathway is well described in aHUS, it is less clear in other forms of TMAs, e.g., Shiga toxin-associated hemolytic uremic syndrome (STEC-HUS) or secondary TMAs [18]. If the alternative pathway is not the primum movens of kidney lesions, then anti-C5 therapies would not be effective.

During the 2011 outbreak of STEC-HUS in northern Europe (mainly Germany), eculizumab was evaluated in two large retrospective studies and did not show efficacy for kidney outcomes or mortality [19,20]. Multiple case reports and case series have demonstrated a potential benefit of eculizumab in secondary TMAs, but all the reports are retrospective, lacking control groups, and the relative efficacy is subject to a publication bias [21,22].

Similar patient profiles are not shown in genetic studies of aHUS or other forms of TMA. Whereas a rare variant (allele frequency < 0.1%) in complement genes or anti-factor H antibodies are found in -50% to 60% of patients with aHUS, it is only present in ~5% of STEC-HUS and secondary HUS cases [23,24]. In contrast, primary aHUS may be encountered after renal transplantation as a recurrence of the initial disease, during or after pregnancy, and during malignant hypertension; in these cases, rare variants are found in, respectively, 29%, 56%, and 51% of patients [25–27]. It is important to remember that genetic analyses in TMAs are complex to interpret and require the expertise of a specialized laboratory. In addition, since results are not rapidly available, therapeutic management cannot be delayed until genetic analysis is performed.

To circumvent this problem, a functional test like ex vivo analysis has been developed by different study groups [28]. It consists of incubating patient serum in vitro on cultured endothelial cells (mainly immortalized human dermal microvascular endothelial [HMEC-1] cells) and quantifying C5b9 deposits using confocal microscopy. Promising results have been published regarding aHUS, with high C5b9 deposition noted in the acute phase of aHUS, which decreases after remission. Interestingly, when HMEC-1 cells are activated by adenosine diphosphate, patients in remission or even those who are asymptomatic carriers of pathogenic variants in complement genes showed an increased deposition of C5b9 [28]. This test has been evaluated in malignant hypertension patients and showed that, in 26
patients, 18 had a massive deposition of C5b9; further, this subgroup included all patients with a pathogenic variant in complement genes (9 of 18, 50%) [29]. This test has also been evaluated in other secondary TMAs, and ex vivo complement activation was found in a proportion of patients varying between 59% and 100% [30–32], with some indirect evidence of eculizumab efficacy. It should be stressed that this functional test is difficult to perform and to reproduce in nonspecialized laboratories, so a robust test allowing rapid identification of complement-mediated aHUS has yet to be developed. In addition, strong clinical evidence of the efficacy of anti-C5 drugs in secondary HUS is lacking.

This year, Alexion Pharmaceuticals (Boston, MA, USA) launched a randomized, placebo-controlled clinical trial to evaluate the efficacy of ravulizumab in some secondary TMAs (NCT0473804) but excluding, for example, patients who are pregnant or who have cancer. AKARI Therapeutics (New York, NY, USA) will also evaluate nomacopan in pediatric hematopoietic stem-cell transplant–associated TMA during a phase III, open-label, uncontrolled trial (NCT04784455). These studies will increase our knowledge of C5 inhibition in secondary TMAs.

**C3 glomerulopathy**

C3G, including dense deposit disease (DDD) and C3 glomerulonephritis (C3GN), is another disease implicating a dysregulation of the alternative pathway. Some patients carry a rare variant in complement-related genes, and others have auto-antibodies potentializing C3 and/or C5 convertase, like C3 and C5 nephritic factors [33]. This disease could theoretically benefit from C5 inhibition.

The incidence of this rare disease is difficult to estimate and may vary between 1 and 3 cases, respectively, per 1,000,000 people [33] and, since classification in C3G is not yet well defined, it is problematic to perform randomized controlled trials. To date, two retrospective studies [34,35] and two prospective uncontrolled trials have attempted evaluation of the efficacy of eculizumab in this indication [36,37]. The first study in 2012 was a proof-of-concept study evaluating the efficacy of eculizumab in six patients (three with DDD and three with C3GN) with a protocol biopsy after 1 year of treatment. As a potential predictive marker of the response to treatment, the authors suggested an elevated soluble C5b9 level in the serum at the initiation of eculizumab. This elevated sC5b9 concerned only three patients of the six; two of whom had a good clinical response [36]. The following two trials were retrospective series, the first reporting seven patients (five with C3GN and two with DDD) [35] and the second assessing all 26 patients with C3G treated by eculizumab from a French registry [34]. Welte et al. [35] reported favorable outcomes (improvement or stabilization of the renal function) in five of their seven patients. The French registry study reported an overall clinical response in 23% and a partial clinical response in another 23% of patients, respectively. Factors associated with the overall clinical response included a greater proportion of rapidly progressive glomerulonephritis, with a low estimated glomerular filtration rate at eculizumab initiation and the presence of cellular crescents on biopsies. No statistical difference was observed in the serum level of soluble C5b9 in this study [36].

A prospective off-on-off-on clinical trial without a control group included six patients with immune complex-mediated membranoproliferative glomerulonephritis (IC-MPGN) and four patients with C3G. All included patients had a serum sC5b9 levels of >1,000 ng/mL and 24-hour proteinuria levels of >3.5 g. Only three of the 10 patients achieved a response to treatment (two partial and one complete remission), defined by a reduction of 50% of proteinuria and the excretion of <3.5 g/24 hr for partial and <0.3 g/24 hr for complete remission, respectively. This study is also interesting in that it shows that eculizumab was effective in dramatically reducing the level of sC5b9 in all patients, with only a few clinical responses [37].

It remains to be determined whether the proximal part of the complement cascade, e.g., C3, C3a, and C3b, actually plays no major part in this disease. To answer this question, there are plans to study three molecules in C3G: iptacopan, a factor B inhibitor; danicopan, a factor D inhibitor; and narsoplimab, a lectin pathway inhibitor.

In conclusion, eculizumab could be of benefit for some patients, such as those with crescentic forms of C3G. However, these observations are based on a low number of patients and should not be considered as recommendations.

**Antineutrophil cytoplasmic antibody vasculitis**

The pathogenesis of ANCA-associated vasculitis is known to involve the complement system. Neutrophils play a
central role in this disease and, after being primed by cytokines, they are responsible for endothelial lesions. At the same time, neutrophils induce the release of properdin and factor B, which are crucial for alternative pathway activation. The alternative pathway results in the generation of C5a, which amplifies the inflammatory response by recruiting and priming other neutrophils [38,39].

In an experimental model of adeno-associated viruses in mice, it was found that C5a and C5aR were key players in the vascular lesions [40]. Thereafter, avacopan, an oral antagonist of C5a receptors, was evaluated in two phase II studies (CLEAR and CLASSIC). The CLEAR study showed noninferiority of avacopan for the clinical response and the safety profile in this pathology [41]. Despite the trial being designated a noninferiority study, there were signs of greater efficacy for avacopan when considering the Birmingham Vasculitis Activity Score (BVAS). The study included 67 patients divided into three study groups: high-dose prednisone (60 mg daily), lower-dose prednisone (20 mg daily) + 30 mg of avacopan twice daily, and 30 mg of avacopan twice daily alone. The CLASSIC study evaluated two different doses of avacopan (10 or 30 mg twice daily) in combination with standard of care (SOC) vs. SOC alone [42]. It also showed a good safety profile, and a higher dose of avacopan seemed to reduce the time to remission.

Recently, there have been reports from a phase III study (ADVOCATE) [43] designed to compare corticosteroids vs. avacopan, both with cyclophosphamide or rituximab. The corticosteroid group received a tapering dose of prednisone until day 140, adapted to each patient's weight and age. This corresponded with a starting dose of 60 mg of prednisone for an adult weighing ≥55 kg. The avacopan group received 30 mg twice daily during the 52 weeks of the study period. Both groups also received a placebo and rituximab for 4 weeks or cyclophosphamide for 12 weeks, followed by azathioprine at week 15. The use of glucocorticoids was authorized during the screening period, and 75% of the patients received a prednisone-equivalent dose of 46.7 ± 53.2 mg/day in the avacopan group.

No differences were observed between the two groups regarding remission at week 26 (72.3% vs. 70.1%, respectively, for avacopan and corticosteroids), but avacopan was superior for achieving sustained remission at week 52 (65.7% vs. 54.9%, respectively). This is an important breakthrough for anticomplement therapies because it could reduce the infectious morbidity associated with this disease (any infection in 68.1% vs. 75.6%, respectively, and any serious opportunistic infection in 3.6% vs. 6.7%, respectively; for avacopan and prednisone).

However, the tapering regimen of the prednisone group is questionable with interruption of the glucocorticoids at week 20. Interruption was faster than other studies in ANCA vasculitis as exemplified by the PEXIVAS study, which conserved glucocorticoids at least until week 52, even in the reduced-dose regimen [44]. A meta-analysis also showed that longer courses of glucocorticoids were associated with fewer relapses [45]. This rapid weaning off of glucocorticoids could increase the rate of relapses at week 52 when, at the same time, continuous treatment was available in the avacopan group. On the other hand, it could underestimate the infectious risk of a longer regimen of glucocorticoids.

In conclusion, avacopan could in part replace glucocorticoids in ANCA vasculitis to reduce the well-known side effects of cortisone, with the limits as previously described—namely, an infusion of glucocorticoids in avacopan patients and a rapid weaning of glucocorticoids in the other group.

**Immunoglobulin A nephropathy and lupus nephritis**

IgA nephropathy (IgAN) is a very common cause of glomerulonephritis worldwide and consequently of chronic kidney disease. The complement system seems to be implicated in the disease, with genome-wide significance studies identifying the CFHR gene family as a susceptibility locus, with opposing effects noted for individual CFHR genes; for example, homozygous CFHR1/CFHR3 deficiency is protective, whereas enhanced FHR5 plasma levels is an independent risk factor [46]. Frequent mesangial depositions of IgA with C3 and C5b9 are observed, and there is even a possible correlation between the intensity of C5b9 deposition and disease severity [7].

Experimental studies in an IgAN mouse model also demonstrated that the knockout strains for C3aR or C5aR had lower IgA deposition in the mesangium. The use of C3aR and C5aR antagonists reduced *in vitro* IgA-induced cell proliferation and production of interleukin-6 and MCP-1, which are involved in inflammation pathways [47].
Few case reports report a potential positive effect of C5 inhibition [48,49], but no randomized control trials have yet been published.

A phase II study was launched in 2015 for the evaluation of the C5aR antagonist avacopan in IgAN (NCT02384317), but no results are available yet. A study of cemdisiran (NCT03841448) is planned for this indication. Cemdisiran is an RNA inhibitor that specifically targets the liver and blocks hepatic production of C5. The efficacy and safety of ravulizumab (NCT04564339) will be assessed in patients with proliferative lupus nephritis or IgAN in a phase II clinical trial.

Lupus nephritis is a frequent clinical manifestation of systemic lupus erythematosus. This disease is associated with deposition of the immune complex with the complement component of the classical pathway (“full house pattern”) in the kidneys. Some mouse models have shown that it could be beneficial to target C3aR or C5aR to reduce kidney inflammation [50].

In conclusion, other glomerular diseases like IgAN or lupus nephritis could benefit from anticomplement therapies, but there is no actual evidence of efficacy available so far.

**Conclusion**

In recent years, there have been remarkable results from C5 inhibition in primary aHUS, including those triggered by pregnancy or after kidney transplantation, and there have been interesting outcomes from the C5aR antagonist in ANCA vasculitis. The efficacy of these drugs needs to be studied in larger clinical trials and to be evaluated in the context of secondary TMA. Several trials are in progress at present. New, long-acting C5 inhibitors, such as ravulizumab or crovalimab, may alleviate the burden of chronic treatments. Subcutaneous and oral forms of complement inhibitors may also improve treatment tolerance and compliance. Importantly, C5 blockade requires careful monitoring as well as antimeningococcal vaccination and prophylactic antibiotic therapy to reduce the infectious risk inherent with these drugs.

**Conflicts of interest**

All authors have no conflicts of interest to declare.

**Authors’ contributions**

Conceptualization, Formal analysis: AW
Writing - original draft preparation: AW
Writing - review & editing: ER
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Management of autosomal dominant polycystic kidney disease in the era of disease-modifying treatment options

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Autosomal dominant polycystic kidney disease (ADPKD) is the reported etiology in 10% of end-stage kidney disease (ESKD) patients and has an estimated prevalence of 12.5 million cases worldwide across all ethnicities. There have been major advancements over the last two decades in understanding the pathogenesis and development of disease-modifying treatment options for ADPKD, culminating in regulatory approval of tolvaptan for ADPKD patients at risk of rapid progression to kidney failure. This review highlights the genetic mutations associated with ADPKD, defines patients at risk of rapid progression to ESKD, and focuses on the management of ADPKD in the era of disease-modifying agents.

**Keywords:** Autosomal dominant polycystic kidney, Biomarkers, Chronic kidney diseases, Prognosis, Tolvaptan

Introduction

The prevalence of autosomal dominant polycystic kidney disease (ADPKD) is an estimated 12.5 million cases worldwide across all ethnicities [1]. ADPKD is the most common inherited kidney disease, accounting for 5% to 10% of global cases of end-stage kidney disease (ESKD) [1,2]. It is a systemic disease characterized by early development of fluid-filled renal cysts that relentlessly grow with time, leading to destruction of kidney parenchyma and loss of kidney function by the fifth to sixth decade of life [3]. There are about 0.6 million to 0.7 million cases of ADPKD in the United States [2,4]. Over the last decade, there have been major advancements in understanding the pathogenesis and natural history of ADPKD, including identification of several disease-causing mutations in genetically unresolved cases and development of disease-modifying treatment options such as tolvaptan. This review highlights the genetic mutations associated with ADPKD, defines patients at risk of rapid progression to ESKD, and focuses on the management of ADPKD in the era of disease-modifying agents.

Genetic variability in autosomal dominant polycystic kidney disease

ADPKD is a genetically heterogeneous disease that is
inherited in an autosomal dominant manner [4]. In the majority of cases, it is attributed to mutations in either the PKD1 gene on chromosome 16 encoding polycystin (PC)-1 or PKD2 on chromosome 4 encoding PC-2, with the former responsible for 78% and latter about 15% of the cases [5]. There is wide phenotypic variability, with PKD1 mutations manifesting more severe disease including more numerous cysts, larger height-adjusted total kidney volume (TKV), lower estimated glomerular filtration rate (eGFR), and earlier development of ESKD compared to PKD2 mutations [4,5]. In addition to the genotype, several other factors contribute to the phenotypic variability observed in ADPKD. These factors include mosaicism, rate of cystic growth, and environmental influences such as water intake, diet, hormonal factors, obesity, and smoking [6,7].

Other diseases can present with kidney cysts and might mimic ADPKD. Thus, it is essential to understand these nuances to allow an accurate diagnosis, which will affect the prognosis and treatment plan. Mutations in PRKCSH, SEC63, LPR5, ALG8, and SEC61B that are associated with autosomal dominant polycystic liver disease (ADPLD) can result in renal cysts and an ADPKD-like phenotype without increased risk of progression to ESKD [8]. Recently, mutations in GANAB, which encodes the glucosidase II subunit a protein necessary for maturation of PC-1 protein, were found to cause mild kidney cystic disease (average 10 cysts total), mild decline in kidney function, and mild to severe polycystic liver disease. GANAB-associated disease represents 0.3% of patients with ADPKD [5,9]. Mutations in PKHD1, which are associated with autosomal recessive polycystic kidney disease (ARPKD) and present with congenital hepatic fibrosis, can mimic ADPKD [8]. Furthermore, mutations in UMOD, REN, MUC1, and HNF1B associated with autosomal dominant tubulointerstitial kidney disease (ADTKD) can present with renal cysts and low kidney function that can mimic ADPKD [8]. In contrast to ADPKD, patients with ADTKD present with smaller cystic burden (i.e., normal to mildly enlarged kidneys and relatively small number of kidney cysts). The predominant feature in ADTKD is interstitial fibrosis, which leads to progressive loss of kidney function [10]. In a recent study by Cornec-Le Gall et al. [11], mutations in DNAJB11 were found to be associated with an ADPKD-like phenotype with an overlap of ADTKD clinical characteristics and the presence of liver cysts. Additional mutations that cause kidney and liver cysts without enlargement of kidneys include those in ALG9 [12].

Mutations associated with impaired ciliary apparatus function and ciliopathies such as those found in OFD1 and NPHP1 can present with corticomедullary cysts in the kidneys that might mimic ADPKD but with distinct extrarenal manifestations and ESKD onset at a younger age [13,14]. Other systemic syndromes such as tuberous sclerosis complex and Von Hippel Lindau disease, due to mutations in TSC and VHL genes, respectively, can present with kidney cysts mimicking ADPKD [15]. Hence, there is considerable phenotypic overlap between ADPKD and other inherited cystic kidney diseases, highlighting the importance of accurate diagnosis of ADPKD as it will affect the renal prognosis and treatment plan to slow the disease process.

Diagnosis of autosomal dominant polycystic kidney disease and situations when genetic testing is required

In most cases, ADPKD is diagnosed clinically by evaluating the number of kidney cysts on imaging adjusted to age in the presence of family history of ADPKD [16]. Fig. 1 summarizes the diagnostic criteria for both ultrasound and computed tomography (CT)/magnetic resonance imaging (MRI) in the presence or absence of family history. In the absence of family history, there are no established criteria. Expert opinion suggests that bilateral renal enlargement with innumerable renal cysts (>10 cysts per kidney) provides a “likely ADPKD” diagnosis [4]. In these situations, molecular genetic testing would be prudent to confirm the diagnosis. As genetic screening is becoming more readily available, the indications for testing will likely be more inclusive as these results enrich the prognostication in ADPKD. Until genetic testing becomes universally accessible, the following indications are considered: 1) confirm the ADPKD diagnosis in the setting of negative family history, 2) ascertain the diagnosis if the extrarenal manifestations are suggestive of syndromes other than ADPKD or if the cystic burden is not congruent with the renal function, 3) exclude ADPKD in young potential kidney donors who are at risk of ADPKD, and 4) confirm the diagnosis and rule out ciliopathies in the setting of early or very early disease onset [17]. Fig. 2 summarizes the indications for genetic testing in patients with renal cysts suspicious for ADPKD.
Figure 1. ADPKD diagnostic criteria for both ultrasound and CT/MRI in the presence or absence of family history.

*Likely ADPKD but must consider other factors such as age of the patient, size of the kidneys, concomitant liver cysts, and clinical features of other cystic or genetic disorders.

ADPKD, autosomal dominant polycystic kidney disease; CT, computed tomography; MRI, magnetic resonance imaging.

Figure 2. Indications for genetic testing in patients with bilateral renal cysts concerning for ADPKD.

ADPKD, autosomal dominant polycystic kidney disease.
Assessment of risk of rapid progression in autosomal dominant polycystic kidney disease

Not all patients with ADPKD reach kidney failure. In fact, 50% of the patients reached ESKD by age of 54 years and 75% by age of 62 years in a recent study with a large tertiary care center cohort [18]. It has also been demonstrated that, within a family, despite shared mutations, there is wide variability in the age at which a family member reaches ESKD [19]. Given the wide heterogeneity and phenotypic variability of ADPKD, it is prudent to identify the group of patients who are at risk of rapid progression toward ESKD to initiate disease-modifying treatment early to slow the progression of the kidney disease. There are several methods available with variable advantages and disadvantages to assess the risk of progression in ADPKD (Fig. 3). Irrespective of the method, the most important factor in this assessment is matching the cystic burden and kidney function with respect to age, as following thresholds indiscriminately might lead to misclassification of the disease and its progression.

The Consortium for Radiologic Imaging Studies of Polycystic Kidney Disease (CRISP) is an ongoing, prospective, multicenter, observational study of 241 ADPKD patients (aged 15 to 45 years with creatinine clearance of >70 mL/min at the time of study initiation) that determined the relationship between kidney volume and decline in kidney function using MRI [20]. Key findings from the study include that exponential increase in TKV is variable among patients, TKV is related to decline in glomerular filtration rate (GFR), and baseline height-adjusted TKV (htTKV) predicts decline of kidney function and progression to kidney failure, validating it as a prognostic marker in ADPKD [21,22]. If there is a discordance between htTKV, age, and decline in kidney function, an alternative diagnosis such as ADTKD and other mimickers of ADPKD should be considered as described above. When interpreting TKV, it is prudent to adjust to the age at time of imaging and ensure

Figure 3. Various prognostic biomarkers including clinical, genomic, and radiological criteria to predict the risk of progression of ADPKD.

ADPKD, autosomal dominant polycystic kidney disease; eGFR, estimated glomerular filtration rate; htTKV, height-adjusted TKV; PROP-KD, predicting renal outcome in ADPKD; TKV, total kidney volume.
that ADPKD is typical in its radiological appearance. These two critical factors are embedded in the Mayo imaging classification (MIC) [23]. This classification delineates the criteria for typical (class 1 or MIC 1) and atypical (class 2 or MIC 2) ADPKD. MIC 1 is defined as bilateral and diffuse renal cystic disease where cysts are contributing almost equally to TKV. MIC 2 is defined as either unilateral, focal, asymmetric cystic involvement (MIC 2A) or bilateral cystic involvement with kidney atrophy (MIC 2B). Furthermore, MIC 1 is divided into five subcategories (MIC 1A through 1E) that predict the rate of kidney volume growth by adjusting htTKV to age. Patients with MIC 1C, 1D, or 1E are considered at risk of rapid progression as their future eGFR decline is predicted to be ≥2.5 mL/min/1.73 m² per year and the mean age of ESKD onset is ≤54 years. The MIC has been validated in a study by Yu et al., and it was concluded that htTKV is a long-term predictor of decline in GFR [24]. In a study by Bae et al. [25], htTKV was recalculated after exclusion of prominent exophytic cysts, and the imaging classification based on recalculated htTKV was more predictive of decline in eGFR. The definition of rapid progression is evolving. There is currently controversy on treating MIC 1C, where the United States practical guide favors treating with tolvaptan, whereas the updated recommendations from the European Renal Association-European Dialysis and Transplantation Association and PKD International advise seeking additional confirmatory evidence of rapid progression such as age-adjusted GFR, genotyping, predicting renal outcome in ADPKD (PROPKD) score, or family history [26]. While there is no consensus, international guidelines will likely be developed through an upcoming Kidney Disease: Improving Global Outcomes (KDIGO) workgroup.

The gold standard for measurement of TKV is planimetry or stereology in which kidney volume is calculated by tracing the kidney in cross-sectional slices or coronal slices with corresponding slice thickness. However, this method is time-consuming and requires specialized training and equipment [27]. A practical alternative includes TKV measurement using an ellipsoid formula that measures sagittal and coronal length, width, and depth. Estimating TKV by ellipsoid equation has been demonstrated to be comparable to planimetry and provides TKV in a few minutes [23,27]. A model developed by the Mayo Clinic for calculating TKV by the ellipsoid formula allows classification of patients into MIC 1A through E and predicts future eGFR decline (http://www.mayo.edu/research/documents/ptd-center-adpkd-classification/doc-20094754).

Experts across the globe have used various biomarkers to assess the risk of ADPKD progression. Fig. 3 summarizes the various prognostic biomarkers for predicting the risk of rapid progression. The biomarkers include clinical, genetic, and radiological criteria to assess the rate of kidney growth and kidney function decline. Annual TKV growth rate of >5% measured by planimetry or stereology has been considered a radiologic biomarker for risk of rapid progression in Japan. However, its applicability is limited given the need for precise measurements and inability to differentiate between PKD1 and PKD2 due to similar TKV growth in these patients [18]. Use of kidney length as a biomarker can delay treatment initiation for young patients with kidney size smaller than 16.5 cm who might be at risk of rapid progression to ESKD [18]. Conversely, the use of kidney length alone might misclassify patients with atypical ADPKD (focal disease with few large kidney cysts) as rapid progressors. Genomic and clinical data such as PKD1 vs. PKD2 mutation status (truncating vs. non-truncating) and family history of developing kidney failure at a younger age might predict the severity but are highly variable at population as well as intrafamilial levels [5–7]. Thus, these factors would be helpful to enrich prognostication but lack the individual precision for patients when used in silico without the overall clinical context. The PROPKD scoring system incorporates sex, onset of hypertension before age of 35 years, urologic events before age of 35 years, and type of mutation (PKD1 truncating, PKD1 non-truncating, and PKD2) to predict the risk of rapid progression to ESKD before age of 60 years. This system has a positive predictive value of 91% for a score of >6 but is limited by cost and availability of genetic testing and lacks accuracy due to phenotypic variability within a family [28]. European regulatory agencies have used eGFR rate of decline of at least 2.5 mL/min/1.73 m² per year over 5 years or at least 5 mL/min/1.73 m² in 1 year as a marker for rapid progression. However, use of this marker alone can delay treatment initiation in younger age groups at risk of rapid progression but with preserved kidney function and might erroneously include patients who have concomitant diagnoses that lead to GFR decline independent of ADPKD risk of progression such as diabetic nephropathy [18]. In our opinion, the most practical ap-
proach available at the moment is the MIC system, which allows prediction of the intrinsic TKV rate of growth using one hTKV measurement adjusted by age. Patients with MIC 1C, 1D, or 1E are considered at risk of rapid progression.

**Basic kidney protective measures in autosomal dominant polycystic kidney disease**

Basic kidney protective measures such as control of blood pressure, limiting dietary sodium and caloric intake, hydration, and management of dyslipidemia must be implemented in all ADPKD patients irrespective of progression risk. Blood pressure in ADPKD patients aged 18 to 50 years who are at risk of rapid progression (MIC 1C, 1D, or 1E) should be targeted to less than 110/75 mmHg as this strict blood pressure control could slow the TKV rate of growth and potentially slow the decline in eGFR [29,30]. In all other ADPKD patients, blood pressure can be targeted to less than 130/80 mmHg [29]. Renin-angiotensin-aldosterone blockade with angiotensin-converting enzyme inhibitors and angiotensin receptor blockers are the recommended first-line therapy for management of hypertension in ADPKD patients [29]. In addition, patients should be on moderate dietary sodium restriction (2.3–3.0 g) and daily dietary protein intake of 0.8–1.0 g/kg ideal body weight to slow progression of chronic kidney disease [29]. Based on animal model observations, enhanced water intake to suppress vasopressin levels might be associated with slower TKV growth and eGFR decline. Hence, all ADPKD patients should be advised to increase hydration to target a urine osmolality of <280 mOsm/L [29]. In a recent multicenter, open-label, randomized control clinical trial studying the effect of a water prescription on slowing the disease process in ADPKD, the prescribed water prescription was not associated with slower growth of TKV over 3 years compared with ad libitum water intake. However, only 50% of the patients were able to reach the target urine osmolality despite coaching, indicating that maintaining a suppressed vasopressin level without pharmacological intervention is challenging in a practical clinical setting. Additionally, 30% of the patients included in this clinical trial were at risk of slow progression (MIC 1B), which could have affected the study result as interventions are less likely to be shown in a short period of time in this group given their small TKV rate of growth [31,32]. Other recommendations include treatment of dyslipidemia to target low-density lipoprotein (<100 mg/dL) and high-density lipoprotein (HDL, >50 mg/dL) and maintaining normal body mass index (BMI) as lower serum HDL cholesterol and higher BMI have been associated with faster increase in TKV and decline in GFR [29,33].

**Vasopressin antagonists in autosomal dominant polycystic kidney disease**

In 2018, the U.S. Food and Drug Administration approved tolvaptan, a vasopressin V2 receptor antagonist, as a disease-modifying treatment option for ADPKD patients at risk of rapid progression to kidney failure [34]. The PC proteins present across the cilium in kidney tubules regulate intracellular calcium and cyclic adenosine monophosphate levels. Mutations of these proteins lead to elevation in cyclic adenosine monophosphate (cAMP) level and eventual dysregulation of several downstream pathways leading to cyst formation, fluid secretion, interstitial inflammation, and fibrosis [8]. Vasopressin has been demonstrated to reduce cAMP level in mouse models through its antagonism of the V2 receptor and subsequently inhibition of cystogenesis [35].

In 2012, a randomized, double-blind, placebo-controlled trial (TEMPO 3:4) was conducted to evaluate tolvaptan efficacy in ADPKD patients aged 18 to 50 years with creatinine clearance greater than 60 mL/min and TKV of >750 mL [36]. Tolvaptan treatment was associated with a slower rate of increase in TKV (2.8% vs. 5.5%, p < 0.001) as well as a slower decline in kidney function in the tolvaptan group compared to placebo [36]. This was followed by another randomized, double-blind, placebo-controlled clinical trial (REPRISE) in 2017 to evaluate the efficacy of tolvaptan in ADPKD patients aged 18 to 65 years with eGFR of 25 to 65 mL/min [37]. The results were consistent with the previous study, with a slower decline in eGFR in the tolvaptan group compared to placebo (2.34 mL/min/yr vs. 3.61 mL/min/yr, p < 0.001) [37]. Tolvaptan was associated with a 5.6% risk of hepatic aminotransferase elevation compared to 1.2% in the placebo arm. This hepatic enzyme dysregulation was reversible after discontinuation of the drug [37].

Tolvaptan is currently recommended for ADPKD patients in the United States aged 18 to 55 years, at risk of rapid
progression as determined by htTKV and risk of rapid GFR decline in the future (MIC 1C, 1D, 1E) with an eGFR greater than 25 mL/min [18]. For patients aged 55 to 62 years, emerging evidence favors the use of tolvaptan. Shared decision-making is recommended in this age group for patients who have evidence of rapid progression (i.e., MIC 1C, 1D, or 1E with an average eGFR rate of decline ≥ 2.5 mL/min/yr over the past 5 years). The shared decision-making will entail a discussion of risks, potential benefits, and patient preferences. Fig. 4 depicts examples of patients who should and should not be considered for disease-modifying treatment options. Patients with discordance between htTKV and eGFR should be evaluated for concomitant disease processes such as diabetic nephropathy, vascular disease, or ADPKD mimickers such as ADTKD and should not be considered for disease-modifying treatment options. Representative cases covering common clinical scenarios are detailed in the section below.

Most common adverse effects of tolvaptan resulting from vasopressin receptor blockade that patients should be advised of are polyuria, excessive thirst, polydipsia, and nocturia [38]. Idiosyncratic hepatocellular injury in the form of elevated aminotransferases was observed in 4.4% and 5.6% of patients treated with tolvaptan in the TEMPO 3:4 and REPRISE trials, respectively. A risk evaluation and mitigation strategy with frequent liver function monitoring before and after initiation of tolvaptan are required to assess abnormalities in aminotransferases and risk of serious hepatotoxicity that might necessitate discontinuation of tolvaptan [38].

**Representative cases**

Once ADPKD diagnosis is confirmed, the next step involves assessing the risk of rapid progression. Fig. 4 summarizes the various clinical scenarios where disease-modifying treatments such as tolvaptan are indicated or not and where shared decision-making is required to balance risks and benefits with patient preference.

**Case 1**

A 29-year-old female with typical ADPKD (MIC 1) had a TKV of 2,627 mL, corresponding to MIC 1E. Her eGFR was already low at 29 mL/min/1.73 m² despite her young age. Thus, she was considered at risk of rapid progression and

![Figure 4: Clinical scenarios of ADPKD patients depicting whether disease-modifying treatments (such as tolvaptan) are indicated or not and where shared decision-making is required to balance risks and benefits with patient preference.](www.krcp-ksn.org)
was showing evidence of rapid progression given the low GFR. However, her kidney length was only 16 cm, which highlighted the disadvantage of only using this criterion to assess rapid progression. Furthermore, her PKD mutation type (PKD1 non-truncating) and PROPKD score of 3 had a good relative prognostication. This highlights the lack of individualized prognosis when only using genomic data and highlights the importance of not using these factors in silo to assess rapid progression. Tolvaptan could be continued until the need for renal replacement therapy.

Case 2
A 30-year-old male with typical ADPKD (MIC 1) had a TKV of 1,351 mL and MIC 1D. His eGFR was 81 mL/min/1.73 m². Despite his PKD1 truncating mutation, his prognosis was better than that of case 1 (with PKD1 non-truncating mutation), highlighting the complex interaction of factors that dictate disease progression beyond the PKD genotype. This patient would benefit from tolvaptan as he was at risk of rapid progression based on the MIC.

Case 3
A 35-year-old male with typical ADPKD, TKV of 820 mL, MIC 1C, and eGFR of 85 mL/min/1.73 m² was eligible for tolvaptan treatment as he is at risk of rapid progression despite his favorable PROPKD score and PKD2 non-truncating mutation.

Case 4
A 52-year-old female with typical ADPKD, TKV of 380 mL, MIC 1A, and eGFR of 76 mL/min/1.73 m² was not eligible for tolvaptan as she is considered a slow progressor despite a PKD1 non-truncating mutation.

Case 5
A 51-year-old female with typical ADPKD, TKV of 1,131 mL, MIC 1B, and eGFR of 51 mL/min/1.73 m² who would not benefit from tolvaptan given the risk outweighing the benefits. Despite the patient carrying the PKD1 truncating mutation, her prognosis was very good. This case highlights the complex interaction with other factors that determine disease progression. These factors can include other genetic factors such as modifiers and epigenetic modifications and environmental factors such as healthy lifestyle including hydration, normal BMI, and dietary restrictions.

Case 6
A 46-year-old male with atypical ADPKD (MIC 2A, lopsided). TKV was high at 2,760 mL. However, this patient had atypical features including four very large cysts that accounted for >50% of the TKV. Correlating TKV with cystic burden and renal parenchyma as well as kidney function was essential to assess prognostication. This patient was predicted to have a good prognosis (slow progressor) and was less likely to reach ESKD at an early age. In this patient, kidney length was large, which would have misclassified the patient as a rapid progressor if the cystic burden was not evaluated on CT/MRI using the imaging classification system.

Case 7
A 53-year-old female with typical ADPKD, TKV of 517 mL, and MIC 1A had a low eGFR of 26 mL/min/1.73 m² discordant with her low renal cystic burden, raising the question of a possible concomitant process leading to such low GFR. Additional investigation revealed oxalate nephropathy. Thus, the GFR decline was not related to ADPKD, and disease-modifying treatments directed to slow cystic disease progress were not indicated. This case highlights the importance of evaluating GFR rate of decline and chronic kidney disease stage in the context of cystic burden.

Case 8
A 65-year-old male with atypical ADPKD, TKV of 619 mL, and MIC 2B (bilateral renal cysts with low eGFR and atrophic kidneys). His low GFR was consistent with MIC 2B, which carries a poor prognosis as the main process is renal atrophy and renovascular disease in the setting of vascular pathology. Disease-modifying treatments directed to slow cystic disease progress were not indicated.
Case 9

A 67-year-old male with bilateral renal cystic disease. The relatively low cystic burden (TKV of 561 mL) and low eGFR (27 mL/min/1.73 m²) were discordant, raising the question of a renal cystic disease other than ADPKD or ADPKD with another concomitant renal disease. Thus, genetic study was indicated. This patient had DNJAB11-associated disease, which also has autosomal dominant inheritance with interstitial fibrosis as a major contributor to GFR decline.

Case 10

A 57-year-old male with typical ADPKD, TKV of 3,558 mL, and MIC 1D. His eGFR was 39 mL/min/1.73 m². This patient had evidence of rapid progression and would benefit from initiation of tolvaptan to slow his disease process. However, there should be discussion with the patient for shared decision-making to balance risks, benefits, and patient preferences.

Conclusion

In the era of disease-modifying treatments intended to slow the disease progression of ADPKD, five main points need to be addressed in an individualized fashion: 1) confirm the diagnosis of ADPKD by ensuring the cystic burden matches the observed kidney function; 2) assess the risk of rapid progression using available biomarkers such as age and htTKV; 3) implement renal protective measures for all ADPKD patients; 4) evaluate eligibility for disease-modifying treatments such as tolvaptan by discussing the risks, benefits, and patient preference; and 5) implement safe prescription of tolvaptan based on regulatory guidance for serial liver function testing.

Conflicts of interest

All authors have no conflicts of interest to declare.

Authors’ contributions

Conceptualization: YR, FTC
Methodology, Project administration: All authors
Writing–original draft: YR, FTC
Writing–review & editing: All authors
All authors read and approved the final manuscript.

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Mayo imaging classification is a good predictor of rapid progress among Korean patients with autosomal dominant polycystic kidney disease: results from the KNOW-CKD study

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Background: Mayo imaging classification (MIC) is a useful biomarker to predict disease progression in autosomal dominant polycystic kidney disease (ADPKD). This study was performed to validate MIC in the prediction of renal outcome in a prospective Korean ADPKD cohort and evaluate clinical parameters associated with rapid disease progression.

Methods: A total of 178 ADPKD patients were enrolled and prospectively observed for an average duration of 6.2 ± 1.9 years. Rapid progressor was defined as MIC 1C through 1E while slow progressor was defined as 1A through 1B. Renal composite outcome (doubling of serum creatinine, 50% decline of estimated glomerular filtration rate [eGFR], or initiation of renal replacement therapy) as well as the annual percent change of height-adjusted total kidney volume (mHTKV-α), and eGFR decline (mGFR-α) were compared between groups.

Results: A total of 110 patients (61.8%) were classified as rapid progressors. These patients were younger and showed a higher proportion of male patients. Rapid progressor was an independent predictor for renal outcome (hazard ratio, 4.09; 95% confidence interval, 1.23–13.54; p = 0.02). The mGFR-α was greater in rapid progressors (~3.58 ml/min per year in 1C, ~3.7 in 1D, and ~4.52 in 1E) compared with that in slow progressors (~1.54 in 1A and ~2.06 in 1B). The mHTKV-α was faster in rapid progressors (5.3% per year in 1C, 9.4% in 1D, and 11.7% in 1E) compared with that in slow progressors (1.2% in 1A and 3.8% in 1B).

Conclusion: MIC is a good predictive tool to define rapid progressors in Korean ADPKD patients.

Keywords: Autosomal dominant polycystic kidney, Computer-assisted image interpretation, Glomerular filtration rate, Prognosis, Renal insufficiency
Introduction

Autosomal dominant polycystic kidney disease (ADPKD) is the most common inherited cystic kidney disease resulting in end-stage kidney disease [1]. In ADPKD, as multiple cysts grow from kidney tubules, they compress renal tissue and vascular structures, and renal ischemia and inflammation eventually result in kidney failure [2]. Recently, novel drugs including the vasopressin receptor antagonist have been introduced to attenuate cyst growth and renal function decline for ADPKD patients [3]. Since renal function remains stable in the early stage of ADPKD and starts to decline only after cysts substitute normal renal tissues, identifying rapid progressors among ADPKD patients for whom novel drugs may be beneficial is useful [4].

Mayo imaging classification (MIC) is currently the best prediction model for selecting rapid progressors among ADPKD patients. With this prediction model, patients with typical ADPKD can be subclassified into class 1A through 1E according to height-adjusted total kidney volume (htTKV) for age [5]. From a theoretical starting htTKV of 150 mL/m, class 1A patients have a yearly htTKV increase of less than 1.5% while class 1B patients show an increase of 1.5% to 3.0%, class 1C patients 3.0% to 4.5%, class 1D patients 4.5% to 6.0%, and class 1E patients more than 6.0%. Recent papers suggested that prognostic enrichment strategies such as MIC are useful for designing clinical trials for ADPKD to increase the power of the study and reduce cost [6,7]. However, this has not been validated in a Korean ADPKD population. A recent report from Higashihara et al. [8] showed that a starting htTKV of 130 mL/m instead of 150 mL/m resulted in the prediction of more constant htTKV growth rates. However, the clinical efficacy of different equations on the prediction of renal outcome has not been evaluated.

This study was performed to evaluate the validity of MIC in defining rapid progressors among Korean ADPKD patients and to describe the clinical characteristics of rapid progressors among Korean ADPKD patients.

Methods

Study population

Among 364 adult ADPKD patients who were enrolled in the KNOW-CKD (KoreaN Cohort Study for Outcomes in Patients With Chronic Kidney Disease) from 2011 to 2016, a total of 178 typical ADPKD patients with ≥two kidney image studies with more than 1 year apart were included in this analysis. The detailed study design and methods are described in the previous studies [9,10]. We excluded the following patients from the analysis: 140 patients without initial kidney images, 37 patients without follow-up kidney images, and nine patients who received Tolvaptan treatment during follow-up (Fig. 1). The study proposal was approved by the Institutional Review Board at Seoul National University Hospital (No. 1104-089-359). Informed consent was obtained from all participants upon study enrollment.

Total kidney volume measurement

Abdominal computed tomography (CT) with or without contrast enhancement was performed. All CT exams were performed with 3 to 5 mm thickness, and axial, coronal, and sagittal views were obtained to calculate total kidney volume (TKV). TKV was measured by one professional radiologist using both ellipsoid equation (TKVe) and stereologic method (TKVs) using ImageJ [5,11]. The ellipsoid equation used was TKVe = π/6 × L × W × D; where D = maximum depth, L = average of sagittal and coronal maximal longitudinal length, and W = maximal width perpendicular to L.

Definition of rapid progressors

In the original MIC, the htTKV growth rate was estimated for classification using the equation [htTKV at age t] = K (1 + α/100)(t-Ä), where K (theoretical initial htTKV) = 150 and Ä (theoretical starting age) = 0 [5]. However, a Japanese group recently suggested using K = 130 instead of K = 150 for the stable estimated htTKV slope (eHTKV-α) from baseline through follow-up in patients without Tolvaptan treatment [8]. We, therefore, calculated eHTKV-α by both equations using K = 130 and K = 150. We compared the two equations to finalize the prediction model for the Korean ADPKD population. Rapid progressor was defined as eHTKV-α ≥ 3.0%, which corresponds to MIC 1C through 1E.

Data collection

Baseline characteristics were collected during the enrollment period. Age, sex, presence of hypertension, height,
weight, body mass index, and systolic and diastolic blood pressure were collected at the initial visit. Laboratory parameters including plasma hemoglobin, serum uric acid and albumin, serum creatinine, and random urine protein-to-creatinine ratio were assessed at the initial visit. The glomerular filtration rate (GFR) was estimated by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. The estimated GFR (eGFR) was measured annually and hTKV was measured biannually until March 31, 2020.

Genotyping

A total of 162 patients had available genotype data from an inherited cystic kidney disease study [12]. Genomic DNA was extracted from whole blood and targeted exome sequencing was performed for 89 ciliopathy genes included in the gene panel. Genotype was subclassified as truncating mutation of PKD1 (PKD1-PT), in-frame insertion/deletion of PKD1 (PKD1-ID), non-truncating mutation of PKD1 (PKD1-NT), and PKD2 mutations.

Outcome measurement

Primary outcome was renal composite outcome, which consists of doubling of serum creatinine, 50% decline of eGFR, or initiation of renal replacement therapy. Secondary outcomes were annual percent change of hTKVs (mHTKV-α) and annual decline rate of eGFR (mGFR-α). The mGFR-α was measured by a slope-based parameter using a mixed-effects model [13].

Statistical analyses

The correlation between TKVe and TKVs was compared using linear regression analysis. Baseline characteristics were compared between rapid progressors and slow progressors using Student t test for continuous variables and chi-square...
test for categorical variables. Multivariable Cox regression analysis was performed to evaluate rapid progressor as an independent factor for renal composite outcome after adjustment for sex, body mass index, systolic blood pressure, serum uric acid, baseline eGFR, and genotype. To compare mHTKV-α and mGFR-α among different MIC classes or genotypes, the Kruskal-Wallis test was performed. Statistical analyses were performed using SPSS version 20.0 (IBM Corp., Armonk, NY, USA).

**Results**

**Correlation between total kidney volumes using ellipsoid and stereologic methods**

TKVe was highly correlated with TKVs ($R^2 = 0.938$) (Fig. 2A). However, TKVe was more likely to overestimate the TKVs value, showing a mean deviation of 5.3% and standard deviation of 17% in the Bland-Altman plot (Fig. 2B). As the TKV gets larger, the TKVe value gets larger than the TKVs value. Therefore, we decided to use TKVs in the current analysis.

**Comparison of estimated height-adjusted total kidney volume slopes using different prediction models**

We compared eHTKV-α ($A = 0$ and $K = 130$) and eHTKV-α ($A = 0$ and $K = 150$) in our cohort. We calculated eHTKV-α from the initial and final hTKV measurements and compared the stability between values. When we applied the original equation used in MIC ($A = 0$ and $K = 150$) (Fig. 3A), the difference between initial and final values was larger than the modified equation from Higashihara’s group ($A = 0$ and $K = 130$) (Fig. 3B). The mHTKV-α according to the initial eHTKV-α showed good correlation in both equations (Fig. 3C, D). When we analyzed the proportion of Higashihara MIC according to original MIC at the individual level, the Higashihara MIC tended to overestimate MIC classes compared with the original MIC (Supplementary Table 1, available online). Therefore, slow progressors by original MIC may be included in the rapid progressors when using the modified equation from Higashihara’s group ($A = 0$ and $K = 130$).

When we compared the change in MIC classes from initial to last CT exam, the prediction model using eHTKV-α ($A = 0$ and $K = 130$) showed an overall more stationary proportion of classes compared with that using eHTKV-α ($A = 0$ and $K = 150$) (Supplementary Fig. 1, available online). However, at the individual level, approximately the same number of patients changed from rapid progressors to slow progressors and vice versa between the two prediction models (Supplementary Table 2, available online). Those who changed MIC classes during follow-up were of younger age than those who did not change their classes during follow-up.
Clinical parameters associated with rapid progressors among Korean autosomal dominant polycystic kidney disease

A total of 110 patients (61.8%) were classified as rapid progressors and 68 patients (38.2%) were classified as slow progressors according to eHTKV-α (A = 0 and K = 150) (Table 1). Rapid progressors were younger at initial visit and predominantly male (60.0% vs. 35.3%, p = 0.001). Rapid progressors also showed higher systolic and diastolic blood pressures, higher body mass index, and higher serum uric acid. Baseline eGFR was significantly lower for rapid progressors compared with that of slow progressors (73.3 ± 27.6 mL/min/1.73 m² vs. 86.4 ± 25.3 mL/min/1.73 m², p = 0.002). However, the proportion of PKD1 genotype was not different between groups (83.2% vs. 80.4%, p = 0.69). The distribution of PKD genotype subclasses (PKD1-PT, PKD1-ID, PKD1-NT, PKD2, and no mutation) did not differ among

follow-up (42.9 ± 11.0 years vs. 47.5 ± 10.3 years, p = 0.03).

Figure 3. Difference between eHTKV-α at initial and final points of TKV measurement. The eHTKV-α was predicted from hTKV at a certain age. The eHTKV-α at the initial point of TKV measurement and at the final point of TKV measurement was compared in each patient. Using the original equation in MIC (A = 0 and K = 150), the difference between initial and final values was larger than the modified equation from Higashihara’s group (A = 0 and K = 130). (A) Using the original equation (A = 0 and K = 150), 10 of the 178 patients (5.6%) showed more than 1% change in final eHTKV-α from the initial value. (B) Using the modified equation (A = 0 and K = 130), only six out of 178 patients (3.4%) showed more than 1% difference from the initial value. (C, D) We analyzed the associations between eHTKV-α and mHTKV-α, and both equations demonstrated good association between eHTKV-α and mHTKV-α.

eHTKV-α, estimated hTKV slope; hTKV, height-adjusted TKV; mHTKV-α, annual percent change of hTKVs; MIC, Mayo imaging classification; SD, standard deviation; TKV, total kidney volume.
MIC classes (Supplementary Fig. 2, available online).

Renal outcome according to Mayo imaging classification

A total of 46 renal events occurred during the mean follow-up duration of 6.2 ± 1.9 years. Renal events occurred more frequently among rapid progressors compared with slow progressors defined by original MIC (42 events vs. four events, p < 0.001) (Fig. 4). The clinical characteristics of the patients with renal outcome are described in Supplementary Table 3 (available online). The Cox-proportional hazard model was used to evaluate independent predictors of renal outcome. Age, male sex, body mass index, systolic blood pressure, serum uric acid, PKD1 genotype, baseline eGFR, macroalbuminuria, and rapid progressors were included as covariates. We compared the renal outcomes between slow progressors and rapid progressors using MIC (A = 0 and K = 130) and found that rapid progressor was not an independent predictor for renal outcome (hazard ratio [HR], 1.86; 95% confidence interval [CI], 0.60–5.76; p = 0.28). However, when we applied MIC (A = 0 and K = 150, an original equation), rapid progressor was an independent predictor for renal outcome (HR, 4.09; 95% CI, 1.23–13.54; p = 0.02) (Table 2) together with baseline eGFR and macroalbuminuria.

### Table 1. Clinical parameters associated with Korean ADPKD rapid progressors

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total (n = 178)</th>
<th>Slow progressors (n = 68)</th>
<th>Rapid progressors (n = 110)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>46.9 ± 10.6</td>
<td>49.0 ± 11.2</td>
<td>45.7 ± 10.0</td>
<td>0.04</td>
</tr>
<tr>
<td>Male sex</td>
<td>90 (50.6)</td>
<td>24 (35.3)</td>
<td>66 (60.0)</td>
<td>0.001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>157 (88.2)</td>
<td>58 (85.3)</td>
<td>99 (90.0)</td>
<td>0.34</td>
</tr>
<tr>
<td>htTKV (mL/m)</td>
<td>784.9 (430.1–1,177.7)</td>
<td>398.1 (276.5–537.1)</td>
<td>1,030.9 (819.2–1,390.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PKD1 genotype</td>
<td>116 (82.3)</td>
<td>37 (80.4)</td>
<td>79 (83.2)</td>
<td>0.69</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>23.5 ± 2.97</td>
<td>22.5 ± 2.57</td>
<td>24.0 ± 3.1</td>
<td>0.001</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>127.7 ± 12.3</td>
<td>124.7 ± 11.8</td>
<td>129.5 ± 12.4</td>
<td>0.01</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>81.1 ± 10.0</td>
<td>79.0 ± 9.8</td>
<td>82.4 ± 10.0</td>
<td>0.03</td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>13.5 ± 1.56</td>
<td>13.5 ± 1.36</td>
<td>13.6 ± 1.66</td>
<td>0.83</td>
</tr>
<tr>
<td>Uric acid (mg/dL)</td>
<td>5.8 ± 1.42</td>
<td>5.4 ± 1.34</td>
<td>6.0 ± 1.44</td>
<td>0.007</td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>4.44 ± 0.25</td>
<td>4.47 ± 0.27</td>
<td>4.42 ± 0.24</td>
<td>0.25</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>1.1 ± 0.43</td>
<td>0.94 ± 0.38</td>
<td>1.2 ± 0.43</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>eGFR (mL/min/1.73 m²)</td>
<td>78.3 ± 27.4</td>
<td>86.4 ± 25.3</td>
<td>73.3 ± 27.6</td>
<td>0.002</td>
</tr>
<tr>
<td>Urinary protein-to-creatinine ratio (g/g)</td>
<td>0.08 (0.05–0.15)</td>
<td>0.06 (0.04–0.12)</td>
<td>0.1 (0.05–0.21)</td>
<td>0.06</td>
</tr>
</tbody>
</table>

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

ADPKD, autosomal dominant polycystic kidney disease; BP, blood pressure; eGFR, estimated glomerular filtration rate; htTKV, height-adjusted total kidney volume.

*Rapid progressor was defined as 1C to 1E by the original equation of the Mayo imaging classification (A = 0 and K = 150). 

Figure 4. Renal outcome by the original MIC (A = 0 and K = 150). A total of 46 renal events occurred within 6.2 years. No renal event occurred in patients with MIC 1A. Four events (7.8%) occurred in 1B, 21 events (33.9%) in 1C, 15 events (42.9%) in 1D, and six events (46.2%) in 1E. Rapid progressors defined by original MIC predicted more frequent renal events compared to slow progressors (p < 0.001). MIC, Mayo imaging classification.
Annual percent change of height-adjusted total kidney volumes and annual decline rate of estimated glomerular filtration rates according to Mayo imaging classification

To validate the clinical utility of MIC among the Korean ADPKD population, we evaluated mHTKV-α and mGFR-α according to MIC classes (Table 3). The mHTKV-α was calculated from repeated measures of TKVs during the follow-up. During a mean follow-up duration of 5.8 ± 8.8 years, 3.3 CT exams were taken on average. The mHTKV-α was larger in rapid progressors (5.26% per year in 1C, 9.39% in 1D, and 11.72% in 1E) compared with that in slow progressors (1.22% in 1A and 3.83% in 1B). In addition, mGFR-α was the fastest in class 1E (−4.52 mL/min/yr) and the slowest in class 1A (−1.54 mL/min/yr). Neither mHTKV-α nor mGFR-α showed statistical differences according to genotype (Supplementary Table 4, available online).

Discussion

This study evaluated the clinical utility of MIC among Korean ADPKD patients to predict renal outcome. We have confirmed that TKVe and TKVs are strongly correlated. We compared the original equation from MIC (A = 0 and K = 150) and the modified equation from Higashihara’s group (A = 0 and K = 130) and found that the Higashihara equation showed more stable prediction over years. However, Higashihara’s equation did not predict renal outcome according to MIC. Rapid progressor applied by original equation from MIC was an independent predictor for renal outcome together with macroalbuminuria and baseline eGFR. Rapid progressors also demonstrated greater mHTKV-α and mGFR-α compared with slow progressors. This is the first study to validate the clinical utility of MIC to predict renal outcome in a Korean ADPKD population. Recently, Higashihara’s group suggested to use a theoretical starting htTKV of 130 mL/m instead of 150 mL/L when estimating annual TKV growth \[8\]. The authors stated that the modified equation showed a more stationary htTKV growth rate. Our study also demonstrated that Higashihara’s equation resulted in a more stable eHTKV-α. However, while eHTKV-α was more stable during follow-up when using Higashihara’s equation (A = 0 and K = 130), the change in MIC at the individual level did not differ between the original and modified equations. Moreover, rapid progressors based on a modified equation did not predict poor renal outcome while the original MIC did. Therefore, the original MIC (A = 0 and K = 150) can be useful in the prediction of renal out-

Table 2. Multivariable Cox regression analysis for renal outcome in patients with ADPKD

<table>
<thead>
<tr>
<th>Variable</th>
<th>HR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>0.97 (0.93–1.02)</td>
<td>0.12</td>
</tr>
<tr>
<td>Male sex (vs. female sex)</td>
<td>0.78 (0.39–1.55)</td>
<td>0.47</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>0.95 (0.82–1.09)</td>
<td>0.44</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>1.00 (0.97–1.03)</td>
<td>0.98</td>
</tr>
<tr>
<td>Serum uric acid (mg/dL)</td>
<td>1.12 (0.84–1.45)</td>
<td>0.43</td>
</tr>
<tr>
<td>Baseline eGFR (mL/min/1.73 m²)</td>
<td>0.94 (0.92–0.96)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Macroalbuminuria (vs. normoalbuminuria or microalbuminuria)</td>
<td>3.53 (1.66–7.49)</td>
<td>0.001</td>
</tr>
<tr>
<td>PKD1 genotype (vs. PKD2)</td>
<td>2.45 (0.71–8.44)</td>
<td>0.16</td>
</tr>
<tr>
<td>Rapid progressor* (vs. slow progressor)</td>
<td>4.09 (1.23–13.54)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

ADPKD, autosomal dominant polycystic kidney disease; BP, blood pressure; CI, confidence interval; eGFR, estimated glomerular filtration rate; HR, hazard ratio.

*Rapid progressor was defined as 1C to 1E by the original equation of the Mayo imaging classification (A = 0 and K = 150).

Table 3. mHTKV-α and mGFR-α according to MIC (A = 0 and K = 150) in the Korean ADPKD cohort

<table>
<thead>
<tr>
<th>Mayo class</th>
<th>1A (n = 17)</th>
<th>1B (n = 51)</th>
<th>1C (n = 62)</th>
<th>1D (n = 35)</th>
<th>1E (n = 13)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>mHTKV-α</td>
<td>1.22 (–0.3 to 2.73)</td>
<td>3.83 (2.62–5.05)</td>
<td>5.26 (4.16–6.36)</td>
<td>9.39 (5.3–13.49)</td>
<td>11.72 (6.84–16.59)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>mGFR-α</td>
<td>–1.54 (–2.3 to –0.77)</td>
<td>–2.06 (–2.48 to –1.64)</td>
<td>–3.58 (–4.05 to –3.11)</td>
<td>–3.7 (–4.31 to –3.09)</td>
<td>–4.52 (–6.2 to –2.83)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Data are expressed as mean (95% confidence interval). ADPKD, autosomal dominant polycystic kidney disease; MIC, Mayo imaging classification; mGFR-α, annual decline rate of glomerular filtrate rate; mHTKV-α, annual change to height-adjusted total kidney volume.
come among Korean ADPKD patients.

Our data demonstrated that TKVe strongly correlates with TKVs ($R^2 = 0.938$). A previous study by Irazabal et al. [5] also showed similar results ($R^2 = 0.979$). However, our study showed a wider difference between TKVe and TKVs. The difference may come from the different modalities used in the studies. The previous study by Irazabal [5] measured TKVe using magnetic resonance imaging, whereas our study used enhanced CT. The difference may also come from the level of expertise in TKVe measurement. Higashihara’s group suggested to use a modified ellipsoid equation of $\pi/24 \times L \times (W + WW)^2$ to accurately estimate TKV, where $L$ = maximal longitudinal length, $W$ = maximal width perpendicular to $L$, and $WW$ = width greater than $W$ [14]. However, modified ellipsoid equation takes longer time to measure than original formula, and the reproducibility may even be lower when the measurement is performed by a less experienced researcher. However, previous studies suggested that the ellipsoid method can be reliably applied to clinical management when assessing renal risk in the individual patient [15,16].

Our study showed that MIC classes can change over time in some individuals. Our analysis demonstrated that patients whose MIC classes changed over time were younger than those whose MIC classes were stationary. A previous review by Chebib and Torres [4] also recommended to use a more accurate measurement (planimetry or stereology) for young patients with MIC 1B or 1C. Therefore, we suggest using either the stereologic method or repeated measure of TKVe over time in defining rapid progressors among a young population to avoid denying potential treatment opportunities for patients at risk.

The risk factors associated with rapid progressors defined by MIC were largely in concordance with the results from previous studies. Our study demonstrated that younger age at enrollment, male sex, higher systolic and diastolic blood pressure, higher body mass index, higher serum uric acid, and lower eGFR were risk factors associated with rapid progressors defined by MIC. A previous study demonstrated that younger age at diagnosis and male sex were the nonmodifiable factors associated with rapid progression [17-19]. High blood pressure is one of the strongest risk factors for rapid progression [20,21]. A recent article also showed that overweight and obesity are risk factors for ADPKD [22]. A recent study by a Japanese group also suggested that higher serum uric acid was associated with greater eGFR change overtime [23]. However, when we performed multivariable Cox regression analysis for renal composite outcome, baseline eGFR, rapid progressor defined by MIC, and macroalbuminuria were the independent risk factors for renal composite outcome. Our results are in line with previous studies suggesting that age-adjusted hTKV and baseline eGFR are the most important factors for rapid progression [24,25].

Rapid progressors defined by MIC ($A = 0$ and $K = 150$) also effectively predict renal outcome among the Korean ADPKD population. The mGFR-a declined faster while the mHTKV-a became larger as the MIC classes progressed. However, Korean ADPKD patients showed faster enlargement of the mHTKV-a with a similar mGFR-a according to the MIC classes compared with previous studies with a Caucasian population (Supplementary Table 5, 6; available online) [6,7]. This may be due to ethnic differences or genetic predispositions. Our previous study demonstrated that the median age at end-stage kidney disease in the Korean ADPKD cohort was 7 years later than that of the Caucasian population [25]. In addition, Korean patients with PKD1-PT genotype showed much better renal survival compared with that of the Genkyst cohort. A recent study by Horie et al. [26] also suggested that the effect of Tolvaptan upon renal function may differ from that on TKV. Therefore, cyst growth or TKV growth may not be the only mechanism of renal function decline [27]. Another explanation can be a small number of patients in each MIC class. The mHTKV-a was especially greater in MIC classes 1D and 1E where a small number of patients were included. Therefore, our result should be confirmed in the larger Korean cohort.

Apart from MIC, genotype neither was an independent factor for renal composite outcome nor significant factors affecting mGFR-a and mHTKV-a. In addition, the proportion of each PKD genotype was not different according to MIC classes. This result may be because of the small number of cases in each subgroup.

Our study has several limitations. First, we did not investigate other risk factors for renal progression including smoking, history of gross hematuria, cholesterol profile, or glucose level. The study population was from a single ethnic group, and therefore the results cannot be generalized. We did not evaluate and compare results from various methods of volumetry. Lastly, the numbers of patients included in each MIC class and genotype were too small.
This is the first study to demonstrate the clinical characteristics and renal outcome among Korean ADPKD patients according to rapid progressor defined by MIC. MIC (A = 0 and K = 150) can be used effectively to define rapid progressors for candidates of Tolvaptan treatment among Korean ADPKD patients.

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**Conflicts of interest**

All authors have no conflicts of interest to declare.

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**Authors’ contributions**

Conceptualization: CA, YKO
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Formal analysis: HCP
Funding acquisition: KHO
Investigation: YH, JHY, HR
Methodology: YH, JHY
Supervision: CA, KHO, YKO
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Genetic variants of interferon lambda-related genes and chronic kidney disease susceptibility in the Korean population

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Background: Chronic kidney disease (CKD) is a common condition leading to renal dysfunction and is closely related to increased cardiovascular and mortality risk. CKD is an important public health issue, and recent genetic studies have verified common CKD susceptibility variants. This research examines the interrelationship between candidate genes polymorphisms of interferon lambda (IFNL) induction, its signaling pathway, and CKD.

Methods: Seventy-five patients with advanced CKD and 312 healthy subjects (as controls) participated in this research. A replication set composed of 172 patients with advanced CKD and 365 controls was used for additional analysis. The genotype of single nucleotide polymorphisms (SNPs) was determined by the Axiom Genome-Wide Human Assay and SNaPshot assay.

Results: The SNP of IFNL3 was significantly associated with CKD in the codominant (p = 0.02) and dominant models (p = 0.02). In addition, the SNPs of IFNL2 were significantly associated with CKD in the dominant model (p = 0.03), and the SNP of interferon alpha receptor 2 (IFNAR2) was significantly associated with CKD in the log-additive model (p = 0.03). Concerning rs148543092, in the IFNL3 gene, a significant association was observed after pooling the original and replication sets.

Conclusion: These results indicate that SNPs in the IFNL induction and signal pathway may be associated with CKD risk in the Korean population. Finally, our results also show that the IFNL3 gene variant may be associated with CKD risk.

Keywords: Chronic renal insufficiency, DNA replication, Interferon type III, Single nucleotide polymorphism

Introduction

Chronic kidney disease (CKD) is a worldwide health problem. The overall prevalence of CKD globally is estimated to be 11% to 13% [1,2], and CKD is a major risk factor for cardiovascular diseases and all-cause mortality [3]. Addi-
tionally, CKD has become a socioeconomic and medical issue for global healthcare \[4\]. Therefore, it is paramount to identify individuals that are at risk for the development and progression of CKD.

A significant association between large numbers of genes, their polymorphisms, and kidney function was observed in genetic studies. Therefore, it can be concluded that a strong genetic component exists in CKD \[5,6\]. The pathogenesis of CKD is complex and dependent on a broad spectrum of diverse etiologies. A major pathophysiology of CKD is persistent, chronic inflammation \[7\]. In the active phase of inflammation, immune cells migrate to the injury site, resolve the damage, and initiate the healing process. However, persistent inflammation is problematic, as it can lead to tissue damage and fibrosis. In addition, chronic inflammation is associated with various diseases including CKD \[8\].

Interferon (IFN), a marker of inflammation, may play a role in CKD development. However, the role of IFN in CKD is not well understood. Type I IFNs are central mediators of antiviral immunity and kidney inflammation \[9\]. Although type III IFN, known as IFN lambda (IFNL), has several similarities in function with type I IFNs, little is known about the role of IFNL in CKD.

The IFNL signaling pathway is initiated as IFNL binds to the heterodimeric IFNL receptor. The IFNL receptor is composed of interleukin 28 receptor alpha (IL28RA) and interleukin 10 receptor beta (IL10RB) subunits, where the Janus kinase (JAK)-signal transducer and activator of the transcription (STAT) signaling cascade induces hundreds of IFN-stimulated genes (RIG-1-like receptor, toll-like receptor \[TLR\], nuclear factor kappa-light-chain-enhancer of activated B cells, \textit{IL-28RA}, \textit{IL-10RB}, \textit{JAK1}, tyrosine kinase 2, \textit{STAT}, IFN regulatory factor \[IRF\], IFN-stimulated response element, IFN-induced GTP-binding protein Mx1, and 2'-5’-oligoadenylate synthetase) \[10\].

This study explores the association between IFNL induction and signaling pathway candidate genes consisting of \textit{IFNL3}, \textit{IFNL2}, IFN alpha receptor 1 (\textit{IFNAR1}), \textit{IFNAR2}, \textit{TLR9}, \textit{IL22}, \textit{IL-10RB}, \textit{IRF7}, \textit{JAK2}, and \textit{STAT3} polymorphisms and CKD.

**Methods**

**Study subjects**

This study enrolled 90 patients with CKD who were distributed by the Keimyung Human Bio-Resource Bank in 2012. In addition, 312 control subjects who participated in health checkup programs from the health promotion center from July to October 2008 participated in this study. The control group was defined as those with no clinical evidence for kidney impairment, cancer, hypertension, diabetes mellitus, dyslipidemia, and cardiovascular diseases. Among the 90 patients with CKD, 75 (83.3%) had an estimated glomerular filtration rate (eGFR) of less than 15 mL/min/1.73 m\(^2\). Since these patients could not represent the entire CKD group, we excluded patients with eGFR values above 15 mL/min/1.73 m\(^2\). A replication set consisting of 172 patients with advanced CKD and 365 controls was used for additional analysis.

Samples from 172 patients with advanced CKD were consecutively distributed by the Keimyung Human Bio-Resource Bank in 2018, and the controls were collected at the health promotion center of the Keimyung University Dongsan Medical Center (Daegu, Korea). Written informed consent was obtained from all the subjects. The approved protocol from the Institutional Review Board of the Keimyung University Dongsan Medical Center was used for this study (No. 2018-02-029).

**Clinical characteristics and biomedical measurement**

Participants’ clinical characteristics, such as systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured. The body mass index (BMI) was calculated by weight divided by the square of the height (kg/m\(^2\)).

Biochemical markers were measured using samples in the fasted state. The levels of fasting blood sugar (FBS), triglyceride, total cholesterol (TC), low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, aspartate aminotransferase, alanine aminotransferase, albumin, blood urea nitrogen (BUN), creatinine, and uric acid were measured using an auto-analyzer (ADVIA2400 Chemistry System; Siemens Healthcare Diagnostics Inc., Tarrytown, NY, USA). eGFR was calculated using the simplified prediction equation derived from chronic
kidney epidemiology collaboration (modification of diet in renal disease): eGFR = 175 × standardized Scr$^{-1.154}$ × age$^{-0.203}$ × 0.742 [if female], where GFR is expressed as mL/min/1.73 m$^2$ of the body surface area and serum creatinine is expressed in mg/dL [11]. CKD was defined as eGFR of <60 mL/min/1.73 m$^2$ for 3 months or more.

**Single nucleotide polymorphism selection and genotyping of the interferon lambda-related gene single nucleotide polymorphisms**

Seventeen single nucleotide polymorphisms (IFNL3 gene 2SNPs, IFNL2 gene 2SNPs, IFNAR2 gene 2SNPs, TLR9 gene 2SNPs, IL-22 gene 2SNPs, IL10RB gene 2SNPs, IFNAR1 gene 1SNP, IRF7 gene 1SNP, JAK2 gene 1SNP, and STAT3 gene 1SNP) of the IFNL-related gene were selected based on database searches (http://ncbi.nlm.nih.gov/SNP). SNPs with <0.05 minor allele frequency, <0.1 heterozygosity, and unknown genotype frequencies in Asian populations were excluded. Human genomic DNA was extracted from peripheral blood samples using the Qiagen DNA Extraction Kit (Qiagen, Tokyo, Japan) and then stored at 20°C. The SNPs of the IFNL3, IFNL2, IFNAR2, TLR9, IL-22, IL-10RB, IFNAR1, IRF7, JAK2, and STAT3 genes were genotyped by direct sequencing. The following primers for the 17 SNPs were used to amplify the genomic DNA (Table 1). Polymerase chain reaction (PCR) conditions included 32 cycles at 92°C for 30 seconds, 60°C for 50 seconds, and 70°C for 40 seconds. PCR products were identified on 1.5% agarose gel by electrophoresis. Furthermore, the PCR products were sequenced by the DNA analyzer (ABI Prism 3730XL; Applied Biosystems, Foster City, CA, USA) to analyze the genotypes of each SNP. Finally, the genotypes were determined using SeqManII software (DNASTAR Inc., Madison, WI, USA).

**Genotyping of replication SNPs was screened using the single base primer extension assay with ABI PRISM SNaPShot Multiplex kit (ABI, Foster City, CA, USA) according to the manufacturer’s protocol. Analysis was conducted using the Genemapper software (version 4.0; Applied Biosystems).**

**Statistical analysis**

IBM SPSS version 24 (IBM Corp., Armonk, NY, USA) and R version 3.2.2 (R Foundation for Statistical Computing, Vienna, Austria) were used for statistical analysis. The results were considered statistically significant when p < 0.05. Student t test was used for comparisons between the two groups among continuous variables. Additionally, con-

<table>
<thead>
<tr>
<th>Gene</th>
<th>SNP</th>
<th>Forward</th>
<th>Reverse</th>
<th>Product size</th>
</tr>
</thead>
<tbody>
<tr>
<td>IFNL3</td>
<td>rs148543092</td>
<td>5'-GAGGATATGGTGAGGGTTGT-3'</td>
<td>5'-CTCTATCTCTCTCCCTCCCAAC-3'</td>
<td>201 bp</td>
</tr>
<tr>
<td>IFNL3</td>
<td>rs150748693</td>
<td>5'-GAAGGGTGACAGACGACAGT-3'</td>
<td>5'-GAGCCAGAAACCCAGACAG-3'</td>
<td>152 bp</td>
</tr>
<tr>
<td>IFNL2</td>
<td>rs8103362</td>
<td>5'-CCCTCACCTGCTTCTCTCTCA-3'</td>
<td>5'-GAGGATATGGTGAGGGTTGT-3'</td>
<td>163 bp</td>
</tr>
<tr>
<td>IFNL2</td>
<td>rs59746524</td>
<td>5'-CCCAAGATCAGTCGAGCCTAG-3'</td>
<td>5'-TGAGGAGGAGGAGGATG-3'</td>
<td>183 bp</td>
</tr>
<tr>
<td>IFNAR2</td>
<td>rs2229207</td>
<td>5'-CCAAAGATGCTTTTGAGCCACA-3'</td>
<td>5'-TTGCTCCTCTACTCTCAG-3'</td>
<td>208 bp</td>
</tr>
<tr>
<td>IFNAR2</td>
<td>rs1051393</td>
<td>5'-TTGATCACCTAAATGGTTGATTCTCAG-3'</td>
<td>5'-AGGGTGACTGGGTTCTCT-3'</td>
<td>234 bp</td>
</tr>
<tr>
<td>TLR9</td>
<td>rs187084</td>
<td>5'-GCTGGGTGTACATAATTCAGCA-3'</td>
<td>5'-GAGCTCTTTTGCTGCTCTA-3'</td>
<td>220 bp</td>
</tr>
<tr>
<td>TLR9</td>
<td>rs5743836</td>
<td>5'-GGGGTTGAGGAGTGGTGTAAG-3'</td>
<td>5'-CTGTTCCCTGAGTGCTCT-3'</td>
<td>217 bp</td>
</tr>
<tr>
<td>IL-22</td>
<td>rs2227513</td>
<td>5'-CTTCTACCTTCTGCCACACA-3'</td>
<td>5'-GTTCCCCATAAGGAAAGGC-3'</td>
<td>218 bp</td>
</tr>
<tr>
<td>IL-22</td>
<td>rs2227484</td>
<td>5'-GATAATTTATCTCTGCTTTAGT-3'</td>
<td>5'-GGACCCATCTCTATCTCCT-3'</td>
<td>220 bp</td>
</tr>
<tr>
<td>IL-22</td>
<td>rs2227485</td>
<td>5'-TCCTGAGCACAATATGCTTACTC-3'</td>
<td>5'-ACGCTCATACTGAGCCCCG-3'</td>
<td>165 bp</td>
</tr>
<tr>
<td>IL-10RB</td>
<td>rs8178562</td>
<td>5'-TCGAAGTTGCTGCTGCTAGA-3'</td>
<td>5'-CGCCATCTGCTCTGCTAAT-3'</td>
<td>231 bp</td>
</tr>
<tr>
<td>IL-10RB</td>
<td>rs2834167</td>
<td>5'-CTCTCTACCTTCTGGCTGTTCTCA-3'</td>
<td>5'-GTTCCCCATAAGGAAAGGC-3'</td>
<td>223 bp</td>
</tr>
<tr>
<td>IFNAR1</td>
<td>Affx-52347487</td>
<td>5'-GAGAATCTGGGGTTGCTCCC-3'</td>
<td>5'-GCTCGGGTGTAGGTCG-3'</td>
<td>104 bp</td>
</tr>
<tr>
<td>IRF7</td>
<td>Affx-52325648</td>
<td>5'-GCTCAGCCAGGAACTGTCG-3'</td>
<td>5'-GCTGGCCAGAATACCTCTGG-3'</td>
<td>203 bp</td>
</tr>
<tr>
<td>JAK2</td>
<td>rs77375493</td>
<td>5'-AGCAAGTATGATGAGGAGCAAGCT-3'</td>
<td>5'-ACCTAGCCTTGTGCTCCTGAACT-3'</td>
<td>163 bp</td>
</tr>
<tr>
<td>STAT3</td>
<td>rs113994139</td>
<td>5'-TTCTTCCATGCTCCTGTA-3'</td>
<td>5'-CTGGGGCAAAATATCTTC-3'</td>
<td>203 bp</td>
</tr>
</tbody>
</table>

SNP, single nucleotide polymorphism.
Results

Demographic and clinical characteristics of the participants

The demographic characteristics and clinical parameters of the study subjects are summarized in Table 2. The original set consisted of 312 control subjects included 157 males and 155 females with a mean age of 46.7 ± 10.3 years. The CKD group was composed of 75 adults and involved 36 males and 39 females with a mean age of 50.2 ± 12.1 years. In the replication set, 365 control subjects included 177 males and 188 females with a mean age of 50.6 ± 13.8 years. The CKD group was composed of 172 adults and included 92 males and 80 females with a mean age of 59.2 ± 15.1 years. In the original and replication sets, the sex distribution of the subjects was not significantly different in the two groups. Additionally, in the original and replication sets, BMI, SBP, DBP, BUN, creatinine, uric acid, FBS, and triglyceride levels in the CKD group were significantly higher compared to the control group. Conversely, eGFR, total protein, albumin, TC, HDL cholesterol, and LDL cholesterol levels in the CKD group were significantly lower compared to the control group. In the control and CKD groups, the genotype distribution of the 17 polymorphic SNPs was in the HWE.

Genotype and allele frequencies of the IFNL3, IFNL2, IFNAR2, TLR9, IL-10RB, IL-22, IFNAR, IRF7, JAK2, and STAT3 genes’ single nucleotide polymorphisms

The SNPs of IFNL3, rs148543092 (T > C), were significantly associated with CKD in the codominant and dominant models (T/T vs. T/C and T/T vs. T/C + C/C, p = 0.02, OR = 2.61, 95% CI = 1.28–5.80). The SNPs of IFNL2, rs8103362 (A > G), were significantly associated with CKD in the codominant, dominant, and log-additive models (A/A vs. A/G, p = 0.06, OR = 2.61, 95% CI = 1.18–5.80; A/A vs. A/G + G/G, p = 0.03, OR = 2.45, 95% CI = 1.11–5.40; A/A vs. A/G vs. G/G, p = 0.05, OR = 2.17; 95% CI = 1.02–4.63, respectively). The SNP of IFNAR2, rs1051393 (G > T), was significantly associated with CKD in the codominant and log-additive models (G/G vs. T/T, p = 0.05, OR = 2.10, 95% CI = 1.00–4.40; G/G vs. G/T vs. T/T, p = 0.047, OR = 1.42, 95% CI = 1.01–2.00, respectively) (Table 3). There was no significant difference in the genotype and allele frequencies between the control and CKD group in the SNP of TLR9, rs187084 (T > C), SNP of IL-22, rs2227484 (G > A), IL-10RB gene polymorphisms (rs8178562 G > A, rs 2834167 A > G), and IRF7 gene polymorphism (Affix-52325648 T/del). Finally, there were no polymorphisms, but only major allele homozygotes in IFNAR1 (Affix-52347487), JAK2 (rs77375493), and STAT3 (rs113994139) (data not shown). Genotype and allele frequencies of the IFNL-related genotype in the replication set are shown in Supplementary Table 1 (available online).

Replication of the IFNL3, IFNL2, and IFNAR2 genes’ single nucleotide polymorphisms

Comparing genotypic frequencies between cases and controls for all SNPs analyzed achieved a significant nominal value in three polymorphisms located in three genetic regions. We attempted to replicate associations involving IFNL3, IFNL2, and IFNAR2 using a second sample set (Table 4).

No significant associations involving IFNL2 and IFNAR2 were observed in the replication set. Regarding rs148543092, in the IFNL3 gene, a significant association was observed after pooling the original and replication sets (p = 0.02, OR = 2.50, 95% CI = 1.14–5.47; p < 0.001, OR = 0.92, 95% CI, 0.89–0.95) (Table 4).
Association of IFNL3 single nucleotide polymorphism with clinical characteristics

After adjustments for age, sex, BMI, hypertension, diabetes mellitus, and dyslipidemia as covariates, we examined whether the genotype distribution of IFNL3 gene polymorphism, rs148543092, is associated with clinical characteristics (creatinine, eGFR, uric acid, total protein, and albumin) in the original and replication sets of the CKD group. In addition, in the original and replication sets, creatinine, eGFR, uric acid, total protein, and albumin levels exhibited no significant difference in the genotype distribution (Table 5).

Discussion

This study examines the association between the polymorphisms of IFNL3 (rs148543092 T > C), IFNL2 (rs8103362 A > G), IFNAR2 (rs1051393 G > T), TLR9 (rs187084 T > C), IL-22 (rs2227513 T > C), and CKD development in patients...
Table 3. Distribution of frequencies of the interferon lambda-related genotype in controls and chronic kidney disease patients in the model of inheritance

<table>
<thead>
<tr>
<th>Gene</th>
<th>SNP number</th>
<th>Function</th>
<th>Codominant genetic model</th>
<th>Dominant genetic model</th>
<th>Recessive genetic model</th>
<th>Log-additive genetic model</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>OR (95% CI) p-value</td>
<td>OR (95% CI) p-value</td>
<td>OR (95% CI) p-value</td>
<td>OR (95% CI) p-value</td>
</tr>
<tr>
<td>IFNL3</td>
<td>rs148543092</td>
<td>Missense</td>
<td>2.61 (1.28–5.80) 0.02</td>
<td>2.61 (1.28–5.80) 0.02</td>
<td>NA NA</td>
<td>NA NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IFNL2</td>
<td>rs8103362</td>
<td>Missense</td>
<td>2.61 (1.18–5.40) 0.06</td>
<td>2.45 (1.11–5.40) 0.03</td>
<td>NA NA</td>
<td>2.17 (1.02–4.63) 0.05</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IFNAR2</td>
<td>rs1051393</td>
<td>Missense</td>
<td>1.53 (0.82–2.88) 0.18</td>
<td>1.68 (0.92–3.06) 0.08</td>
<td>1.59 (0.87–2.90) 0.14</td>
<td>1.42 (1.01–2.00) 0.047</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TLR9</td>
<td>rs187084</td>
<td>NearGene-5'</td>
<td>1.38 (0.73–2.62) 0.32</td>
<td>1.56 (0.86–2.84) 0.13</td>
<td>1.61 (0.90–2.86) 0.11</td>
<td>1.41 (0.98–2.01) 0.06</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>IL-22</td>
<td>rs2227513</td>
<td>NearGene-5'</td>
<td>1.97 (0.32–12.28) 0.48</td>
<td>1.97 (0.32–12.28) 0.48</td>
<td>NA NA</td>
<td>NA NA</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T-111C</td>
<td></td>
<td></td>
<td>2.10 (1.00–4.40) 0.05</td>
<td>NA NA</td>
<td>NA NA</td>
<td>NA NA</td>
</tr>
</tbody>
</table>

CI, confidence interval; OR, odds ratio; SNP, single nucleotide polymorphism; NA, not applicable.

Table 4. Distribution of the frequencies of the IFNL3 genotype

<table>
<thead>
<tr>
<th>IFNL3 rs148543092 genotype</th>
<th>Original set</th>
<th>Replication set</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CKD (n = 75)</td>
<td>Control (n = 312)</td>
</tr>
<tr>
<td>TT</td>
<td>64 (85.3)</td>
<td>291 (93.6)</td>
</tr>
<tr>
<td>TC</td>
<td>11 (14.7)</td>
<td>20 (6.4)</td>
</tr>
<tr>
<td>CC</td>
<td>0 (0.0)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

Data are expressed as number (%).

TT vs. TC + CC.

CKD, chronic kidney disease.

The p-values were analyzed using the chi-square test: a p = 0.02, odds ratio (OR), 2.50 (95% confidence interval [CI], 1.14–5.47); b p < 0.001, OR, 0.92 (95% CI, 0.89–0.95).

Table 5. Association of IFNL3 SNP with the clinical characteristics

<table>
<thead>
<tr>
<th>SNP</th>
<th>Parameter</th>
<th>Genotype</th>
<th>p-value&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Genotype</th>
<th>p-value&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs148543092</td>
<td>Creatinine (mg/dL)</td>
<td>T/T (n = 64)</td>
<td>T/C + C/C (n = 11)</td>
<td>0.64</td>
<td>T/T (n = 172)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>8.32 ± 2.95</td>
<td>8.78 ± 3.64</td>
<td>8.86 ± 3.14</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6.79 ± 2.74</td>
<td>6.74 ± 2.89</td>
<td>7.18 ± 2.68</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>8.53 ± 2.76</td>
<td>8.55 ± 1.86</td>
<td>8.69 ± 2.62</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6.36 ± 0.71</td>
<td>5.90 ± 1.09</td>
<td>6.25 ± 0.78</td>
<td>NA</td>
</tr>
<tr>
<td>eGFR (mL/min/1.73 m²)</td>
<td></td>
<td>3.53 ± 0.45</td>
<td>3.35 ± 0.67</td>
<td>3.53 ± 0.56</td>
<td>NA</td>
</tr>
<tr>
<td>Uric acid (mg/dL)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Total protein (g/dL)</td>
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<tr>
<td>Albumin (g/dL)</td>
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</tr>
</tbody>
</table>

Data are expressed as mean ± standard deviation.
eGFR, estimated glomerular filtration rate; SNP, single nucleotide polymorphisms; NA, not applicable.
The p-values were analyzed using the t test: a original set and b replication set.
with advanced CKD. The SNPs of IFNAR2 (rs1051393), IFNL2 (rs1803362), and IFNL3 (rs148543092) were significantly associated with CKD. Among them, the frequency of rs148543092 in IFNL3 was significantly higher in CKD than the control group in the original and replication sets.

Persistent, low-grade inflammation is considered an essential component of CKD, playing an important role in its pathophysiology [12]. Patients with CKD exhibit elevated cytokine levels and dysregulated cytokine metabolism, leading to increased circulating acute-phase proteins [13]. In addition, IFN, an inflammatory cytokine, may play a regulatory role in the development and progression of CKD. However, the role of IFN in CKD is not well understood, especially in IFNL.

Additionally, type III IFN (IFNL) is associated with a cytokine family that has several similarities in functions with type I IFNs (either IFN-α, IFN-β, or IFN-α/β). The four IFNL proteins (IFNL1, IFNL2, IFNL3, and IFNL4) and 17 IFN-α/β proteins (13 IFN-α subtypes, IFN-β, IFN-ω, IFN-ε, and IFN-κ) are encoded by genes in humans [14]. Located in human chromosome 19, genes encoding IFNL have a similar gene structure with the 5-exon gene of the IL-10 cytokine family [15]. IFNL has several biological features, which begin with IFNL effectiveness. The efficacy of IFNL is most pronounced in epithelial cells where it explicitly strengthens the immune systems that protect the surface of the upper skin that is exposed to general and pathogenic microorganisms [16]. IFNL is involved in inflammation, one of the main pathophysiologies of CKD, and is expected to affect CKD development. This is the first study to identify the association between IFNL and CKD to the best of our knowledge.

IFNL has emerged as a new immune control cytokine with a particular function controlling damage to maintain an immune balance and limit immunology. In addition, IFNA limits inflammation to prevent damage to the host by chronic illnesses including asthma, auto-immune diseases, and colitis [17]. The genetic association of IFNL gene polymorphisms among humans expands to various illnesses such as allergies, nonalcoholic fatty liver disease, and several other viral diseases caused by human immunodeficiency virus and hepatitis C virus infections [18]. The difference in expression levels by the IFNL3 genotype was shown in numerous studies. For example, recent research outcomes verified this result in ex/in vivo conditions. These results demonstrate that differences in IFNL3 expression levels by the alleles at the three functional SNPs (rs28416813, rs4803217, and rs59702201) may play a role in the disease [19–21]. Furthermore, a recent study revealed that genetic variants of IFN3/4 play an essential role in developing lupus nephritis and systemic lupus erythematosus in the Taiwanese population [22]. However, little is known about the association between IFNL and CKD. In the present study, we demonstrate that the SNP of IFNL3 (rs148543092) is significantly associated with CKD development in patients with advanced CKD. Furthermore, these results are consistent with the entire CKD cohort (Supplementary Table 2, available online).

Additionally, several researchers have reported SNPs of IFNAR2 in hepatitis B virus (HBV) infections. Specifically, IFNAR2 polymorphisms may be involved in chronic HBV infection susceptibility among the Thai population [23]. It may also be involved when determining IFN response and predictive markers of HBV infections among the Chinese Han population [24]. Ma et al. [25] reported that the polymorphism of IFNAR2 (rs1051393 G > T) is a missense changing from phenylalanine to valine. This SNP may be important in the risk of HBV infection by influencing the expression of IFNAR2 protein on the cell’s surface, resulting in an antiviral response and damaged signal transduction. Our result also suggests that IFNAR2 polymorphisms (rs1051393 G > T) are associated with CKD. This research found that the T allele of IFNAR2 (rs1051393 G > T) was higher in the CKD group compared with the control. The interrelationship of this SNP may be a codominant effect shown by the inheritance analysis model (major allele homozygotes vs. minor allele homozygotes). Therefore, this study indicates that the mechanism underlying the association between IFNAR2 SNP (rs1051393 G > T) and CKD may control IFNAR2 expression, which affects the type I IFN effect.

CKD and end-stage kidney disease are featured by increased proinflammatory cytokine levels and inflammatory labeling. Cytokines may control the risk of developing kidney disease [13] and induce resident cells to proliferate and influence metalloproteinases, bioactive lipids, the expression of adhesion receptors, reactive oxygen/nitrogen species, procoagulant activity of the endothelium, and aberrant matrix metabolism. In addition, these molecules may be the action mediators of the renin-angiotensin sys-
tem and hemodynamic factors [26–33]. IL-10, an anti-inflammatory cytokine with numerous functions, is primarily secreted by monocytes and lymphocytes. IL-22, an IL-10–related cytokine, activates the upward adjustment of the acute-phase reactor. It also guides JAK/STAT activation in several cell lines, including hepatomas, intestinal epithelial cells, and mesangial cells [34]. Meta-analysis outcomes have shown that the IL-22 gene rs1179251 polymorphism (but not rs2227485 polymorphism) may be a cancer risk factor [35]. The rs2227485 SNP of IL-22 may have a connection with the risk and multifocality of primary thyroid cancers according to Eun et al. [36]. However, this research did not show that the association between polymorphisms (rs2227513 T > C; rs2227485 G > A) of the IL-22 gene and CKD development exhibited an association with rs2227484 polymorphisms.

Furthermore, the second sample set was used to analyze replicate associations involving IFNL3, IFNL2, IFNAR2, TLR9, and IL-22. No significant associations involving IFNL2, IFNAR2, TLR9, and IL-22 were observed in the replication set. Whereas concerning rs148543092, in the IFNL3 gene, a significant association was observed after pooling the original and replication sets. These results suggest that IFNL3 polymorphisms are associated with CKD. However, there were no significant differences between the clinical characteristics and genotypes of IFNL3.

There are several limitations to this study. First, this study was a single-center study and the sample size was relatively small. However, we performed a genetic analysis of the association between IFNL induction and signal pathway genes, such as IFNL3, IFNL2, IFNAR2, TLR9, IL-22, and IL-10RB and CKD, for the first time. Second, we analyzed advanced CKD rather than entire CKD patients due to the characteristics of our study cohort. However, even when entire CKD patients were analyzed, the same SNP of IFNL3 was associated with CKD. Third, homozygous genotypes were observed in CKD patients in the replication set. However, the heterozygous genotypes were observed in the original set which indicated that CKD had IFNL3 polymorphisms.

In conclusion, the outcome of this study indicates the possibility of an association between IFNL induction polymorphisms and signal pathway genes with CKD in the Korean population. Furthermore, our results indicate that the IFNL3 gene variant may be associated with CKD risk. Therefore, early interventions in patients with high-risk genotypes may delay CKD progression. However, further large-scale prospective studies are necessary to establish the role of IFNL in CKD.

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

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Authors’ contributions
Conceptualization: JHK, DHS, KJ
Data curation: JHK, JHP
Formal analysis: JHK, JHP, GIY
Funding acquisition: KJ
Investigation: GIY
Writing–original draft: JHK, DHS, GIY, SH, WYP, YK
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A multicenter, randomized, open-label, comparative, phase IV study to evaluate the efficacy and safety of combined treatment with mycophenolate mofetil and corticosteroids in advanced immunoglobulin A nephropathy

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Background: It remains unclear whether immunosuppressive agents are effective in patients with immunoglobulin A nephropathy (IgAN). We investigated the efficacy of a mycophenolate mofetil (MMF) and corticosteroid combination therapy in patients with advanced IgAN.

Methods: We conducted a multicenter, randomized, placebo-controlled, parallel-group study of 48 weeks administration of MMF and corticosteroids in biopsy-proven advanced IgAN patients with estimated glomerular filtration rate (eGFR) of 20–50 mL/min/1.73 m² and urine protein-to-creatinine ratio (UPCR) of >0.75 g/day. The primary outcome was complete (UPCR < 0.3 g/day) or partial (>50% reduction of UPCR compared to baseline) remission at 48 weeks.

Results: Among the 48 randomized patients, the percentage that achieved complete or partial remission was greater in the combination therapy group than in the control group (4.2% vs. 0% and 29.1% vs. 5.0%, respectively). Compared with the combination therapy group, eGFR in the control group decreased significantly from week 36 onward, resulting in a final adjusted mean change of –4.39 ± 1.22 mL/min/1.73 m² (p = 0.002). The adjusted mean changes after 48 weeks were 0.62 ± 1.30 and –5.11 ± 1.30 mL/min/1.73 m² (p = 0.005) in the treatment and control groups, respectively. The UPCR was significantly different between the two groups; the adjusted mean difference was –0.47 ± 0.17 mg/mgCr and 0.07 ± 0.17 mg/mgCr in the treatment and control group, respectively (p = 0.04). Overall adverse events did not differ between the groups.

Conclusion: In advanced IgAN patients with a high risk for disease progression, combined MMF and corticosteroid therapy appears to be beneficial in reducing proteinuria and preserving renal function.

Keywords: Corticosteroids, IgA nephropathy, Immunosuppressants, Mycophenolate mofetil, Proteinuria
Introduction

Immunoglobulin A nephropathy (IgAN) is the most common type of glomerulonephritis and is particularly prevalent among East Asian populations [1]. Although several pathogenetic mechanisms have been suggested, the precise mechanism of IgAN remains controversial. Overproduction of abnormal undergalactosylated IgA autoantibodies has been reported to play an important role in antibody deposition in the glomerular mesangium, leading to mesangial cell proliferation and matrix accumulation [2]. The prognosis of IgAN varies among patients, with the daily amount of proteinuria and kidney function at the time of diagnosis serving as important prognostic factors. The disease slowly progresses to end-stage kidney disease at 10 years after disease onset in approximately 27% of patients, and the prognosis for patients of Pacific Asian origin is worse than that of Western populations [3,4].

There is no definitive treatment for IgAN. The Kidney Disease: Improving Global Outcomes (KDIGO) 2020 guidelines for IgAN suggest that patients who remain at high risk of chronic kidney disease progression despite maximal supportive care be considered for a 6-month course of corticosteroid therapy [5], which is known to reduce IgA deposition and circulating IgA autoantibodies [6,7]. However, this recommendation is problematic due to the significant risk of toxicity associated with corticosteroid use, and risk stratification prior to administration is imperative.

In addition to corticosteroids, another immunosuppressant used in clinical practice is mycophenolate mofetil (MMF), although its role is controversial. Several studies investigating the efficacy of MMF have reported conflicting results. According to Beckwith et al. [8], in a prospective, randomized clinical trial involving 40 IgAN patients, MMF treatment resulted in statistically significant improvements in endocapillary hypercellularity and cellular crescents at 2-year follow-up after the initial biopsy, and stabilization of serum creatinine levels at three years. Although several additional studies investigating the efficacy of MMF have been conducted, studies have reported conflicting results [9-14]. According to the most recent KDIGO guidelines, MMF has been suggested as a potential steroid-sparing agent in Chinese patients [5]. As Chinese and Korean individuals have similar ethnic backgrounds, MMF could also be considered in Korean IgAN patients.

This study, a multicenter, randomized, open-label, parallel-group study of 48-weeks of MMF and corticosteroids in biopsy-proven advanced IgAN patients with estimated glomerular filtration rate (eGFR) of 20–50 mL/min/1.73 m², was designed to demonstrate the efficacy of combination therapy in patients with advanced IgAN.

Methods

Study population

From September 2016 through July 2018, we screened 50 patients with biopsy-proven IgAN at seven tertiary institutions in Korea. After screening out two patients who failed the eligibility criteria, a total of 48 patients were enrolled in the present study (Fig. 1). The key eligibility criteria were biopsy-proven IgAN; age of 19 to 65 years; urine protein-to-creatinine ratio (UPCR) above 0.75 g/day; and an eGFR between 20 and 50 mL/min/1.73 m² using the Modification of Diet in Renal Disease (MDRD) equation [15]. Major exclusion criteria were an eGFR lower than 20 mL/min/1.73 m², systolic blood pressure above 160 mmHg or diastolic blood pressure above 100 mmHg, systemic inflammation or malignancy within the 5 years prior to screening, white blood cell count less than 3,000/mm³, or immunosuppression within 12 weeks prior to screening. During a 3-month run-in phase, all the patients received comprehensive supportive care, including renin-angiotensin-system (RAS) blockers.

The study was conducted in compliance with the Declaration of Helsinki, Good Clinical Practice guidelines, and standard operating procedures of the sponsor and was approved by the Institutional Review Board (IRB) of each participating center (host research institute, Yonsei University College of Medicine; IRB No. 4-2015-1199). Informed consent was obtained from each patient before the screening process.

Study design

This multicenter, randomized, open-labeled study was performed for 48 weeks (ClinicalTrial.gov NCT02981212; https://clinicaltrials.gov/ct2/show/NCT02981212). The eligible participants were randomized in a 1:1 ratio of MMF (Myrept, ChongKunDang Pharmaceutical, Seoul, Korea)
and corticosteroid or control. The dose of MMF was 1,500 to 2,000 mg/day based on body weight. Prednisolone was prescribed at 0.5 mg/kg for 8 weeks and then tapered by 5 mg weekly until a final dose of 5 mg of prednisolone was maintained for the rest of the study period. Participants assigned to the control group received supportive care that included blood pressure management by prescription of maximally tolerated dose of RAS blockers and lifestyle modifications, consistent with treatment guidelines proposed by the KDIGO Glomerular Diseases Work Group [5].

Data collection

Demographic, medication, and laboratory data were collected at the time of study enrollment. Serum creatinine levels were determined using an isotope dilution mass spectrometry-traceable method at the central laboratories of each participating institution, with calibration against the reference. The eGFR was calculated using the MDRD creatinine equation [15]. Study participants visited the outpatient clinics of participating institutions every 12 weeks for a total of 48 weeks, where follow-up anthropometric, medication, and laboratory data (including blood chemistry tests and urinalysis), as well as safety data were collected at each visit.

Participant allocation

In this study, the size of the block was selected to be a multiple of two so that each subject was assigned a balanced allocation. Random number generation was performed using SAS version 9.3 (SAS Institute, Cary, NC, USA), and

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**Figure 1.** Flow diagram for study participant enrollment and randomization.
random assignment was carried out with a 1:1 allocation ratio between the treatment and control groups. A random identification number was assigned to each subject who met the inclusion and exclusion criteria using the Interactive Web Response System.

Efficacy and safety assessments

The primary outcome of the study was to evaluate the response rate of complete or partial remission at 48 weeks, defined as a UPCR less than 0.3 g/day and greater than 50% reduction of proteinuria compared to baseline, respectively. Additional study outcomes were response rates of complete and partial remission at 12, 24, and 36 weeks; changes in eGFR and UPCR at 24, 36, and 48 weeks; and the rate of kidney replacement therapy. The safety outcomes included adverse events including infections, gastrointestinal and hematological disorders, edema, and changes in vital signs and various laboratory parameters.

Statistical analyses

The proportion of remission in the treatment and the control group was set at 65% and 30%, respectively. The ratio of the groups was 1:1, and the level of significance (two-sided test) was 5% and 90%, respectively. As a result, it was necessary to include 40 subjects in each group, and assuming a dropout rate of 20%, an initial group size of 50 subjects. The total number of subjects required to be enrolled (treatment group plus control group) was calculated to be 100.

Survival curves and median survival time were estimated using the Kaplan-Meier method, and comparison between the groups was performed using the log-rank test. Continuous data were tested by an independent t test or Wilcoxon rank-sum test, and the results are presented as mean ± standard deviation or mean ± standard error. Categorical data were assessed using the chi-square test or Fisher exact test, and the results are presented as number and percentage. All analyses were conducted using STATA version 15 (STATA Corp., College Station, TX, USA).

Results

Baseline characteristics

Of the 48 randomized patients originally enrolled in the study, 44 were included in the full analyses, and 30 were included in the per-protocol analyses. The reasons for exclusion from the per-protocol analyses were major protocol violation (n = 1), adverse reaction (n = 4), no medication for more than 7 days (n = 1), withdrawal (n = 2), use of contraindicated medications (n = 1), study drug compliance <80% (n = 2), and other protocol violations (n = 7).

There were no statistically significant differences in baseline demographics or disease characteristics between the two groups (Table 1). At baseline, the mean age was 44.0 ± 10.6 years in the treatment group and 46.1 ± 7.8 years in the control group. The mean eGFR and UPCR were 36.3 ± 9.4 mL/min/1.73 m² and 1.7 ± 0.6 mg/mgCr in the treatment group, respectively; and 33.0 ± 7.7 mL/min/1.73 m² and 2.2 ± 1.0 mg/mgCr in the control group, respectively. All patients had taken RAS blockers for more than 3 months. No differences in physical examination or laboratory and electrocardiogram findings between the two groups were noted.

Of the 48 enrolled participants of this study, kidney biopsy results were available for 33, and their results are summarized in Supplementary Table 1 (available online). Kidney biopsy findings were similar among the two treatment groups.

Efficacy

In the full analysis, the percentage of patients achieving remission at 48 weeks tended to be higher in the treatment group than in the control group (29.1% vs. 5.0% for partial remission, p = 0.05) (Table 2). One participant in the treatment group was in complete remission at 12 weeks after study enrollment. Changes in eGFR differed between the two groups. In the treatment group, the eGFR increased significantly at 4, 12, and 24 weeks after randomization compared to the baseline value (Fig. 2A). At 36 and 48 weeks, the adjusted mean changes were not significantly different compared to baseline, and the eGFRs were stable. In the control group, however, eGFR decreased significantly after 36 weeks; eGFR further decreased significantly at 48 weeks, resulting in an adjusted mean change of −4.39 ± 1.22
Comparing the results between the two groups, the treatment group was superior to the control with regard to adjusted mean change at 48 weeks (p = 0.01). The superiority was also significant at 12 weeks after randomization, and this effect was similar in the per-protocol analyses. Ultimately, the adjusted mean changes were 0.62 ± 1.30 and -5.11 ± 1.30 (p = 0.005) in the treatment and control groups at 48 weeks, respectively (Fig. 2B).

Table 1. Baseline demographic and clinical characteristics of the study participants

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Treatment</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>24</td>
<td>20</td>
</tr>
<tr>
<td>Demographic characteristic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (yr)</td>
<td>44.0 ± 10.6</td>
<td>46.1 ± 7.8</td>
</tr>
<tr>
<td>Male sex</td>
<td>15 (62.5)</td>
<td>10 (50.0)</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>24.5 ± 3.9</td>
<td>24.3 ± 3.5</td>
</tr>
<tr>
<td>Clinical characteristic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>124.5 ± 10.6</td>
<td>129.5 ± 9.8</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>79.8 ± 9.03</td>
<td>78.7 ± 8.3</td>
</tr>
<tr>
<td>Blood urea nitrogen (mg/dL)</td>
<td>29.4 ± 10.3</td>
<td>30.6 ± 12.7</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>2.0 ± 0.6</td>
<td>2.0 ± 0.5</td>
</tr>
<tr>
<td>eGFR (mL/min/1.73 m²)</td>
<td>36.3 ± 9.4</td>
<td>33.0 ± 7.7</td>
</tr>
<tr>
<td>UPCR (mg/mgCr)</td>
<td>1.7 ± 0.6</td>
<td>2.2 ± 1.0*</td>
</tr>
</tbody>
</table>

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

Table 2. Primary outcomes among study participants at the end of the 48-week clinical trial

<table>
<thead>
<tr>
<th>Remission</th>
<th>Treatment (n = 24)</th>
<th>Control (n = 20)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete remission, n (%)</td>
<td>1 (4.2)</td>
<td>0 (0)</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>Duration to complete remission (wk)</td>
<td>12.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Partial remission, n (%)</td>
<td>7 (29.2)</td>
<td>1 (5.0)</td>
<td>0.05</td>
</tr>
<tr>
<td>Duration to partial remission (wk)</td>
<td>37.5</td>
<td>12.0</td>
<td></td>
</tr>
</tbody>
</table>

Figure 2. Time course of changes in eGFR in each group. (A) Changes in eGFR (mean profile plot). (B) Adjusted mean changes in eGFR (mean difference vs. baseline).

Although the percentage of patients achieving partial remission was marginally different between the two groups, the amount of proteinuria was significantly different (Table 3, Fig. 3). In the treatment group, the UPCR decreased significantly compared to baseline after 12 weeks (adjusted mean difference, -0.50 ± 0.69; p = 0.04), and this effect persisted until the end of the study period. However, there was no interval change in the UPCR in the control group. Overall, the UPCR differed significantly between the two groups, with adjusted mean differences of -0.47 ± 0.17 in the treatment group and 0.07 ± 0.17 in the control group (p = 0.04).

No participants in either group had initiated kidney replacement therapy. No significant differences were noted between the two groups at 48 weeks with respect to clinical parameters, including blood pressure, heart rate, temperature, and weight, with the exception of white blood cell, eosinophil, and basophil counts (Table 4). The adjusted
mean difference in white blood cell count was greater in the treatment group than in the control group (p = 0.02). The eosinophil and basophil counts were significantly reduced in the treatment group.

Safety

There was no significant difference in overall adverse events between the two groups (Table 5), with 23 patients (88.5%) in the treatment group and 15 patients (68.2%) in the control group experiencing such events (p = 0.15). No significant difference in the incidence of severe adverse events was observed between the two groups. However, two serious adverse events occurred in both groups. In the treatment group, one patient experienced sudden death of unknown cause, and one patient experienced urinary tract infection. In the control group, one patient experienced foot fracture, and one patient experienced shoulder and cervical sprain.

Drug-related adverse events in 12 patients (46.2%) of the treatment group included fatigue, abdominal pain, diarrhea, dysgeusia, gastritis, sinusitis, hypertension, urinary tract infection, esophagitis, dermatitis acniform, dyspepsia, abdominal discomfort, vomiting, nausea, epigastric

Table 3. Urine protein-to-creatinine ratio at each visit

<table>
<thead>
<tr>
<th>Follow-up (wk)</th>
<th>Parameter</th>
<th>Treatment (n = 26)</th>
<th>Control (n = 22)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ± SD</td>
<td>1.71 ± 0.56</td>
<td>2.26 ± 0.91</td>
<td>0.03</td>
</tr>
<tr>
<td>12</td>
<td>Mean ± SD</td>
<td>1.24 ± 0.64</td>
<td>2.04 ± 1.41</td>
<td>0.04</td>
</tr>
<tr>
<td></td>
<td>Difference vs. baseline</td>
<td>-0.50 ± 0.69</td>
<td>-0.10 ± 0.99</td>
<td>0.16</td>
</tr>
<tr>
<td></td>
<td>Adjusted mean difference ± SE</td>
<td>-0.52 ± 0.19</td>
<td>-0.08 ± 0.21</td>
<td>0.14</td>
</tr>
<tr>
<td>24</td>
<td>Mean ± SD</td>
<td>1.32 ± 0.67</td>
<td>1.92 ± 0.77</td>
<td>0.02</td>
</tr>
<tr>
<td></td>
<td>Difference vs. baseline</td>
<td>-0.38 ± 0.72</td>
<td>-0.12 ± 0.77</td>
<td>0.18</td>
</tr>
<tr>
<td></td>
<td>Adjusted mean difference ± SE</td>
<td>-0.47 ± 0.15</td>
<td>-0.02 ± 0.17</td>
<td>0.06</td>
</tr>
<tr>
<td>36</td>
<td>Mean ± SD</td>
<td>1.33 ± 0.68</td>
<td>1.92 ± 0.95</td>
<td>0.42</td>
</tr>
<tr>
<td></td>
<td>Difference vs. baseline</td>
<td>-0.35 ± 0.80</td>
<td>-0.11 ± 0.78</td>
<td>0.26</td>
</tr>
<tr>
<td></td>
<td>Adjusted mean difference ± SE</td>
<td>-0.43 ± 0.18</td>
<td>-0.03 ± 0.19</td>
<td>0.14</td>
</tr>
<tr>
<td>48</td>
<td>Mean ± SD</td>
<td>1.27 ± 0.52</td>
<td>1.97 ± 0.89</td>
<td>0.01</td>
</tr>
<tr>
<td></td>
<td>Difference vs. baseline</td>
<td>-0.38 ± 0.68</td>
<td>-0.03 ± 0.79</td>
<td>0.35</td>
</tr>
<tr>
<td></td>
<td>Adjusted mean difference ± SE</td>
<td>-0.47 ± 0.17</td>
<td>0.07 ± 0.17</td>
<td>0.04</td>
</tr>
</tbody>
</table>

SD, standard deviation; SE, standard error.

Figure 3. Time course of changes in urine protein-to-creatinine ratio in each group. (A) Changes in urine protein-to-creatinine ratio (mean profile plot). (B) Adjusted mean changes in urine protein-to-creatinine ratio (mean difference vs. baseline).
discomfort, facial edema, dry eye, and abdominal pain, all of which were tolerable. Drug compliance was good, at greater than 90% during the entire study period.

**Discussion**

The current study showed that the percentage of study participants achieving complete or partial remission of proteinuria was greater among those receiving MMF and corticosteroid combination therapy than in those receiving supportive care alone. We decided to stop this study due to ethical issues based on results of the interim analyses. Although the interim analyses revealed a marginally significant difference in primary outcome between the two groups, the secondary outcomes of eGFR and proteinuria were significantly different, with the difference in eGFR being greater at 48 weeks than at either 24 or 36 weeks. We also found changes in serum potassium, leukocyte, eosinophil, and basophil counts, where the increase in leukocytes and decrease in eosinophils and basophils might have been influenced by corticosteroids. The findings of this study add evidence to the current literature that MMF could potentially be prescribed as a steroid-sparing agent in patients with advanced IgAN.

The reported effects of combination therapy with corticosteroids and cytotoxic agents are inconsistent. In the STOP-IgA (Supportive Versus Immunosuppressive Therapy for the Treatment of Progressive IgA Nephropathy) trial, combination treatment with a corticosteroid and cyclophosphamide was not effective for changes in eGFR and proteinuria [16]. Furthermore, in another study, the addition of azathioprine to corticosteroids was not effective in IgAN patients [17]. However, combination therapy has shown beneficial effects in other studies; for example,

| Table 4. Laboratory parameters among study participants at 48 weeks |
|---------------------------------------------|-----------------|-----------------|-----------------|
| Parameter                          | Treatment (n = 26) | Control (n = 22) | p-value |
| White blood cell (/µL)             | 7,910 ± 1,580     | 6,980 ± 1,050    | 0.06   |
| Neutrophils (%)                    | 60.9 ± 8.9        | 56.3 ± 7.2       | 0.13   |
| Absolute neutrophil count         | 4,840 ± 1,340     | 3,930 ± 750      | 0.08   |
| Lymphocytes (%)                    | 30.0 ± 8.0        | 33.2 ± 7.0       | 0.25   |
| Monocytes (%)                      | 7.6 ± 2.4         | 6.1 ± 1.4        | 0.04   |
| Eosinophils (%)                    | 1.1 ± 0.5         | 3.8 ± 2.8        | <0.001 |
| Basophils (%)                      | 0.4 ± 0.2         | 0.7 ± 0.3        | 0.02   |
| Hemoglobin (g/dL)                  | 13.4 ± 2.1        | 12.9 ± 2.1       | 0.53   |
| Platelets (10^9/L)                 | 245 ± 35          | 254 ± 54         | 0.56   |
| Blood urea nitrogen (mg/dL)        | 28.5 ± 11.8       | 35.1 ± 13.7      | 0.09   |
| Total protein (g/dL)               | 6.5 ± 0.5         | 6.8 ± 0.6        | 0.10   |
| Albumin (g/dL)                     | 4.1 ± 0.3         | 4.0 ± 0.3        | 0.27   |
| Glucose (mg/dL)                    | 98.4 ± 12.3       | 107.0 ± 23.4     | 0.22   |
| Sodium (mEq/L)                     | 141 ± 2           | 140 ± 3          | 0.59   |
| Potassium (mEq/L)                  | 4.4 ± 0.4         | 4.9 ± 0.2        | <0.001 |
| Chloride (mEq/L)                   | 105.9 ± 2.5       | 107.7 ± 2.6      | 0.11   |

Data are expressed as mean ± standard deviation.

| Table 5. Adverse events among study participants during the 48-week clinical trial |
|---------------------------------------------|-----------------|-----------------|-----------------|
| Adverse event                          | Treatment (n = 26) | Control (n = 22) | p-value |
| Serious adverse event                   | 2 (7.7)          | 2 (9.1)         | >0.99   |
| Type of serious adverse events          | 1 (3.8)          | 0 (0)           |         |
| Death                                  | 1 (3.8)          | 0 (0)           | <0.001  |
| Adverse event                          | 23 (88.5)        | 15 (68.2)       | 0.15    |
| Drug-related adverse event             | 12 (46.2)        | 0 (0)           | <0.001  |
| Type of adverse events                  |                 |                 |         |
| Infection                              | 9 (34.6)         | 9 (40.9)        |         |
| Gastrointestinal disorder              | 11 (42.3)        | 2 (9.1)         |         |
| Hematologic disorder                   | 1 (3.8)          | 0 (0)           |         |
| Edema                                  | 3 (11.5)         | 0 (0)           |         |
| Other disorders                        | 6 (23.1)         | 0 (0)           |         |

Data are expressed as number (%).
coadministration of corticosteroids and cytotoxic agents stabilized eGFR in patients with IgAN in two prospective, randomized, controlled trials [18,19]. The results of our study are consistent with the findings of previous studies, demonstrating clinical remission and significant changes in eGFR and proteinuria among treatment groups. The eGFR improved with combination therapy at 12 weeks after treatment, and this beneficial effect was more prominent at 48 weeks. Proteinuria exhibited a pattern similar to that of eGFR, significantly decreasing in the treatment group but increasing in the control group.

It is unclear why the effects of combination therapy were different among groups, but one of several plausible explanations could be the effect of MMF. Indeed, inconsistent results have been documented for MMF monotherapy and combination therapy in several studies [9,10,19–22]. Among 33 children with steroid-resistant IgA nephropathy or nephrotic syndrome, 21 and six patients receiving combined MMF and corticosteroid therapy were able to achieve complete or partial remission of proteinuria, respectively [22]. Recent randomized clinical trials have indicated that combination therapy with MMF and corticosteroids had a similar effect on proteinuria reduction and fewer adverse events than full-dose corticosteroids in IgAN patients [13]. Overall, MMF has been reported to be superior to cyclophosphamide. Combination therapy using MMF and corticosteroids achieved a higher remission rate than combination therapy using cyclophosphamide and corticosteroid in patients with severe IgAN, and the MMF and corticosteroid combination reduced proteinuria and improved renal function. In addition, the incidence of adverse events was significantly lower in patients taking MMF than in those taking cyclophosphamide [12].

Immunosuppression-related adverse events represent one of the main obstacles for treatment of IgAN. The TEST-ING (Therapeutic Evaluation of Steroids in IgA Nephropathy Global) trial indicated that corticosteroids significantly reduced adverse renal outcomes; however, the rate of serious adverse events was 14.7% in the treatment group versus 3.2% in the control group [23]. As expected, adverse events in the present study occurred in a significantly greater percentage of participants in the combination therapy group. However, with the exception of one patient who died of an unknown cause, most of the side effects were tolerable. Given the lower incidence of side effects of combination therapy with MMF and corticosteroids than with high-dose corticosteroids alone [13], this combination regimen could be an alternative to high-dose corticosteroids in patients prone to drug-related side effects.

Some limitations of our study are worth noting. First, this study was not completed as scheduled; only 50% of subjects were randomized. As only patients with advanced IgA nephropathy, defined as those with eGFR of <50 mL/min/1.73 m², were included, participant enrollment was more difficult than anticipated. A larger study population would have strengthened the findings of this study. Second, although kidney biopsy findings were available for 33 of 48 participants, more detailed findings, such as duration between pathologic diagnosis and initiation of immunosuppressant therapy, could have provided further insights into how different pathologic characteristics could affect treatment outcomes. Third, the dropout rate was high; only 30 of the 44 patients completed the study. Fourth, the control group had higher baseline proteinuria than the treatment group, which might account for the difference in outcomes of proteinuria. Nonetheless, the primary outcome of complete or partial remission tended to be significant, and the secondary outcomes were significantly beneficial in the MMF and corticosteroid combination therapy group.

In patients with advanced IgAN with a high risk of disease progression, combination therapy with MMF and corticosteroid appears to be beneficial in reducing proteinuria and preserving renal function, with relatively tolerable safety profiles. Although the results of this study suggest a potential benefit, further studies are warranted to validate the conclusion.

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Conflicts of interest

This study was sponsored by ChongKunDang Pharmaceutical. All authors have no conflicts of interest to declare.

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Authors’ contributions

Conceptualization: BSK, BSC
Data curation: All authors
Formal analysis: SYH, CYJ, BSC, BSK
Investigation: All authors
Supervision: BSC, BSK
Writing-original draft: All authors
Writing-review & editing: All authors
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References


Background: Hemodialysis patients with chronic kidney disease exhibit impaired exercise tolerance and functional decline. Despite the life-saving benefits of adequate dialysis, those declines translate into frailty and deteriorating quality of life (QoL). This study evaluated the effects of an intradialytic aerobic exercise program on frailty, dialysis adequacy, and QoL among hemodialysis patients.

Methods: Patients at an university hospital-affiliated hemodialysis center were randomly assigned to an exercise group (n = 18) or a control group (n = 21). The 12-week aerobic exercise program comprised 40 to 70 minutes of ergometer cycling 3 times/wk and a single education session. The control group completed only the education session. Outcomes were assessed at the time of enrollment, week 4, week 8, and week 12 using Fried’s frailty phenotype measures (gait speed, grip strength, vitality, body mass index, and physical activity), the short physical performance battery (SPPB), Kt/V urea, and the Short Form-36 questionnaire.

Results: There were significant interactions between groups and follow-up times in the frailty score (p < 0.001), gait speed (p < 0.001), SPPB (p < 0.001), and mental QoL (p = 0.03). The intention-to-treat and per-protocol analyses revealed that the exercise group exhibited significant improvements in frailty score (p < 0.001), gait speed (p < 0.001), grip strength (p < 0.001), exhaustion (p = 0.02), SPPB (p = 0.01), dialysis adequacy (p = 0.01), and physical QoL (p = 0.003).

Conclusion: An intradialytic aerobic exercise program could be a safe, feasible, and appropriate additional strategy to routine care among hemodialysis patients for improvements in frailty, dialysis adequacy, and QoL.

Keywords: Exercise, Frailty, Quality of life, Renal dialysis
Introduction

The survival of patients undergoing hemodialysis has been improved by advances in hemodialysis therapy, standard expert practice, and affordable national healthcare support [1]. However, hemodialysis patients still experience physical and psychosocial burdens from living with chronic kidney disease [2]. Despite the life-saving benefits of adequate dialysis, the uremic milieu continues to impair bodily functions and structures, leading to exercise intolerance, impaired mobility, and disability among hemodialysis patients [3]. Those burdens predispose hemodialysis patients to adverse behaviors, such as a lack of motivation, sedentary lifestyle, and reduced physical activity, which can translate into frailty, which is known to affect approximately one-half of hemodialysis patients [2–4]. Frailty is a geriatric syndrome characterized as a multidimensional construct (slow gait speed, muscle weakness, exhaustion, weight loss, and low physical activity) [5].

Intradialytic aerobic exercise for hemodialysis patients improves aerobic capacity, muscular functioning, cardiovascular function, walking capacity, dialysis adequacy, and quality of life (QoL) without any adverse effects in clinical practice, although the structure of the intradialytic exercise varied widely in intensity, frequency, and duration [6–8]. Therefore, intradialytic aerobic exercise is recommended as a safe, feasible, and appropriate way to enhance physical functioning and QoL [9] that is associated with a low dropout rate, no need to find extra time for exercise, good compliance, and supervision by dialysis experts. However, it does have the drawbacks of adding to the workload of dialysis care providers, and its adoption into routine care has been slow [4,6,7]. The coexistence of frailty and dialysis markedly aggravates functional declines and health in all age groups [2]. Low physical activity contributes directly and indirectly to the development of frailty, and increased physical activity can prevent or reverse frailty, a non-permanent progressive condition that reflects physical performance and QoL [10,11]. However, few controlled trials have rigorously explored the effects of an intradialytic aerobic exercise program on the multidimensional nature of frailty among hemodialysis patients in Korea. Therefore, in this study, we evaluated the effects of an intradialytic aerobic exercise program on frailty, dialysis adequacy, and QoL among Korean hemodialysis patients.

Methods

Participants and setting

A sample of 42 hemodialysis patients was enrolled at a university hospital-affiliated hemodialysis center. All participants were undergoing regular hemodialysis (3 times/wk for 3–4 hours per session) with bicarbonate dialysate. The eligibility criteria were the age of ≥18 years, hemodialysis duration of ≥3 months for dialysis adjustment, no perfusion problems through an arteriovenous fistula to maintain adequate blood flow (250 mL/min), no severe hemodialysis-related complications, no history of completing an intradialytic aerobic exercise program (3 times/wk), the ability to use a cycle ergometer while lying in the dialysis bed, and the cognitive ability to read and comprehend the questionnaire. To minimize exercise-related risks, participants were excluded if they had a history of mental illness, any cardiac risk factors (myocardial infarction, angina pain, or uncontrolled hypertension), musculoskeletal risk factors, or a diagnosis of glaucoma during the previous 6 months. The required sample size was 18 patients/group using a repeated-measures within–between interaction model (α = 0.05, 1 – β = 0.8, effect size = 0.35, correlation among repeated measures = 0.5, non-sphericity correction ε = 0.5). To account for dropouts, 42 eligible hemodialysis patients from six sequentially numbered coupled dialysis shifts were enrolled and randomly assigned to either the exercise group (n = 21) or the control group (n = 21). Given the design of the exercise program, the participants, researchers, and dialysis care providers were not blinded. The exercise group completed a 12-week program of intradialytic aerobic exercise and a single education session (n = 18), while the control group completed only the education session (n = 21). In the exercise group, one patient dropped out because of exhaustion after week 4, and two patients missed their dialysis appointments after week 8 (Fig. 1).

Ethical considerations

The study protocol was approved by the Institutional Review Board of Bundang CHA Medical Center (No. BD2015-095) and registered at a primary national clinical trial registration site (https://cris.nih.go.kr/cris/index.jsp; registration No., KCT0006774). All participants provided written consent before participation.
informed consent before being enrolled. The researchers provided the participants with information regarding the study’s aims and methods, the right to withdraw at any time without reprisal, and their right to privacy.

**Intradialytic aerobic exercise program**

An intradialytic aerobic exercise program was developed based on the literature and previous studies [4,11–14]. The content of the exercise program was validated by a group of experts: three nephrologists, two dialysis nursing specialists, and a nursing professor with 10-year experience in nephrology nursing (content validity index = 0.95). The researchers performed an initial feasibility study with three hemodialysis patients to standardize the intradialytic cycle ergometer exercise program and ensure its safety; those patients also provided informed consent. The preliminary findings indicated that the intradialytic exercise program, which consisted of warm-up, cycle ergometer exercise, and cool-down stages, was feasible, safe, and tolerable.

The exercise program began with a 50-minute education session called “Exercise guide for patients undergoing hemodialysis,” with sections titled “Exercise and its effects on health,” “Hemodialysis patients can do exercise,” “Types of

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**Figure 1.** Consolidated standards for reporting trials flow diagram.
exercise for people undergoing hemodialysis,” “Principles of exercise,” “Making exercise part of your life,” and “Behavioral change” to boost participant understanding of the intervention [12]. The 12-week aerobic exercise program involved 40 to 70 minutes of ergometer cycling 3 times/wk. Each exercise session comprised a stretching warm-up phase (5 minutes), the main exercise phase (30–60 minutes), and a cool-down phase (5 minutes). During the warm-up phase, the participants completed 10 cycles of neck/arm/hand stretches, shoulder shrugs and rotations, chest and upper back stretching exercises, single knee pulls, front and back leg stretches, and calf stretches [12,13]. During the main phase, the cycle ergometer exercise was safely performed during the first 1 to 1.5 hours of each dialysis session without cardiac decompensation. The leg ergometer (Mbike; Hong Jin Company, Shanghai, China) was fixed at the foot of the patients’ beds to allow them to pedal while remaining in the supine position during dialysis [4]. Exercise intensity was individually determined based on the rate of perceived exertion from the Borg scale, with a gradual increase from very light/light intensity (score of 7–9 for 5 minutes) to somewhat hard/hard intensity (score of 12–15 for 20–50 minutes) and then a decrease again to very light/light intensity (score of 7–9 for 5 minutes) [12,13,15]. Intermittent breaks were permitted during the exercise to prevent exhaustion and blood pressure elevation. The cool-down phase involved 10 cycles of arm, shoulder, and leg stretches in a 5-minute period. The control group completed only the education session after the baseline measurements.

All participants’ exercise durations and intensities during each session were supervised by nephrologists, dialysis nurses, and researchers to ensure that all hemodialysis-related and exercise-related parameters remained stable and safe (blood pressure, heart rate, pulse oxygen saturation, and the overexertion symptoms of fainting, chest pain, dyspnea, abdominal pain, nausea, vomiting, muscle pain, joint pain, etc.), based on the protocols of previous studies [4,14].

Measurements of study outcomes

Demographic, dialytic, and clinical assessments
Data regarding the participants’ demographic characteristics were collected using a self-administered questionnaire. Hemodialysis-related and clinical data were collected from the patients’ electronic medical records at the time of enrollment. Each participant’s Charlson’s comorbidity index was calculated (http://touchcalc.com/calculators/cci.js). Body composition parameters (skeletal muscle mass, body fat, and lower leg muscle) were measured with a body composition analyzer (Inbody S10; InBody Corp., Ltd., Seoul, Korea) using the direct segmental measurement bioelectrical impedance method at the time of enrollment and week 12 of the exercise program.

Frailty stage based on the Fried phenotype and the short physical performance battery measurements
Frailty was assessed using Fried’s frailty phenotype (gait speed, grip strength, vitality, body mass index, and physical activity) [5]. Each factor is scored as 1 (present) or 0 (absent): gait speed of <0.8 m/sec [16], grip strength of <30 kg for men or <20 kg for women [17], vitality score of <55 from the Short Form-36 (SF-36) tool, body mass index of ≤18.5 kg/m² [5], and light physical activity for <30 minutes on 5 days of the week or moderate physical activity for <150 min/wk [18]. Patients with a score of ≥3 (i.e., three or more factors present) are considered frail [4]. A stopwatch was used to measure the participants’ 4-m gait speeds at a comfortable pace on a flat and straight surface. Maximum handgrip strength was evaluated in kilograms using a handheld dynamometer (JAMAR Hydraulic Hand Dynamometer; Patterson Medical Ltd., Chicago, IL, USA). All measurements were performed 1 hour after the hemodialysis session at the time of enrollment and at weeks 4, 8, and 12.

The validated short physical performance battery (SPPB) is based on scores of 0 to 4 points in three sections (balance, gait speed, and chair stand test), with a maximum score of 12, a minimum score of 0, and scores classified as normal mobility function (≥10 points) and frail mobility function (<10 points) [18]. Cronbach’s alpha value for the SPPB in this study was 0.83. The SPPB values were determined 1 hour after the hemodialysis session at the time of enrollment and at weeks 4, 8, and 12.

Dialysis adequacy
Hemodialysis adequacy was evaluated using Kt/V urea at the time of enrollment and at weeks 4, 8, and 12 of the exercise program.
Quality of life-based on the Short Form-36 questionnaire
Quality Metrics (https://www.qualitymetric.com) provided the validated Korean edition (version 2) of the SF-36 questionnaire (license No. QM027199), which contains eight multi-item scales that generate a physical component summary (PCS) score and a mental component summary (MCS) score. Those scores are transformed linearly into a 0 to 100-point scale, with higher scores indicating better health [19]. The Cronbach's alpha value was 0.82. The QoL values were evaluated at the time of enrollment and at weeks 4, 8, and 12.

Data analysis
All data were analyzed using IBM SPSS version 23 (IBM Corp., Armonk, NY, USA). Data normality was determined using the Shapiro-Wilk test. The baseline characteristics of the two groups were compared using the chi-square test, Fisher exact test, or unpaired t test. Outcome data were analyzed using the chi-square test, analysis of covariance, and repeated-measures analysis of covariance with Bonferroni correction. If the data failed Mauchly’s sphericity assumption, the results are presented using Greenhouse-Geisser correction method. If the data failed Mauchly’s sphericity assumption, the results are presented using Greenhouse-Geisser correction method. The Mann-Whitney U test was used for the intention-to-treat analysis with multiple imputations (regression method).

Results
Participant homogeneity
The exercise and control group participants were homogeneous except for the significantly lower dialysis vintage in the exercise group (p = 0.004) (Table 1).

Changes in the incidence of frailty and body composition parameters
At baseline, the exercise and control groups had similar incidences of frailty. After 12 weeks, the exercise group had less frailty as reflected by Fried’s frailty score (p < 0.001), gait speed (p < 0.001), physical activity (p < 0.001), exhaustion (p = 0.002), and SPPB score (p = 0.002) (Table 2). The body composition parameters showed no significant improvements (Table 2).

Within- and between-group interaction effects on frailty, dialysis adequacy, and quality of life
At baseline, the exercise and control groups had similar frailty scores, SPPB scores, and QoL scores. There was a significant interaction in the overall frailty score (p < 0.001), gait speed (p < 0.001), and SPPB score (p < 0.001). The exercise group had a significant interaction in the overall MCS score (p = 0.03) (Table 3).

Differences in frailty, dialysis adequacy, and quality of life according to the intention-to-treat and per-protocol analyses
The intention-to-treat and per-protocol analyses revealed that the exercise group exhibited significant improvements in the overall frailty score (p < 0.001, p < 0.001), gait speed (p < 0.001, p < 0.001), grip strength (p < 0.001, p < 0.001), exhaustion (p = 0.02, p = 0.02), SPPB score (p = 0.04, p = 0.01), dialysis adequacy (p = 0.01, p = 0.01), and PCS score (p = 0.005, p = 0.003) (Table 4).

Discussion
This study determined whether an intradialytic aerobic exercise program could improve frailty, dialysis adequacy, and QoL for hemodialysis patients.

Education and counseling are required to increase physical activity and drive behavioral change in hemodialysis patients [4]. However, a single 50-minute education session about physical activity did not reduce the incidence of frailty in the control group. In contrast, the exercise group had fewer cases of frailty after the program, as shown by Fried’s frailty score (0% vs. 66.7%), as well as its parameters of gait speed (5.6% vs. 66.7%) and exhaustion (38.9% vs. 90.5%) and the SPPB score (0.0% vs. 41.9%). Although this intradialytic aerobic exercise program did not entirely reverse the frailty phenotype, physical exercise could be essential for reducing frailty in hemodialysis patients.

Estimates of body composition can be more informative than the body mass index in hemodialysis patients, especially when considering physical performance rather than nutritional status [20]. We found no significant changes in skeletal muscle, leg muscle, or fat mass values in the exercise or control group. This result is consistent with that...
Table 1: Homogeneity test for demographic, dialytic, and clinical characteristics (n = 39)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Exercise group</th>
<th>Control group</th>
<th>χ² or t</th>
<th>p-value</th>
</tr>
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<tr>
<td><strong>Demographic characteristic</strong></td>
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<tr>
<td>No. of patients</td>
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<td>21</td>
<td></td>
<td></td>
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<tr>
<td>Age (yr)</td>
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<td>56.76 ± 12.32</td>
<td>0.20</td>
<td>0.84</td>
</tr>
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<td></td>
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<tr>
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<td>10 (55.6)</td>
<td>10 (47.6)</td>
<td>0.24</td>
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<td>Female</td>
<td>8 (44.4)</td>
<td>11 (52.4)</td>
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<td>Spouse</td>
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<tr>
<td>Yes</td>
<td>17 (94.4)</td>
<td>18 (85.7)</td>
<td>0.80</td>
<td>0.61*</td>
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<td>≤High school</td>
<td>10 (55.6)</td>
<td>16 (76.2)</td>
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<td>≥College</td>
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<td>12 (66.7)</td>
<td>11 (52.4)</td>
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<td>Religion</td>
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<td>Yes</td>
<td>14 (77.8)</td>
<td>12 (57.1)</td>
<td>1.86</td>
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<td>No</td>
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<td>9 (42.9)</td>
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<td>16 (76.2)</td>
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<td>&lt;2,000</td>
<td>12 (66.7)</td>
<td>18 (85.7)</td>
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<td>≥2,000</td>
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<td>Dialysis-related characteristic</td>
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<tr>
<td>Hemodialysis vintage (yr)</td>
<td>2.38 ± 2.72</td>
<td>5.74 ± 3.99</td>
<td>-3.10</td>
<td>0.004</td>
</tr>
<tr>
<td>Dialysis duration/session (min)</td>
<td>223.61 ± 17.81</td>
<td>228.10 ± 19.14</td>
<td>0.75</td>
<td>0.46</td>
</tr>
<tr>
<td>Blood flow rate (mL/min)</td>
<td>281.67 ± 23.58</td>
<td>276.19 ± 24.39</td>
<td>0.71</td>
<td>0.48</td>
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<td>Dialysate flow rate (mL/min)</td>
<td>516.67 ± 70.71</td>
<td>571.43 ± 130.93</td>
<td>1.67</td>
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<tr>
<td>High</td>
<td>12 (66.7)</td>
<td>17 (81.0)</td>
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<td>2 (9.5)</td>
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<td>Low</td>
<td>1 (5.6)</td>
<td>2 (9.5)</td>
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<td>Fistula type</td>
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<td>Arteriovenous fistula</td>
<td>16 (88.9)</td>
<td>16 (76.2)</td>
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<tr>
<td>Arteriovenous graft</td>
<td>2 (11.1)</td>
<td>5 (23.8)</td>
<td>1.06</td>
<td>0.42*</td>
</tr>
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<td>Clinical characteristic</td>
<td></td>
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</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>10.70 ± 1.18</td>
<td>10.25 ± 1.04</td>
<td>-1.27</td>
<td>0.21</td>
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<tr>
<td>Albumin (g/dL)</td>
<td>3.87 ± 0.18</td>
<td>3.77 ± 0.49</td>
<td>-0.92</td>
<td>0.37</td>
</tr>
<tr>
<td>Calcium (mg/dL)</td>
<td>8.65 ± 0.65</td>
<td>8.77 ± 0.67</td>
<td>-0.58</td>
<td>0.57</td>
</tr>
<tr>
<td>Phosphorus (mg/dL)</td>
<td>5.04 ± 1.32</td>
<td>4.81 ± 1.50</td>
<td>0.48</td>
<td>0.62</td>
</tr>
<tr>
<td>Potassium (mEq/L)</td>
<td>5.10 ± 0.71</td>
<td>4.69 ± 0.68</td>
<td>1.80</td>
<td>0.08</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>10.09 ± 2.44</td>
<td>10.38 ± 2.21</td>
<td>-0.38</td>
<td>0.71</td>
</tr>
<tr>
<td>Urea reduction ratio (%)</td>
<td>74.78 ± 3.83</td>
<td>74.98 ± 4.00</td>
<td>0.16</td>
<td>0.88</td>
</tr>
<tr>
<td>Cause of renal failure</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>7 (38.9)</td>
<td>11 (52.4)</td>
<td>0.82</td>
<td>0.70*</td>
</tr>
<tr>
<td>Hypertension</td>
<td>7 (38.9)</td>
<td>6 (28.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>4 (22.2)</td>
<td>4 (15.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Charlson comorbidity index</td>
<td>5.33 ± 2.35</td>
<td>5.14 ± 2.26</td>
<td>0.26</td>
<td>0.80</td>
</tr>
<tr>
<td>Dry body weight (kg)</td>
<td>58.95 ± 10.30</td>
<td>56.57 ± 9.95</td>
<td>0.73</td>
<td>0.47</td>
</tr>
</tbody>
</table>

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

*Fisher exact test.
of another study, wherein appendicular muscle mass and other body composition parameters did not improve after a 4-month program of cycle ergometer exercise [21]. Additional research is needed to determine whether prolonged exercise or aerobic exercise with various sessions, durations, and intensities might be useful for increasing body muscle in hemodialysis patients.

The only noticeable baseline difference between the exercise and control groups was their baseline dialysis vintage, which influences functioning, frailty, and QoL [3,11]. Because we did not achieve selection balance, dialysis vintage should be considered a confounding variable to determine the within–between interaction effects. The exercise group experienced significant improvements in the average frailty score ($f = 0.78$), average gait speed ($f = 0.93$), and SPPB score ($f = 0.45$) during the 12-week program. These results agree with those of a previous report that a 6-week predialysis exercise training program (20 min/session) improved normal gait speed, fast gait speed, and sit-to-stand performance [22]. Another intradialytic program combining cardiovascular exercise (supine cycle ergometer) and resistance exercise also improved physical capacity in terms of the timed up-and-go, sit-to-stand, and gait speed outcomes [23]. A 4-month intradialytic cycle ergometer exercise program facilitated an increase in walking distance [21]. Gait speed is a sensitive health indicator that has been called the 6th vital sign among hemodialysis patients [16,24]. In the present study, both the exercise and control groups had limited gait speeds at baseline [3,24]. A change of 0.1 m/sec in gait speed reflects a meaningful

<table>
<thead>
<tr>
<th>Table 2. Changes in the incidence of frailty and body composition parameters (n = 39)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variable</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Frailty (score)</td>
</tr>
<tr>
<td>Not frail, 0–2</td>
</tr>
<tr>
<td>Frail, 3–5</td>
</tr>
<tr>
<td>Frailty phenotype</td>
</tr>
<tr>
<td>Gait speed (m/sec)</td>
</tr>
<tr>
<td>Not frail, ≥0.8</td>
</tr>
<tr>
<td>Frail, &lt;0.8</td>
</tr>
<tr>
<td>Grip strength (kg)</td>
</tr>
<tr>
<td>Not frail, M: ≥30 and F: ≥20</td>
</tr>
<tr>
<td>Frail, M: &lt;30 and F: &lt;20</td>
</tr>
<tr>
<td>Physical activity</td>
</tr>
<tr>
<td>Not frail</td>
</tr>
<tr>
<td>Frail</td>
</tr>
<tr>
<td>Exhaution (vitality, score)</td>
</tr>
<tr>
<td>Not frail, ≥55</td>
</tr>
<tr>
<td>Frail, &lt;55</td>
</tr>
<tr>
<td>Weight loss, BMI (kg/m²)</td>
</tr>
<tr>
<td>Not frail, &gt;18.5</td>
</tr>
<tr>
<td>Frail, ≤18.5</td>
</tr>
<tr>
<td>SPPB (score)</td>
</tr>
<tr>
<td>Not frail, 10–12</td>
</tr>
<tr>
<td>Frail, &lt;10</td>
</tr>
<tr>
<td>Skeletal muscle mass (kg)</td>
</tr>
<tr>
<td>Body fat (%)</td>
</tr>
<tr>
<td>Lower leg muscles (kg)</td>
</tr>
</tbody>
</table>

Data are expressed as number (%) or mean ± standard deviation.
BMI, body mass index; F, female; M, male; SPPB, short physical performance battery.
*Fisher exact test, analysis of covariance adjusted for dialysis vintage.
### Table 3. Within- and between-group interaction effects on frailty, dialysis adequacy, and quality of life (n = 39)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Time (wk)</th>
<th>Exercise group (n = 18)</th>
<th>Control group (n = 21)</th>
<th>F</th>
<th>p-value</th>
<th>Repeated measures of ANCOVA</th>
<th>F</th>
<th>p-value</th>
<th>η²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frailty (score)a</td>
<td>Baseline</td>
<td>2.22 ± 1.22</td>
<td>2.52 ± 0.87</td>
<td>0.35</td>
<td>0.56</td>
<td>Time</td>
<td>1.80</td>
<td>0.17</td>
<td>0.048</td>
</tr>
<tr>
<td></td>
<td>4th</td>
<td>1.33 ± 1.14</td>
<td>2.95 ± 1.02</td>
<td>17.52</td>
<td>&lt;0.001</td>
<td>Group</td>
<td>18.55</td>
<td>&lt;0.001</td>
<td>0.340</td>
</tr>
<tr>
<td></td>
<td>8th</td>
<td>1.11 ± 0.90</td>
<td>3.05 ± 1.02</td>
<td>26.47</td>
<td>&lt;0.001</td>
<td>T*G</td>
<td>21.74</td>
<td>&lt;0.001</td>
<td>0.376 (0.78)</td>
</tr>
<tr>
<td></td>
<td>12th</td>
<td>0.94 ± 0.93</td>
<td>3.10 ± 1.04</td>
<td>34.71</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gait speed (m/sec)</td>
<td>Baseline</td>
<td>0.89 ± 0.22</td>
<td>0.83 ± 0.24</td>
<td>0.21</td>
<td>0.65</td>
<td>Time</td>
<td>8.18</td>
<td>0.003</td>
<td>0.185</td>
</tr>
<tr>
<td></td>
<td>4th</td>
<td>1.14 ± 0.30</td>
<td>0.76 ± 0.22</td>
<td>11.88</td>
<td>0.001</td>
<td>Group</td>
<td>12.64</td>
<td>0.001</td>
<td>0.260</td>
</tr>
<tr>
<td></td>
<td>8th</td>
<td>1.18 ± 0.31</td>
<td>0.72 ± 0.19</td>
<td>20.23</td>
<td>&lt;0.001</td>
<td>T*G</td>
<td>32.2</td>
<td>&lt;0.001</td>
<td>0.464 (0.93)</td>
</tr>
<tr>
<td></td>
<td>12th</td>
<td>1.21 ± 0.31</td>
<td>0.71 ± 0.19</td>
<td>24.26</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grip strength (kg)</td>
<td>Baseline</td>
<td>23.58 ± 9.79</td>
<td>26.10 ± 8.83</td>
<td>1.27</td>
<td>0.27</td>
<td>Time</td>
<td>1.92</td>
<td>0.15</td>
<td>0.051</td>
</tr>
<tr>
<td></td>
<td>4th</td>
<td>24.00 ± 9.16</td>
<td>21.13 ± 9.51</td>
<td>0.18</td>
<td>0.68</td>
<td>Group</td>
<td>0.05</td>
<td>0.83</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>8th</td>
<td>25.28 ± 8.45</td>
<td>22.40 ± 9.78</td>
<td>0.52</td>
<td>0.48</td>
<td>T*G</td>
<td>9.73</td>
<td>&lt;0.001</td>
<td>0.213 (0.52)</td>
</tr>
<tr>
<td></td>
<td>12th</td>
<td>25.61 ± 8.88</td>
<td>22.07 ± 8.41</td>
<td>0.75</td>
<td>0.39</td>
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<tr>
<td>Exhaustion (vitality in SF-36, score)</td>
<td>Baseline</td>
<td>48.46 ± 12.80</td>
<td>46.24 ± 10.79</td>
<td>1.27</td>
<td>0.27</td>
<td>Time</td>
<td>1.17</td>
<td>0.33</td>
<td>0.031</td>
</tr>
<tr>
<td></td>
<td>4th</td>
<td>53.16 ± 12.06</td>
<td>44.11 ± 9.78</td>
<td>7.60</td>
<td>0.009</td>
<td>Group</td>
<td>9.96</td>
<td>0.003</td>
<td>0.217</td>
</tr>
<tr>
<td></td>
<td>8th</td>
<td>53.66 ± 8.99</td>
<td>41.68 ± 8.34</td>
<td>15.08</td>
<td>&lt;0.001</td>
<td>T*G</td>
<td>2.27</td>
<td>0.09</td>
<td>0.059 (0.25)</td>
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<tr>
<td></td>
<td>12th</td>
<td>53.82 ± 10.06</td>
<td>43.26 ± 8.60</td>
<td>12.38</td>
<td>0.001</td>
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<tr>
<td>Weight loss (BMI, kg/m²)</td>
<td>Baseline</td>
<td>21.55 ± 2.31</td>
<td>21.68 ± 3.06</td>
<td>0.03</td>
<td>0.88</td>
<td>Time</td>
<td>3.35</td>
<td>0.05</td>
<td>0.085</td>
</tr>
<tr>
<td></td>
<td>4th</td>
<td>21.53 ± 2.16</td>
<td>21.68 ± 3.02</td>
<td>0.03</td>
<td>0.86</td>
<td>Group</td>
<td>0.03</td>
<td>0.88</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>8th</td>
<td>21.53 ± 2.01</td>
<td>21.64 ± 2.77</td>
<td>0.04</td>
<td>0.84</td>
<td>T*G</td>
<td>1.67</td>
<td>0.20</td>
<td>0.044 (0.21)</td>
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<tr>
<td></td>
<td>12th</td>
<td>21.58 ± 1.98</td>
<td>21.79 ± 3.01</td>
<td>0.24</td>
<td>0.63</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SPPB (score)b</td>
<td>Baseline</td>
<td>10.67 ± 1.61</td>
<td>10.10 ± 2.02</td>
<td>0.07</td>
<td>0.79</td>
<td>Time</td>
<td>4.31</td>
<td>0.03</td>
<td>0.009</td>
</tr>
<tr>
<td></td>
<td>4th</td>
<td>11.56 ± 0.98</td>
<td>9.52 ± 2.06</td>
<td>8.73</td>
<td>0.005</td>
<td>Group</td>
<td>8.73</td>
<td>0.006</td>
<td>0.142</td>
</tr>
<tr>
<td></td>
<td>8th</td>
<td>11.72 ± 0.67</td>
<td>9.86 ± 2.20</td>
<td>6.96</td>
<td>0.01</td>
<td>T*G</td>
<td>28.81</td>
<td>&lt;0.001</td>
<td>0.168 (0.45)</td>
</tr>
<tr>
<td></td>
<td>12th</td>
<td>11.83 ± 0.51</td>
<td>9.76 ± 2.28</td>
<td>9.89</td>
<td>0.003</td>
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<tr>
<td>Kt/V urea</td>
<td>Baseline</td>
<td>1.64 ± 0.19</td>
<td>1.67 ± 0.19</td>
<td>0.14</td>
<td>0.71</td>
<td>Time</td>
<td>0.46</td>
<td>0.67</td>
<td>0.013</td>
</tr>
<tr>
<td></td>
<td>4th</td>
<td>1.68 ± 0.24</td>
<td>1.71 ± 0.24</td>
<td>0.05</td>
<td>0.82</td>
<td>Group</td>
<td>0.29</td>
<td>0.59</td>
<td>0.008</td>
</tr>
<tr>
<td></td>
<td>8th</td>
<td>1.70 ± 0.23</td>
<td>1.71 ± 0.28</td>
<td>0.14</td>
<td>0.71</td>
<td>T*G</td>
<td>2.85</td>
<td>0.05</td>
<td>0.073 (0.28)</td>
</tr>
<tr>
<td></td>
<td>12th</td>
<td>1.76 ± 0.30</td>
<td>1.64 ± 0.18</td>
<td>2.40</td>
<td>0.13</td>
<td></td>
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</tr>
<tr>
<td>Physical component summary</td>
<td>Baseline</td>
<td>45.51 ± 6.48</td>
<td>44.50 ± 8.76</td>
<td>1.30</td>
<td>0.26</td>
<td>Time</td>
<td>5.59</td>
<td>0.003</td>
<td>0.134</td>
</tr>
<tr>
<td></td>
<td>4th</td>
<td>49.41 ± 4.94</td>
<td>43.81 ± 7.38</td>
<td>8.35</td>
<td>0.007</td>
<td>Group</td>
<td>8.52</td>
<td>0.006</td>
<td>0.191</td>
</tr>
<tr>
<td></td>
<td>8th</td>
<td>50.31 ± 4.50</td>
<td>44.76 ± 6.68</td>
<td>7.41</td>
<td>0.01</td>
<td>T*G</td>
<td>1.98</td>
<td>0.13</td>
<td>0.052 (0.23)</td>
</tr>
<tr>
<td></td>
<td>12th</td>
<td>51.80 ± 4.51</td>
<td>42.79 ± 8.38</td>
<td>10.95</td>
<td>0.002</td>
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<td></td>
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<tr>
<td>Mental component summary</td>
<td>Baseline</td>
<td>50.35 ± 11.04</td>
<td>49.81 ± 9.17</td>
<td>0.12</td>
<td>0.73</td>
<td>Time</td>
<td>0.90</td>
<td>0.97</td>
<td>0.003</td>
</tr>
<tr>
<td></td>
<td>4th</td>
<td>53.98 ± 7.83</td>
<td>45.22 ± 8.64</td>
<td>9.41</td>
<td>0.004</td>
<td>Group</td>
<td>5.11</td>
<td>0.03</td>
<td>0.124</td>
</tr>
<tr>
<td></td>
<td>8th</td>
<td>53.24 ± 7.28</td>
<td>44.95 ± 8.65</td>
<td>7.66</td>
<td>0.009</td>
<td>T*G</td>
<td>3.04</td>
<td>0.03</td>
<td>0.078 (0.29)</td>
</tr>
<tr>
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<td>12th</td>
<td>53.23 ± 8.60</td>
<td>48.95 ± 8.14</td>
<td>2.92</td>
<td>0.10</td>
<td></td>
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</tr>
</tbody>
</table>

Data are expressed as mean ± standard deviation.
BMI, body mass index; Kt/V, K = dialyzer’s capacity to clear urea at the blood flow rate, t = treatment time, V = distribution volume of urea; SF-36, Short Form-36 tool; SPPB, short physical performance battery; T*G, time*group.
F is effect size calculated using the analysis of covariance (ANCOVA) model adjusted for dialysis vintage in G*Power (small = 0.10, medium = 0.25, large = 0.40); F-score calculated using ANCOVA adjusted by dialysis vintage (exercise group vs. control group).
Score range: *0–5, *0–12. *Statistically significant based on Bonferroni correction (p < 0.013); *Greenhouse-Geisser correction according to Mauchly’s sphericity test (p < 0.05).
Table 4. Differences* in frailty, dialysis adequacy, and QoL according to the intention-to-treat and per-protocol analyses

<table>
<thead>
<tr>
<th>Variable</th>
<th>Intention-to-treat analysis (n = 42)</th>
<th>Per-protocol analysis (n = 39)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Exercise group (n = 21)</td>
<td>Control group (n = 21)</td>
</tr>
<tr>
<td>Frailty score</td>
<td>−1.26 ± 0.96</td>
<td>0.57 ± 0.81</td>
</tr>
<tr>
<td></td>
<td>0.11 ± 0.15</td>
<td>−5.08</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Slowness (gait speed, m/sec)</td>
<td>0.27 ± 0.22</td>
<td>−0.11 ± 0.15</td>
</tr>
<tr>
<td></td>
<td></td>
<td>−4.77</td>
</tr>
<tr>
<td>Weakness (grip strength, kg)</td>
<td>1.58 ± 3.94</td>
<td>−4.02 ± 4.52</td>
</tr>
<tr>
<td></td>
<td></td>
<td>−4.03</td>
</tr>
<tr>
<td>Exhaustion (vitality, score)</td>
<td>4.57 ± 7.74</td>
<td>−2.98 ± 9.91</td>
</tr>
<tr>
<td></td>
<td></td>
<td>−2.30</td>
</tr>
<tr>
<td>Weight loss (BMI, kg/m²)</td>
<td>0.18 ± 1.20</td>
<td>0.48 ± 1.79</td>
</tr>
<tr>
<td></td>
<td></td>
<td>−0.57</td>
</tr>
<tr>
<td>SPPB (0–12, score)</td>
<td>0.88 ± 1.43</td>
<td>−0.33 ± 1.68</td>
</tr>
<tr>
<td></td>
<td></td>
<td>−2.06</td>
</tr>
<tr>
<td>Dialysis adequacy (Kt/V urea)</td>
<td>0.13 ± 0.22</td>
<td>−0.03 ± 0.13</td>
</tr>
<tr>
<td></td>
<td></td>
<td>−2.48</td>
</tr>
<tr>
<td>PCS</td>
<td>5.69 ± 5.58</td>
<td>−1.72 ± 9.04</td>
</tr>
<tr>
<td></td>
<td></td>
<td>−2.79</td>
</tr>
<tr>
<td>MCS</td>
<td>2.49 ± 7.28</td>
<td>−0.86 ± 9.41</td>
</tr>
<tr>
<td></td>
<td></td>
<td>−1.59</td>
</tr>
</tbody>
</table>

Data are expressed as mean ± standard deviation.

BMI, body mass index; Kt/V, K = dialyzer’s capacity to clear urea at the blood flow rate, t = treatment time, V = distribution volume of urea; SPPB, short physical performance battery; MCS, mental component summary; PCS, physical component summary; QoL, quality of life.

*Value at the 12th week–value at baseline. ’z-score calculated using the Mann-Whitney U test.

change [25], and our exercise group exhibited an increase from 0.89 m/sec to 1.21 m/sec, which is sufficient for independent daily living, community ambulation, and crossing the street [3,16,26]. However, although handgrip strength had a significant within–between interaction, there was no significant difference in grip strength at any follow-up time after Bonferroni correction method was applied. In contrast, the previous 4-month intradialytic cycle ergometer program showed an improvement in handgrip strength [21], which could suggest that a longer period of intradialytic aerobic exercise (>12 weeks) is needed to improve handgrip strength and reach a non-frail state. The exercise group in the present study also experienced improvements in the average MCS score during the first 8 weeks (f = 0.29), although the small effect size might indicate a risk of bias. Therefore, large randomized controlled trials are needed to identify the optimal duration and timing of intradialytic cycle ergometer exercise and evaluate the effect on handgrip strength and mental QoL.

Data were missing for 3.6% of all variables in three patients (7.1%) in the exercise group. The intention-to-treat and per-protocol analyses revealed that the exercise group exhibited significant increments in Kt/V urea (0.12), grip strength (2.03 kg), exhaustion score (5.36), and PCS score (6.29), as well as improvements in Fried’s frailty score (−1.28), gait speed (0.31 m/sec), and SPPB score (1.17). During dialysis, exercise increases blood uremic solute removal by increasing blood flow to low perfusion tissue beds [8]. In the present study, the exercise group had a significant increase in Kt/V urea (+7.37%), and the control group had a decrease in Kt/V urea (−1.32%). This result is consistent with the previous finding that among hemodialysis patients, a 15-minute intradialytic aerobic exercise program safely and effectively improved Kt/V urea by 38% after 8 weeks [14]. Moreover, different types of intradialytic training might improve dialysis adequacy (based on Kt/V urea), cardiorespiratory fitness, and prognosis [6,22,23]. Profound and relentless exhaustion in hemodialysis patients leads to weakness, decreased vitality, and reduced ability to perform daily activities [27]. Furthermore, a 10-point increase in the vital score is associated with a 10% increase in mean survival time [28]. Our exercise group exhibited an increase of 5.36 in vitality score, which is consistent with the finding of a previous report [21]. Therefore, it could be prudent to incorporate exercise programs into the routine care of frail patients who are undergoing hemodialysis.

To determine the participants’ ability to engage in exercise, our nephrologists and dialysis nurses evaluated symptoms such as systolic blood pressure of ≥200 mmHg, diastolic blood pressure of ≥100 mmHg, and Borg score of ≥15, including subjective symptoms such as dizziness, chest tightness, dyspnea, nausea, vomiting, muscle pain, and joint pain [4]. Participants were encouraged to report any issues that they experienced to help identify the support required during or after the intradialytic exercise. Because we observed several episodes of elevated systolic blood
pressure during the intradialytic exercise, careful screening and monitoring by nephrologists and dialysis nurses were essential to maintain the participants’ safety, which means that ongoing exercise programs would add to healthcare providers’ work burden. Two participants missed two sessions of the exercise program due to elevation of their systolic blood pressure of ≥190 mmHg during the stretching warm-up phase. Additionally, two participants had an episode of systolic blood pressure elevation to 170 mmHg (from 140 mmHg) during the main exercise phase. After 10 minutes of rest, the high blood pressure had normalized, and the participants safely completed their exercise sessions. In addition, one 48-year-old female participant with intradialytic hypotension experienced improvement in her dialysis-induced hypotension.

The present study has several limitations that warrant consideration. First, we included only patients undergoing treatment at a single hemodialysis center, and the results might not be generalizable to other centers and patient populations. Second, the small effect size for the MCS score improvement (f < 0.35) could indicate a risk of bias. Third, the small sample size precluded the use of factorial statistics for exercise and frailty factors. Fourth, the different statistical measures produced variable efficacies in terms of Kt/V. Because the effects of intradialytic aerobic exercise on Kt/V have been controversial [6], this discrepancy should be checked through further research by modifying the duration, time, and intensity of the intradialytic aerobic exercise program in a larger, multicenter population.

Although the 12-week intradialytic exercise program did not entirely reverse the frailty phenotype, and different statistical measures produced various results, our findings imply that an intradialytic cycle ergometer exercise program could reduce frailty and improve dialysis adequacy and QoL. Intradialytic exercise programs have not been incorporated into routine care due to the practical burden on dialysis health care professionals. A government health policy should be established to correct the lack of trained dialysis health care professionals available to supervise exercise programs and the lack of financial support for ongoing exercise programs.

Conflicts of interest

All authors have no conflicts of interest to declare.

Acknowledgments

The authors owe special thanks to all the hemodialysis patients who participated in this study. We also thank the dialysis care providers at the hospital-affiliated hemodialysis center.

Authors’ contributions

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

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References


Background: Hyperparathyroidism is common in patients with chronic kidney disease with reduced renal function and has been observed after kidney transplantation. The optimal treatment for cases in which hyperparathyroidism persists after kidney transplantation has not been determined.

Methods: This retrospective study included 83 patients with tertiary hyperparathyroidism who underwent kidney transplantation between 2000 and 2018 at a single tertiary center in Korea. Sixty-four patients underwent parathyroidectomy and 19 patients were treated with cinacalcet following renal transplantation. Biochemical parameters and clinical outcomes were compared between the two groups.

Results: Serum calcium and parathyroid hormone (PTH) levels improved in both the parathyroidectomy and cinacalcet groups. One year after treatment, parathyroidectomy resulted in a lower mean serum calcium level than cinacalcet (9.7 ± 0.7 mg/dL vs. 10.5 ± 0.7 mg/dL, p = 0.001). Regarding serum PTH, the parathyroidectomy group showed a significantly lower PTH level than the cinacalcet group at 6 months (129.1 ± 80.3 pg/mL vs. 219.2 ± 92.5 pg/mL, p = 0.002) and 1 year (118.8 ± 75.5 pg/mL vs. 250.6 ± 94.5 pg/mL, p < 0.001). There was no statistically significant difference in the incidence of kidney transplant rejection, graft failure, cardiovascular events, fracture risk, or bone mineral density changes between the two groups.

Conclusion: Parathyroidectomy appears to reduce PTH and calcium levels effectively in tertiary hyperparathyroidism. However, creatinine level and allograft rejection should be monitored closely.

Keywords: Cinacalcet, Hyperparathyroidism, Kidney transplantation, Parathyroidectomy
level is associated with CKD–mineral bone disease, soft tissue and vascular calcification, and cardiovascular disease (CVD); as a result, it reportedly increases the mortality rate of patients [2].

Secondary hyperparathyroidism usually shows improvement after successful kidney transplantation (KT) [3]. Nevertheless, hyperparathyroidism has been observed to persist for up to 1 year after KT in more than 25% of patients. Tertiary hyperparathyroidism refers to the persistence of high serum PTH levels after KT [3,4].

Following tertiary hyperparathyroidism associated with hypercalcemia and hypophosphatemia, the risks of renal allograft dysfunction, graft failure, osteoporosis, and bone fracture increase [5–8]. Persistent hypercalcemia after transplantation causes various problems. According to a study, hypercalcemia can threaten graft function, and the incidence of CVD was noted to increase as the corrected calcium level rose [7]. A study of large cohorts derived from the Assessment of Lescol in Renal Transplantation trial reported that posttransplant persistent hyperparathyroidism is an independent risk factor for renal graft loss and all-cause mortality [9]. A longitudinal study showed that persistent hyperparathyroidism after KT increases the risk of fracture. Other research concurs that the hypophosphatemia associated with KT can induce osteomalacia and increase the risk of fracture [8,10,11].

Medical treatment with cinacalcet or surgical treatment with parathyroidectomy (PTX) are both viable options for addressing tertiary hyperparathyroidism [12]. Cinacalcet is a calcimimetic drug that suppresses the production of PTH by enhancing the sensitivity of the calcium-sensing receptors of the parathyroid gland to calcium [13]. This drug has been reported to be effective in reducing calcium and PTH levels after KT [14–16]. The other axis of treatment, PTX, is generally performed when hypercalcemia that does not respond to medical treatment persists [17]. PTH and serum calcium levels are significantly reduced after PTX; however, the long-term effect of this treatment has not been well-studied [18]. In addition, some studies have reported that renal graft function is impaired after PTX [19,20].

Since the introduction of cinacalcet, few studies have compared its efficacy to that of PTX. Therefore, there is still debate as to which treatment is better. Most of the studies that compared the efficacies of these treatments were retrospective investigations with short follow-up periods [21–25]. The only existing prospective randomized controlled trial had a small sample size [26]. There is a paucity of data available, especially from Korea; thus, this study sought to compare the efficacies of cinacalcet and PTX in patients with tertiary hyperparathyroidism of a single center in Korea.

Methods

Study design and population

This study was performed in accordance with the Declaration of Helsinki. It was approved by the Institutional Review Board of Asan Medical Center (No. 2020-0774), and written informed consent was waived due to its retrospective nature.

This retrospective cohort study initially included 178 patients who either took cinacalcet or underwent PTX after KT between 2000 and 2018 at a tertiary medical center in Korea. The inclusion criteria were persistent PTH elevation (>65 pg/mL) with hypercalcemia (>10.5 mg/dL) after KT and an age of at least 19 years at the time of KT. Among the 178 patients, cases with missing or insufficient follow-up data were excluded. In addition, patients who underwent PTX or took cinacalcet after starting dialysis for end-stage renal disease (ESRD) after KT were excluded. Finally, 83 patients were evaluated altogether.

Outcomes

The biochemical outcomes were serum PTH, calcium, phosphorus, creatinine levels, and estimated glomerular filtration rate (eGFR) at 3 and 6 months and 1, 2, and 3 years after the start of treatment or surgery. The clinical outcomes were the incidence of graft rejection, graft failure, cardiovascular events, fracture, and bone mineral density (BMD) between the PTX group and the cinacalcet group.

Data collection

We collected patient data through electronic charts. Patient baseline characteristics included age, sex, etiology of ESRD, dialysis type before KT, and the duration of dialysis.
KT-related data included the type of KT, ABO incompatibility, human leukocyte antigen (HLA) mismatch, and HLA-sensitization. HLA-sensitized KT was defined as a case in which at least one of the following characteristics was present: B-cell flow cytometry crossmatch, T-cell flow cytometry crossmatch, and complement-dependent cytotoxicity crossmatch. PTX-related data included laboratory data until 3 years after PTX (PTH, albumin-corrected calcium, phosphorus, creatinine, and eGFR), indication of PTX, complications, and medication(s) before PTX. PTH levels were measured using a second-generation assay (Nichols Institute Diagnostics, San Juan Capistrano, CA, USA). The eGFR used the Modification of Diet in Renal Disease equation. Cinacalcet (Regpara; Kyowa Hakko Kirin Co., Ltd., Tokyo, Japan) administration group data also included laboratory data until 3 years after treatment.

**Treatment of tertiary hyperparathyroidism**

Cinacalcet was administered at an average dose of 25 mg per day. Subtotal PTX was performed in 58 patients (90.6%) and total PTX was performed in six patients (9.4%). We discussed the advantages, disadvantages, and costs of the two treatments with patients having persistently elevated PTH (>65 pg/mL) and hypercalcemia (>10.5 mg/dL) after KT and considered surgical treatment. The immunosuppressive drugs utilized were calcineurin inhibitors (tacrolimus or cyclosporine), corticosteroids (prednisolone or methylprednisolone), and antimetabolites (mycophenolate or azathioprine).

**Statistical analysis**

Statistical analyses were conducted using R (version 3.5.1; R Foundation for Statistical Computing, Vienna, Austria; http:// www.R.project.org) and GraphPad Prism version 5.0 (GraphPad Software, San Diego, CA, USA; http://www.graphpad.com). Continuous variables were presented as mean ± standard deviation values and categorical variables were presented as frequencies (percentages). We used the t test to compare continuous variables and the chi-square test or Fisher exact test to compare categorical variables. A p-value of less than 0.05 was considered statistically significant.

**Results**

**Study population**

From 2000 to 2018, a total of 178 patients underwent PTX or took cinacalcet from among those who underwent KT. Among the 178 patients, nine patients under the age of 19 years, 46 patients with missing or insufficient follow-up data, and 40 patients who underwent treatment with ESRD after failed KT were excluded (Fig. 1). We identified 83 patients who had tertiary hyperparathyroidism and met all the selection criteria. Nineteen patients were included in the cinacalcet group and 64 patients were included in the PTX group.

**Baseline characteristics**

Baseline characteristics of the patients in both groups at the time of KT are shown in Table 1. The mean age of patients in the cinacalcet group (45.7 ± 7.4 years) was lower than that of patients in the PTX group (50.2 ± 8.6 years, p = 0.04). Considering dialysis duration before KT, the mean duration for patients in the cinacalcet group was shorter
than that of patients in the PTX group (8.1 ± 3.7 years vs. 11.2 ± 5.1 years, p = 0.01). There were no differences in other baseline characteristics. Among all cases of KT, the kidneys were obtained from deceased donors in 71.1% cases, 91.6% of the recipients were ABO-compatible, and 97.6% of the cases were non-sensitized KT. The mean time from KT to PTX in 64 patients was 23.2 ± 22.6 months, and the mean time from KT to cinacalcet administration in 19 patients was 23.1 ± 29.9 months (p = 0.99).

Details of the PTX group are summarized in Table 2. Complications occurred in four of 64 patients (6.3%), with half of these complications being hematoma and the remaining half being postoperative hypocalcemia. No recurrent laryngeal nerve injury occurred in any of the study participants. Before PTX, 50 of 64 patients (78.1%) were not taking medications for hyperparathyroidism, while 14 (21.9%) were taking vitamin D analogs. After PTX, half of the patients were given vitamin D or calcium to prevent hypocalcemia or hungry bone syndrome.

Biochemical outcomes

Posttreatment laboratory values are presented in Table 3. There was no significant difference in serum-corrected calcium levels between the two groups before treatment (p = 0.20); however, these values were higher in the cinacalcet group throughout the follow-up period at 6 months (p < 0.001), 1 year (p = 0.001), and 3 years (p = 0.002) after the start of treatment. Although normocalcemia was not achieved in the cinacalcet group, it was achieved and maintained from three months after surgery in the PTX group. Both groups showed a trend of decreasing calcium levels

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>PTX group (n = 64)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complication of PTX</td>
<td></td>
</tr>
<tr>
<td>Hematoma</td>
<td>2 (3.1)</td>
</tr>
<tr>
<td>Postoperative hypocalcemia</td>
<td>2 (3.1)</td>
</tr>
<tr>
<td>Recurrent laryngeal nerve injury</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Medication before PTX</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>50 (78.1)</td>
</tr>
<tr>
<td>Vitamin D analog</td>
<td>14 (21.9)</td>
</tr>
<tr>
<td>Cinacalcet</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

Data are expressed as number (%).

PTX, parathyroidectomy.
Table 3. Biochemical outcomes: laboratory data during the follow-up period

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cinacalcet group (n = 19)</th>
<th>Parathyroidectomy group (n = 64)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corrected calcium (mg/dL)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pretreatment</td>
<td>11.0 ± 0.8</td>
<td>11.3 ± 0.8</td>
<td>0.20</td>
</tr>
<tr>
<td>3 Mo</td>
<td>10.6 ± 0.9</td>
<td>9.4 ± 0.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>6 Mo</td>
<td>10.6 ± 0.7</td>
<td>9.5 ± 0.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>1 Yr</td>
<td>10.5 ± 0.7</td>
<td>9.7 ± 0.7</td>
<td>0.001</td>
</tr>
<tr>
<td>2 Yr</td>
<td>10.8 ± 1.0</td>
<td>9.3 ± 0.5</td>
<td>0.001</td>
</tr>
<tr>
<td>3 Yr</td>
<td>10.9 ± 0.7</td>
<td>9.4 ± 0.9</td>
<td>0.002</td>
</tr>
<tr>
<td>Parathyroid hormone (pg/mL)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pretreatment</td>
<td>267.9 ± 118.5</td>
<td>334.7 ± 240.0</td>
<td>0.15</td>
</tr>
<tr>
<td>3 Mo</td>
<td>225.8 ± 91.3</td>
<td>124.8 ± 75.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>6 Mo</td>
<td>219.2 ± 92.5</td>
<td>129.1 ± 80.3</td>
<td>0.002</td>
</tr>
<tr>
<td>1 Yr</td>
<td>250.6 ± 94.5</td>
<td>118.8 ± 75.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>2 Yr</td>
<td>247.7 ± 88.2</td>
<td>102.0 ± 41.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>3 Yr</td>
<td>205.6 ± 103.3</td>
<td>107.8 ± 71.2</td>
<td>0.03</td>
</tr>
<tr>
<td>Phosphorus (mg/dL)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pretreatment</td>
<td>2.5 ± 0.6</td>
<td>2.4 ± 0.4</td>
<td>0.51</td>
</tr>
<tr>
<td>3 Mo</td>
<td>2.6 ± 0.6</td>
<td>3.0 ± 0.7</td>
<td>0.08</td>
</tr>
<tr>
<td>6 Mo</td>
<td>2.8 ± 0.4</td>
<td>3.0 ± 0.7</td>
<td>0.23</td>
</tr>
<tr>
<td>1 Yr</td>
<td>2.6 ± 0.5</td>
<td>2.9 ± 0.6</td>
<td>0.11</td>
</tr>
<tr>
<td>2 Yr</td>
<td>2.6 ± 0.7</td>
<td>2.9 ± 0.5</td>
<td>0.31</td>
</tr>
<tr>
<td>3 Yr</td>
<td>2.5 ± 0.4</td>
<td>3.1 ± 0.7</td>
<td>0.06</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pretreatment</td>
<td>1.0 ± 0.3</td>
<td>1.0 ± 0.3</td>
<td>0.96</td>
</tr>
<tr>
<td>3 Mo</td>
<td>1.0 ± 0.2</td>
<td>1.3 ± 1.0</td>
<td>0.03</td>
</tr>
<tr>
<td>6 Mo</td>
<td>1.0 ± 0.2</td>
<td>1.3 ± 1.2</td>
<td>0.22</td>
</tr>
<tr>
<td>1 Yr</td>
<td>1.0 ± 0.3</td>
<td>1.3 ± 1.2</td>
<td>0.30</td>
</tr>
<tr>
<td>2 Yr</td>
<td>1.1 ± 0.3</td>
<td>1.1 ± 0.3</td>
<td>0.99</td>
</tr>
<tr>
<td>3 Yr</td>
<td>0.9 ± 0.2</td>
<td>1.6 ± 2.0</td>
<td>0.22</td>
</tr>
<tr>
<td>eGFR (mL/min/1.73 m²)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pretreatment</td>
<td>78.0 ± 26.3</td>
<td>71.9 ± 21.0</td>
<td>0.33</td>
</tr>
<tr>
<td>3 Mo</td>
<td>75.3 ± 20.2</td>
<td>63.3 ± 21.6</td>
<td>0.08</td>
</tr>
<tr>
<td>6 Mo</td>
<td>80.1 ± 20.1</td>
<td>69.2 ± 21.0</td>
<td>0.12</td>
</tr>
<tr>
<td>1 Yr</td>
<td>75.9 ± 27.8</td>
<td>69.9 ± 23.6</td>
<td>0.46</td>
</tr>
<tr>
<td>2 Yr</td>
<td>76.5 ± 27.2</td>
<td>72.4 ± 19.9</td>
<td>0.67</td>
</tr>
<tr>
<td>3 Yr</td>
<td>84.7 ± 25.0</td>
<td>60.9 ± 27.9</td>
<td>0.11</td>
</tr>
<tr>
<td>ΔeGFR (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 Mo</td>
<td>−4.1 ± 25.8</td>
<td>−15.6 ± 27.1</td>
<td>0.19</td>
</tr>
<tr>
<td>6 Mo</td>
<td>6.3 ± 22.5</td>
<td>−15.7 ± 22.0</td>
<td>0.008</td>
</tr>
<tr>
<td>1 Yr</td>
<td>6.5 ± 22.0</td>
<td>−6.0 ± 28.4</td>
<td>0.18</td>
</tr>
<tr>
<td>2 Yr</td>
<td>1.1 ± 20.5</td>
<td>−9.1 ± 32.0</td>
<td>0.43</td>
</tr>
<tr>
<td>3 Yr</td>
<td>1.8 ± 24.8</td>
<td>−4.4 ± 34.7</td>
<td>0.73</td>
</tr>
</tbody>
</table>

Data are expressed as mean ± standard deviation.
eGFR, estimated glomerular filtration rate; KT, kidney transplantation.

*The delta eGFR (ΔeGFR, %) was calculated as the difference between the current eGFR and baseline eGFR [100 × (current eGFR − baseline eGFR)/baseline eGFR].

After treatment compared to those before treatment. The mean serum PTH level was lower in the cinacalcet group than in the PTX group before treatment (267.9 ± 118.5 pg/mL vs. 334.7 ± 240.0 pg/mL, p = 0.15). Following the initiation of treatment, PTH levels in the cinacalcet group were higher than the PTH group at all follow-up visits, i.e., at 6 months (p = 0.002), 1 year (p < 0.001), and 3 years (p = 0.03). The phosphorus levels did not differ significantly between the groups. Calcitriol levels were significantly higher in the PTX group than in the cinacalcet group at three months after treatment (p = 0.03); however, this difference was not significant thereafter. No significant difference was found in the eGFR values between the two groups. Because the baseline eGFR values of the two groups were different, delta eGFR analysis was further performed to compensate for this difference. At 6 months after intervention, the delta eGFR was higher in the cinacalcet group than in the PTX group (6.3% ± 22.5% vs. −15.7% ± 22.0%, p = 0.008). Despite the lack of significance, the delta eGFR value in the PTX group was continuously negative. Short-term laboratory data collected within 1 month after PTX are presented in Supplementary Fig. 1 (available online).

Clinical outcomes

The rejection, graft failure, cardiovascular event, and fracture rates of the two groups are presented in Table 4. Rejection occurred in 11 of 64 patients (17.2%) in the PTX group but none of the patients in the cinacalcet group; however, the difference in the occurrence of rejection between the

Table 4. Clinical outcomes after management of tertiary hyperparathyroidism

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cinacalcet group (n = 19)</th>
<th>Parathyroidectomy group (n = 64)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rejection</td>
<td></td>
<td></td>
<td>0.06</td>
</tr>
<tr>
<td>None</td>
<td>19 (100)</td>
<td>53 (82.8)</td>
<td></td>
</tr>
<tr>
<td>≥1 time</td>
<td>0 (0)</td>
<td>11 (17.2)</td>
<td></td>
</tr>
<tr>
<td>Graft failure</td>
<td>1 (5.3)</td>
<td>3 (4.7)</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>Cardiovascular event</td>
<td></td>
<td></td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>None</td>
<td>18 (94.7)</td>
<td>62 (96.9)</td>
<td></td>
</tr>
<tr>
<td>≥1 time</td>
<td>1 (5.3)</td>
<td>2 (3.1)</td>
<td></td>
</tr>
</tbody>
</table>

Fracture

<table>
<thead>
<tr>
<th>Fracture</th>
<th>Cinacalcet group (n = 19)</th>
<th>Parathyroidectomy group (n = 64)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>18 (94.7)</td>
<td>62 (96.9)</td>
<td>0.55</td>
</tr>
<tr>
<td>≥1 time</td>
<td>1 (5.3)</td>
<td>2 (3.1)</td>
<td></td>
</tr>
</tbody>
</table>

Values are expressed as frequency (%).
two groups was not statistically significant \( (p = 0.06) \). There were no statistically significant differences between the two groups in terms of the rates of graft failure, cardiovascular events, and fracture. The incidence rates of fracture during follow-up were 5.3% \( (n = 1) \) and 3.1% \( (n = 2) \) in the cinacalcet and PTX groups \( (p = 0.55) \), respectively. In all three cases, steroids were administered after transplantation. According to Kaplan-Meier curve analysis, renal transplant allograft survival was not statistically significant \( (p = 0.77) \) (Fig. 2). In both groups, no significant difference was found in the change in BMD between the pretreatment and post-treatment periods (Table 5).

**Discussion**

In this retrospective cohort study, serum calcium and PTH levels decreased in both the PTX and cinacalcet groups. Serum calcium level was maintained within normal range from three months after PTX. The cinacalcet group showed the lowest serum calcium levels at 1 year after administration compared to that before administration but did not demonstrate normocalcemia during the follow-up period. Renal function showed higher serum creatinine levels in the PTX group at three months after treatment; however, these levels were maintained thereafter without a statistically significant difference between the two groups. In the analysis performed by delta eGFR, the PTX group showed a significant decrease in eGFR compared to the cinacalcet group at 6 months after treatment. The rate of rejection was higher in the PTX group; however, there was no significant difference in the rate of graft survival between the groups. The rates of CVD and fracture events did not differ between the two groups.

Surgical treatment of tertiary hyperparathyroidism was more effective than the administration of cinacalcet in correcting hypercalcemia and lowering PTH levels. Similar findings were confirmed in several other studies \[22,23,27\]. A randomized controlled trial compared surgical treatment with cinacalcet in two cohorts of 15 patients with normocalcemia at 12 months as the primary endpoint. In comparison with 67% of patients treated with cinacalcet, 100% of patients achieved normocalcemia after PTX \[26\].

There are several concerns about surgical treatment. One of them is the rate of postoperative complications. In this study, postoperative complications occurred in only 6% of the participants, and all of these complications were temporary. In another study, Finnerty et al. \[23\] reported that complications, all of which were temporary, occurred in eight patients (24%). Another concern is the deterioration of graft function following PTX. Although the cause is unclear, the mechanism is a rapid decrease in serum PTH levels after PTX reduces renal perfusion, which results in renal function impairment. Because PTH has a favorable influence on hemodynamics in terms of the glomerular filtration rate and renal blood flow, this deterioration of renal graft function is likely caused by the resultant relative hypoparathyroidism that occurs after PTX \[19,20,28\]. Therefore, Litthbarski et al. \[29\] suggested that PTX should be performed at least 1 year after KT to improve long-term outcomes. In our study, the mean time-lapse from KT to PTX in 64 patients was 23.2 ± 22.6 months. Sixteen of 64 patients underwent surgery within 1 year after KT, and two

---

**Figure 2.** Kaplan-Meier curve of the renal transplant graft survival.

PTX, parathyroidectomy.

<table>
<thead>
<tr>
<th>Table 5. Changes in BMD between before and after treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>T-score change</td>
</tr>
<tr>
<td>----------------</td>
</tr>
<tr>
<td>Lumbar spine</td>
</tr>
<tr>
<td>Femur total</td>
</tr>
<tr>
<td>Femur neck</td>
</tr>
</tbody>
</table>

BMD was evaluated in 24 patients whose pre- and post-BMD data were available.

BMD, bone mineral density.
of them experienced acute rejection.

With regard to graft outcome, although there was no graft rejection in the cinacalcet group, it occurred in 11 patients (17.2%) in the PTX group. Although no significant difference was observed in the rate of graft rejection between the two groups (p = 0.06), the cinacalcet group included a small number of patients; thus, it was difficult to conclude about the lack of significant difference. There was no significant difference in the rates of graft failure between the two groups. A 5-year follow-up study revealed that there was no significant difference in kidney function between the two groups [30]. Although our study did not show any significant results with respect to the graft outcome between the two groups, other studies have reported the existence of such differences [23,26]. One retrospective review revealed that the overall rate of transplant allograft failure was lower in the PTX cohort (9% vs. 33%, p = 0.007) [23]. A randomized controlled trial by Cruzado et al. [26] found that both groups experienced a 12-month decline in eGFR, although the cinacalcet group experienced a more severe decline than the PTX group. However, there were no rejection episodes to account for this result. To date, there remains a paucity of studies demonstrating the differences between the two groups in the rates of graft outcome; therefore, further research is needed.

In the case of cinacalcet, the Evaluation of Cinacalcet Hydrochloride Therapy to Lower Cardiovascular Events trial revealed that it does not significantly reduce the rate of major CVD events compared to the placebo in patients with secondary hyperparathyroidism who were undergoing hemodialysis [31]. However, studies on the effects of cinacalcet on CVD events in patients with tertiary hyperparathyroidism remain lacking. PTX was associated with a decreased incidence of significant CVD events after surgery in patients with secondary hyperparathyroidism [32,33]. In a study comparing the effects of PTX and cinacalcet in secondary hyperparathyroidism, PTX decreased the risk of new CVD events by 86% compared to cinacalcet [34]. In our study, there was no significant difference in the incidence of CVD events between the two groups. Because there are few studies comparing the rates of CVD events in both groups undergoing treatment for tertiary hyperparathyroidism, more studies are needed in the future.

Tertiary hyperparathyroidism is associated with an increased risk of osteoporosis and a major risk of fractures [8,10]. PTX and cinacalcet lower the risk of fracture in secondary hyperparathyroidism [35,36]. PTX, which was effective for controlling tertiary hyperparathyroidism, improved BMD 12 months after surgery, whereas cinacalcet did not [26]. In a randomized trial conducted among patients who underwent KT, although cinacalcet improved the biochemical parameters, there was no significant improvement in BMD in the cinacalcet group compared to the placebo group [37]. It is not yet clear whether PTX and cinacalcet lower the fracture risk in KT patients with tertiary hyperparathyroidism. In our study, three patients experienced fractures; however, there was no statistically significant difference in the incidence of fractures between the two groups.

This study had several limitations. First, it was a retrospective study conducted at a single center, which means there is a possibility of selection bias. Second, because of its small sample size, definitive conclusions cannot be drawn, which is the case in many studies on tertiary hyperparathyroidism. Despite the large number of KTs conducted at our medical center, we were only able to identify 83 patients who met the selection criteria for this study over a period of 18 years. To overcome these limitations, our study included patients with a longer follow-up duration than that found in previously reported retrospective studies. Third, in Korea, the use of cinacalcet in KT is not covered by insurance; thus, a sufficient dose to normalize serum calcium and PTH may not have been administered in some cases. Fourth, regarding the BMD results, there was difficulty in deriving significant results because the data of only very few patients were available from both before and after treatment. For future studies, we are currently planning to set up a protocol to measure BMD before and after treatment.

In conclusion, PTX appears to lower PTH and calcium levels effectively in tertiary hyperparathyroidism. However, creatinine level and allograft rejection should be monitored closely. More prospective randomized studies are warranted to determine the appropriate first-line therapy in patients with tertiary hyperparathyroidism based on clinical outcomes.

**Conflicts of interest**

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

Conceptualization: CHB
Formal analysis: CHB, SJ
Investigation: SJ
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References

Ambulatory blood pressure trajectories and blood pressure variability in kidney transplant recipients: a comparative study against chronic kidney disease patients

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Background: Hypertension is a major cardiovascular risk factor in both kidney transplant recipients (KTRs) and patients with chronic kidney disease (CKD). Ambulatory blood pressure monitoring (ABPM) is considered the gold-standard method for hypertension management in these subjects. This is the first study evaluating the full ambulatory blood pressure (BP) profile and short-term BP variability (BPV) in KTRs versus CKD patients without kidney replacement therapy.

Methods: Ninety-three KTRs were matched with 93 CKD patients for age, sex, and estimated glomerular filtration rate. All participants underwent 24-hour ABPM. Mean ambulatory BP levels, BP trajectories, and BPV indices (standard deviation [SD], weighted SD, and average real variability) were compared between the two groups.

Results: There were no significant between-group differences in 24-hour systolic BP (SBP)/diastolic BP (DBP) (KTRs: 126.9 ± 13.1/79.1 ± 7.9 mmHg vs. CKD: 128.1 ± 11.2/77.9 ± 8.1 mmHg, p = 0.52/0.29), daytime SBP/DBP and nighttime SBP; nighttime DBP was slightly higher in KTRs (KTRs: 76.5 ± 8.8 mmHg vs. CKD: 73.8 ± 8.8 mmHg, p = 0.04). Repeated measurements analysis of variance showed a significant effect of time on both ambulatory SBP and DBP (SBP: F = [19, 3002] = 11.735, p < 0.001, partial η² = 0.069) but not of KTR/CKD status (SBP: F = [1, 158] = 0.668, p = 0.42, partial η² = 0.004). Ambulatory systolic/diastolic BPV indices were not different between KTRs and CKD patients, except for 24-hour DBP SD that was slightly higher in the latter group (KTRs: 10.2 ± 2.2 mmHg vs. CKD: 10.9 ± 2.6 mmHg, p = 0.04). No differences were noted in dipping pattern between the two groups.

Conclusion: Mean ambulatory BP levels, BP trajectories, and short-term BPV indices are not significantly different between KTRs and CKD patients, suggesting that KTRs have a similar ambulatory BP profile compared to CKD patients without kidney replacement therapy.

Keywords: Ambulatory blood pressure monitoring, Blood pressure variability, Chronic kidney diseases, Hypertension, Kidney transplantation
Introduction

Hypertension is a major risk factor for cardiovascular disease, renal function decline, and all-cause mortality in patients with chronic kidney disease (CKD), and its prevalence gradually increases alongside advancing CKD stages [1]. Ambulatory blood pressure monitoring (ABPM) is considered the gold-standard method for hypertension diagnosis and management in patients with CKD [2-5] due to several advantages, including high prognostic value for future adverse events [6,7], the identification of different hypertension phenotypes (i.e., white coat and masked hypertension), [6,7] and, finally, the ability to capture short-term blood pressure variability (BPV), which is also an independent risk factor for cardiovascular events and mortality in CKD patients [8].

Kidney transplantation is considered the optimal treatment option for patients with kidney failure, as it greatly improves cardiovascular morbidity and mortality compared to both hemodialysis and peritoneal dialysis treatment [9]. Despite the significant reductions in cardiovascular risk, kidney transplant recipients (KTRs) still have a higher risk of future cardiovascular events and death compared to the general population [10]. The high prevalence of hypertension in this population (70%-90%) [11] is considered a major factor involved in these associations [9,11,12]. Of note, “masked” hypertension, a hypertension phenotype particularly associated with higher risk of cardiovascular disease, renal disease, and death [13], is also highly prevalent in KTRs [14].

Although the role of ABPM in CKD and kidney transplantation has been highlighted in recent consensus documents [4,12], as of this writing, there are only scarce data comparing ambulatory blood pressure (BP) levels between KTRs and CKD patients without kidney replacement therapy. In the only relevant study [14], KTRs had significantly higher ambulatory systolic BP (SBP) levels than individuals with CKD, whereas there were no differences between these two groups in office BP levels; this study, however, only examined average BP levels and not full ambulatory BP trajectories during a typical 24-hour period or short-term BPV. Thus, the aim of the present study was to evaluate for the first time the full ambulatory BP profile, as well as the indices of short-term BPV, in KTRs in comparison to CKD patients without kidney replacement therapy.

Methods

Study participants

This is an observational study that includes matched cases and controls. We recruited KTRs from the renal transplantation outpatient clinic of the Department of Nephrology, Laiko General Hospital in Athens and patients with CKD from the outpatient clinic of the Department of Nephrology, Hippokration Hospital in Thessaloniki, Greece. Adult patients that received a kidney transplant at least 3 months prior to study recruitment were included as cases; a blinded member of our group matched KTRs with potential controls from a large cohort of stage 1-4 CKD patients at a 1:1 ratio on the basis of age, sex, and estimated glomerular filtration rate (eGFR; calculated with the CKD-Epidemiology Collaboration formula) (Supplementary Fig. 1, Supplementary Table 1; available online). Inclusion and exclusion criteria for the two study groups are presented in Supplementary Table 2 (available online). All evaluations were performed according to the Declaration of Helsinki (2013 Amendment); all participants provided informed written consent prior to participation. The study protocol was approved by the Ethics Committee of the Aristotle University of Thessaloniki School of Medicine and by the Data Protection Management of Laiko General Hospital of Athens (No. 8052/15-06-2017).

Data collection and study measurements

Study subjects were evaluated during a scheduled visit at the relevant clinic. Demographics, anthropometric characteristics, comorbidities, concomitant medication, and other CKD-related information were collected for each participant. A physical examination and venous blood sampling for routine hematological and biochemical tests were also performed. Office BP readings were performed at the level of the brachial artery according to the relevant guidelines [3]. All captured information was transferred in a purpose-built electronic datasheet.

In both KTRs and CKD patients, ABPM was performed with the Mobil-O-Graph device (IEM, Stolberg, Germany), a validated oscillometric device [15,16] whose brachial BP-detection unit was validated according to standard protocols and was shown to provide practically identical val-
ues with a widely used ABPM monitor, Spacelabs 90217A (Spacelabs Medical, Inc., Snoqualmie, WA, USA) [17]. ABPM was performed with a cuff of appropriate size for 24 hours as described previously [18,19]. The ABPM device was placed on the opposite arm for KTRs with a functioning arteriovenous fistula. All participants were instructed to continue their regular medication and follow their usual activities. Measurements were included in analysis if >70% of recordings were valid with ≤2 non-consecutive day-hours with <2 valid measurements and ≤1 night-hour without valid recording for each 24-hour period [20]. In order to minimize the possible effect of manual BP measurements, only measurements recorded at the prespecified time intervals at which the device was set to take measurements were used in this analysis.

Furthermore, based on ABPM recordings, BPV indices of brachial SBP and diastolic BP (DBP) (standard deviation [SD], weighted SD, and average real variability) were calculated from validated formulas as described previously (Supplementary Table 3, available online) [18,21]. The dipping pattern of nocturnal BP was calculated with the following formula: 1 – mean night/mean day ratio of SBP (%). Patients were divided into the following groups: extreme dippers (nocturnal BP fall of >20%), dippers (fall of >10% and ≤20%), non-dippers (fall of ≥0% and ≤10%), and reverse dippers (nocturnal increase in SBP).

Statistical analysis

The Kolmogorov-Smirnov test was applied to examine the normality of distribution for quantitative variables. Continuous variables are expressed as mean ± SD or as median (interquartile range) according to the normality of the distribution. Categorical variables are presented as absolute frequencies and percentages (n, %). Between-group comparisons for continuous variables were performed with the independent t test or the Mann-Whitney test, where applicable; categorical variables were compared with the chi-square test or the Fisher exact test. To evaluate the effect of group (KTRs vs. CKD patients) and time on the trends of ambulatory BP levels and to determine whether an interaction between the two existed, we compared the mean hourly values of SBP and DBP between KTRs and CKD patients using two-way mixed analysis of variance (ANOVA) for repeated measurements for a 20-hour period (12:00 PM to 8:00 AM), during which, data were available for all participants following different starting time of the ABPMs. The Greenhouse-Geiser correction was applied to overcome the violation of the sphericity assumption. Moreover, time profiles of BP levels were investigated using linear mixed models (LMM) procedure to create estimates of BP and their association with KTR/CKD status and other covariates during a 24-hour ABPM. A random intercept and random slope model was utilized, and an unstructured covariance structure provided the best fit of the data based on Akaike information criterion and Schwarz’s Bayesian information criterion values after testing other covariance matrices. The p-values of <0.05 (two-tailed) were considered statistically significant for all comparisons. Statistical analysis was performed with IBM SPSS version 22.0 (IBM Corp., Armonk, NY, USA).

Results

Demographic and clinical characteristics of kidney transplant recipients and chronic kidney disease patients

Demographic characteristics, comorbidities, concomitant medication use, and main laboratory data of the two study groups (93 KTRs and 93 CKD patients) are presented in Table 1. As expected, the two groups were not different in terms of age (KTRs: 61.3 ± 9.6 years vs. CKD: 63.8 ± 9.9 years, p = 0.09), sex distribution (KTRs: 32.3% females vs. CKD: 32.3% females, p = 1.00) or eGFR (KTRs: 60.2 ± 22.1 mL/min/1.73 m² vs. CKD: 60.6 ± 24.3 mL/min/1.73 m², p = 0.92). In addition, there were no differences between the two groups regarding all major comorbidities except for diabetes (KTRs: 36.6% vs. CKD: 54.8%, p = 0.01) and smoking (KTRs: 9.7% vs. CKD: 23.7%, p = 0.01), which were less common in KTRs. Among KTRs, 80.6% were receiving tacrolimus, 91.4% were receiving mycophenolate mofetil/mycophenolic acid, and 76.3% were administered corticosteroids for immunosuppression.

KTRs and CKD patients had similar office SBP levels (KTRs: 130.8 ± 17.2 mmHg vs. CKD: 129.9 ± 9.3 mmHg, p = 0.64); however, office DBP was significantly lower in KTRs (KTRs: 74.5 ± 10.8 mmHg vs. CKD: 81.1 ± 7.6 mmHg, p < 0.001). The number of prescribed antihypertensive drugs was slightly but not significantly higher in CKD patients (KTRs: 2.0 ± 1.2 vs. CKD: 2.3 ± 1.4, p = 0.06); the use of angio-
### Table 1. Demographic, anthropometric, and clinical characteristics of the study participants

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>KTR group</th>
<th>CKD group</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>93</td>
<td>93</td>
<td>0.09</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>61.3 ± 9.6</td>
<td>63.8 ± 9.9</td>
<td></td>
</tr>
<tr>
<td>Female sex</td>
<td>30 (32.3)</td>
<td>30 (32.3)</td>
<td>1.00</td>
</tr>
<tr>
<td>Time since the initiation of RRT (mo)</td>
<td>161 [103.2]</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Time since kidney transplantation (mo)</td>
<td>90.3 [128.4]</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>27.7 ± 16.9</td>
<td>30.4 ± 6.0</td>
<td>0.14</td>
</tr>
<tr>
<td>Hypertension</td>
<td>85 (91.4)</td>
<td>83 (89.2)</td>
<td>0.62</td>
</tr>
<tr>
<td>Diabetes</td>
<td>34 (36.6)</td>
<td>51 (54.8)</td>
<td>0.01*</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>59 (63.4)</td>
<td>61 (65.6)</td>
<td>0.65</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>18 (19.4)</td>
<td>25 (26.9)</td>
<td>0.22</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>15 (16.1)</td>
<td>12 (12.9)</td>
<td>0.53</td>
</tr>
<tr>
<td>Stroke</td>
<td>2 (2.2)</td>
<td>4 (4.3)</td>
<td>0.68</td>
</tr>
<tr>
<td>Peripheral arterial disease</td>
<td>4 (4.3)</td>
<td>10 (10.8)</td>
<td>0.01*</td>
</tr>
<tr>
<td>Smoking</td>
<td>9 (9.7)</td>
<td>22 (23.7)</td>
<td>0.01*</td>
</tr>
<tr>
<td>Office SBP (mmHg)</td>
<td>130.8 ± 17.2</td>
<td>129.9 ± 9.3</td>
<td>0.64</td>
</tr>
<tr>
<td>Office DBP (mmHg)</td>
<td>74.5 ± 10.8</td>
<td>81.1 ± 7.6</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>No. of antihypertensive drugs</td>
<td>2.0 ± 1.2</td>
<td>2.3 ± 1.4</td>
<td>0.06</td>
</tr>
<tr>
<td>ACEi/ARBs</td>
<td>44 (47.3)</td>
<td>59 (67.3)</td>
<td>0.03*</td>
</tr>
<tr>
<td>Calcium-channel blockers</td>
<td>43 (46.2)</td>
<td>50 (53.8)</td>
<td>0.31</td>
</tr>
<tr>
<td>MRAs</td>
<td>0 (0.0)</td>
<td>2 (2.2)</td>
<td>0.497</td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>64 (68.8)</td>
<td>44 (47.3)</td>
<td>0.003*</td>
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<tr>
<td>Alpha-blockers</td>
<td>2 (2.2)</td>
<td>13 (14.0)</td>
<td>0.003*</td>
</tr>
<tr>
<td>Nitrates</td>
<td>2 (2.2)</td>
<td>1 (1.1)</td>
<td>1.00</td>
</tr>
<tr>
<td>Central acting agents</td>
<td>12 (12.9)</td>
<td>8 (8.6)</td>
<td>0.34</td>
</tr>
<tr>
<td>Diuretics</td>
<td>17 (18.3)</td>
<td>42 (45.2)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Statins</td>
<td>41 (44.1)</td>
<td>59 (63.4)</td>
<td>0.008*</td>
</tr>
<tr>
<td>Immunosuppressive drugs</td>
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<tr>
<td>Cyclosporine</td>
<td>13 (14.0)</td>
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</tr>
<tr>
<td>Tacrolimus</td>
<td>75 (80.6)</td>
<td></td>
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<tr>
<td>mTORi</td>
<td>11 (11.8)</td>
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<td></td>
</tr>
<tr>
<td>MMF/MPA</td>
<td>85 (91.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Azathioprine</td>
<td>1 (1.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>71 (76.3)</td>
<td></td>
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<tr>
<td>Hemoglobin (g/dL)</td>
<td>13.1 ± 1.6</td>
<td>13.7 ± 1.5</td>
<td>0.005*</td>
</tr>
<tr>
<td>eGFR CKD-EPI (mL/min/1.73 m²)</td>
<td>60.2 ± 22.1</td>
<td>60.6 ± 24.3</td>
<td>0.92</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>1.3 ± 0.5</td>
<td>1.4 ± 0.6</td>
<td>0.63</td>
</tr>
<tr>
<td>Urea (mg/dL)</td>
<td>60.1 ± 32.2</td>
<td>53.9 ± 29.6</td>
<td>0.17</td>
</tr>
<tr>
<td>Uric acid (mg/dL)</td>
<td>6.4 ± 1.4</td>
<td>6.5 ± 1.4</td>
<td>0.94</td>
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<tr>
<td>Sodium (mEq/L)</td>
<td>140.5 ± 3.2</td>
<td>138.9 ± 2.5</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Potassium (mEq/L)</td>
<td>4.5 ± 0.5</td>
<td>4.7 ± 0.4</td>
<td>0.88</td>
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<tr>
<td>Calcium (mg/dL)</td>
<td>9.4 ± 0.6</td>
<td>9.4 ± 0.6</td>
<td>0.001*</td>
</tr>
<tr>
<td>Phosphorus (mg/dL)</td>
<td>3.1 ± 0.7</td>
<td>3.5 ± 0.6</td>
<td>0.07</td>
</tr>
<tr>
<td>Parathyroid hormone (pg/mL)</td>
<td>66.9 (53.6–113.5)</td>
<td>51.5 (37.2–73.5)</td>
<td>0.02*</td>
</tr>
<tr>
<td>C-reactive protein (mg/dL)</td>
<td>3.0 (1.6–3.6)</td>
<td>1.3 (0.8–3.4)</td>
<td>0.001*</td>
</tr>
<tr>
<td>Total cholesterol (mg/dL)</td>
<td>188.3 ± 31.9</td>
<td>163.9 ± 38.5</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>149.4 ± 62.6</td>
<td>158.0 ± 92.2</td>
<td>0.46</td>
</tr>
</tbody>
</table>

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

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blockers; CKD-EPI, CKD-Epidemiology Collaboration; CKD, chronic kidney disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; KTR, kidney transplant recipient; MMF, mycophenolate mofetil; MPA, mycophenolic acid; MRA, mineralocorticoid receptor antagonist; mTORi, mammalian target of rapamycin inhibitors; RRT, renal replacement therapy; SBP, systolic blood pressure.

*p < 0.05 is statistically significant.
tensin-converting enzyme inhibitor/angiotensin II receptor blockers (KTRs: 47.3% vs. CKD: 67.3%, \( p = 0.03 \)), α-blockers (KTRs: 2.2% vs. CKD: 14.0%, \( p = 0.003 \)) and diuretics (KTRs: 18.3% vs. CKD: 45.2%, \( p < 0.001 \)) was less frequent while the use of β-blockers was more frequent in KTRs compared to CKD patients (KTRs: 68.8% vs. CKD: 47.3%, \( p = 0.003 \)).

Comparison of ambulatory blood pressure levels between kidney transplant recipients and chronic kidney disease patients

Table 2 presents the mean ambulatory values for SBP, DBP, and pulse pressure (PP) in KTRs and CKD patients. As noted in the table, there were no significant differences between the two groups in the 24-hour SBP (KTRs: 126.9 ± 13.1 mmHg vs. CKD: 128.1 ± 11.2 mmHg, \( p = 0.52 \)) and DBP (KTRs: 79.1 ± 7.9 mmHg vs. CKD: 77.9 ± 8.1 mmHg, \( p = 0.29 \)). This was also the case for daytime and nighttime BP levels, with the exception of nighttime DBP, which was higher in KTRs compared to CKD patients (KTRs: 76.5 ± 8.8 mmHg vs. CKD: 73.8 ± 8.8 mmHg, \( p = 0.04 \)). PP levels were similar between KTRs and CKD patients over all periods studied.

Table 2. Ambulatory BP levels during the 24-hour, daytime and nighttime period in KTR group and CKD group

<table>
<thead>
<tr>
<th>Variable</th>
<th>KTR group (n = 93)</th>
<th>CKD group (n = 93)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic BP (mmHg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24-Hour</td>
<td>126.9 ± 13.1</td>
<td>128.1 ± 11.2</td>
<td>0.52</td>
</tr>
<tr>
<td>Daytime</td>
<td>127.2 ± 12.9</td>
<td>129.5 ± 11.5</td>
<td>0.20</td>
</tr>
<tr>
<td>Nighttime</td>
<td>125.9 ± 16.5</td>
<td>124.6 ± 13.7</td>
<td>0.57</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24-Hour</td>
<td>79.1 ± 7.9</td>
<td>77.9 ± 8.1</td>
<td>0.29</td>
</tr>
<tr>
<td>Daytime</td>
<td>79.8 ± 8.1</td>
<td>79.5 ± 8.6</td>
<td>0.81</td>
</tr>
<tr>
<td>Nighttime</td>
<td>76.5 ± 8.8</td>
<td>73.8 ± 8.8</td>
<td>0.04*</td>
</tr>
<tr>
<td>Pulse pressure (mmHg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24-Hour</td>
<td>47.8 ± 9.7</td>
<td>50.2 ± 9.6</td>
<td>0.10</td>
</tr>
<tr>
<td>Daytime</td>
<td>47.4 ± 9.6</td>
<td>50.1 ± 9.8</td>
<td>0.06</td>
</tr>
<tr>
<td>Nighttime</td>
<td>49.4 ± 11.5</td>
<td>50.8 ± 10.1</td>
<td>0.38</td>
</tr>
</tbody>
</table>

Data are expressed as mean ± standard deviation. BP, blood pressure; CKD, chronic kidney disease; KTR, kidney transplant recipient.

*\( p < 0.05 \) is statistically significant.

White coat and masked hypertension in kidney transplant recipients and chronic kidney disease patients

Fig. 1 illustrates the prevalence of different BP phenotypes among the two study groups. The prevalence of white coat hypertension was similar between the two groups, and the prevalence of masked hypertension may have been higher in KTRs than CKD patients, though not statistically significant (24.7% vs. 16.1%, \( p = 0.15 \)).

Trajectories of ambulatory blood pressure in kidney transplant recipients and chronic kidney disease patients

The trajectories of hourly mean SBP and DBP levels estimated using two-way mixed ANOVA for repeated measurements in patients with CKD and in KTRs are depicted in Fig. 2. Visual inspection of the figures reveals similar patterns in ambulatory BP between the two groups. After an initial decline in SBP levels during the afternoon, a gradual rise was evident during the evening hours, succeeded by a nocturnal fall and, finally, a morning BP surge in both groups. A similar pattern was noted for ambulatory DBP.

With regards to SBP levels, a significant effect of time (\( F = [19, 3002] = 11.735, p < 0.001, \) partial \( \eta^2 = 0.069 \)) but not of CKD/KTR status (\( F = [1, 158] = 0.668, p = 0.42, \) partial \( \eta^2 = 0.004 \)) was noted. There was no significant interaction between time and status on SBP levels over the examined pe-
With regards to DBP, there was again a significant effect of time ($F = [19, 3002] = 18.930, p < 0.001$, partial $\eta^2 = 0.107$) but not of CKD/KTR status ($F = [1, 158] = 0.052, p = 0.82$, partial $\eta^2 < 0.001$) and similarly no significant interaction between time and status was found ($F = [19, 3002] = 1.614, p = 0.09$, partial $\eta^2 = 0.010$). With regards to DBP, there was again a significant effect of time ($F = [19, 3002] = 18.930, p < 0.001$, partial $\eta^2 = 0.107$) but not of CKD/KTR status ($F = [1, 158] = 0.052, p = 0.82$, partial $\eta^2 < 0.001$) and similarly no significant interaction between time and status was found ($F = [19, 3002] = 1.614, p = 0.09$, partial $\eta^2 = 0.010$).

Supplementary Table 4 (available online) presents the results of the LMM analysis. Similarly, no significant effect of KTR status on BP levels was found over time. Male sex was statistically significantly associated with a 5.58 mmHg increase in BP ($p < 0.001$) after adjustment for other co-variates. This effect was greater than the effect observed for history of cardiovascular disease. Diabetes and smoking status did not appear to have a significant effect on BP trajectories.

Blood pressure variability indices in kidney transplant recipients and chronic kidney disease patients

BPV indices of 24-hour ambulatory BP recordings in KTRs and CKD patients are presented in Table 3. As shown in the table, all BPV indexes in KTRs were numerically lower but not significantly different than those in CKD patients. However, 24-hour DBP SD was significantly lower in KTRs compared to CKD patients ($10.2 ± 2.2$ mmHg vs. $10.9 ± 2.6$ mmHg, respectively; $p = 0.04$).

Dipping pattern

Table 4 presents the dipping profiles of the participants during the 24-hour period. The distribution of dipping profiles was not different between the two KTRs and CKD patients.
Table 4. Dipping patterns of SBP values during 24-hour ABPM in KTR group compared to CKD group

<table>
<thead>
<tr>
<th>24-Hour SBP</th>
<th>KTR group (n = 93)</th>
<th>CKD group (n = 93)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-Type classification</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-dippers</td>
<td>81 (87.1)</td>
<td>75 (80.6)</td>
<td>0.232</td>
</tr>
<tr>
<td>Dippers</td>
<td>12 (12.9)</td>
<td>18 (19.4)</td>
<td></td>
</tr>
<tr>
<td>4-Type classification</td>
<td></td>
<td></td>
<td>0.333</td>
</tr>
<tr>
<td>Reverse dippers</td>
<td>34 (36.6)</td>
<td>26 (27.9)</td>
<td></td>
</tr>
<tr>
<td>Non-dippers</td>
<td>47 (50.5)</td>
<td>49 (52.7)</td>
<td></td>
</tr>
<tr>
<td>Dippers</td>
<td>12 (12.9)</td>
<td>18 (19.4)</td>
<td></td>
</tr>
<tr>
<td>Extreme dippers</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td></td>
</tr>
</tbody>
</table>

Data are expressed as number (%).
ABPM, ambulatory blood pressure monitoring; CKD, chronic kidney disease; KTR, kidney transplant recipient; SBP, systolic blood pressure.

Discussion

The present study is the first to compare BP profile and short-term BPV indices between KTRs and CKD patients without kidney replacement therapy. We found that the mean ambulatory BP levels were not significantly different between the two groups, except for nighttime DBP, which was significantly higher by 2.7 mmHg in the KTR group. Two-way ANOVA for repeated measurements showed a significant effect of time on ambulatory BP, but not a significant effect of group, nor a significant interaction between them. With regards to short-term BPV, all indices studied were not different between the two groups, except for DBP SD, which was higher in CKD patients. The dipping profile was similar between KTRs and CKD patients.

Previous studies in the general population, as well as in CKD patients, suggested that BP differs when measured in the office versus in-out-of-office settings; ABPM is considered to be superior to office BP measurements for the prediction of target organ damage, cardiovascular events, and mortality [7]. Furthermore, out-of-office readings provide additional prognostic information, as they lead to the detection of different BP phenotypes (i.e., white coat and masked hypertension), which are also associated with an increased risk of cardiovascular disease [7]. In line with the above evidence in CKD patients, a recent meta-analysis showed that ambulatory BP was more strongly correlated than office BP with markers of target organ damage and vascular dysfunction, whereas ambulatory BP was a stronger predictor of renal function decline in KTRs [22].

To the best of our knowledge, studies comparing mean ambulatory BP values between KTRs and CKD patients (including both CKD patients without kidney replacement therapy and individuals undergoing hemodialysis) are scarce. A few studies comparing KTRs and hemodialysis patients with ABPM showed that both groups generally display similar BP levels [23,24]; however, in a recent study by our group, which is currently the largest in the field, SBP and PP levels were significantly lower in KTRs compared to hemodialysis patients, and BP trajectories differed accordingly [25]. With regards to CKD patients without kidney replacement therapy, in the only study to date comparing the mean ambulatory BP values between 92 KTRs and 97 CKD patients, 24-hour SBP, as well as awake and sleep SBP were significantly higher in KTRs, while office BP was not [14]. In contrast with the aforementioned findings from Azancot et al. [14], in this study, we observed no significant differences in ambulatory BP levels between KTRs and CKD patients, except for nighttime DBP being slightly higher in the former group. The observed differences in nighttime BP could be meaningful and associated with adverse outcomes, as nighttime BP is strongly associated with GFR loss over time, as well as with markers of vascular health, such as carotid-intimal media thickness [26]. Reduced arterial stiffness observed in KTRs compared to CKD patients without kidney replacement therapy could be a prominent factor for the higher DBP levels observed in KTRs [27].

The differences between our findings and those of Azancot et al. [14] may be due to several reasons. First, there is a time difference of about 7 years in the conduction of the studies; as considerable emphasis on hypertension and its consequences in KTRs has been given in recent years [11], better control rates could have been achieved in organized transplantation centers. This is further supported by the fact that the mean number of antihypertensive agents used in our KTR cohort was considerably higher than that of the previous study (2.0 ± 1.2 vs. 1.6 ± 1.3, respectively) [14]. Furthermore, in the present study we employed a careful matching between KTRs and CKD patients on the basis of sex, age, and eGFR levels. This may have provided a more objective picture, as all of these factors are known to impact ambulatory BP levels [1,28].

BPV is known to be independently associated with target organ damage as well as cardiovascular events and mortality in both the general population and CKD patients [6]. In
a cross-sectional study in 16,546 patients with CKD, short-term SBP variability increased with advancing CKD stages, and this increase in BPV was suggested to be involved in the progressive elevation of cardiovascular risk with kidney disease progression [29]. However, there are only a few works investigating BPV in KTRs. Ozkayar et al. [30] have previously shown that KTRs with endothelial dysfunction have significantly higher BPV compared to those without endothelial dysfunction. In a recent case-control study of our group in 204 KTRs and 102 matched for age and sex hemodialysis patients, we showed that KTRs have significantly lower short-term BPV compared to their hemodialysis counterparts [25]. This is the first study to compare short-term BPV between KTRs and CKD patients without kidney replacement therapy, showing no significant differences between the two study groups in all indices studied except for DBP SD. Based on these observations and previous findings that KTRs have significantly lower BPV compared with hemodialysis individuals [25], one could hypothesize that BPV levels are improved after kidney transplantation to a level comparable to that of CKD patients without kidney replacement therapy with similar eGFR. Possible explanations for this improvement include BP lowering and downregulation of sympathetic nervous system overdrive observed after kidney transplantation [31]. Future studies are warranted to delineate the exact mechanisms of this BPV improvement.

Among the strengths of this study are the careful design, elaborating a blinded matching for a set of crucial parameters (i.e., age, sex, and eGFR), and complex analysis using two-way ANOVA for repeated measurements to evaluate the effects of time and patient group on BP levels. In addition, this is the first study assessing short-term BPV in KTRs, including modern and valid indices and not only the SD and coefficient of variation that are highly influenced by the mean and the weight of BP fall during nighttime [18]. The main limitation of our study is its observational nature, which precludes drawing conclusions about potential associations between ambulatory BP and longitudinal outcomes. Future studies are encouraged to delineate these associations. In addition, the matching variables included three different parameters (age, sex, and eGFR), limiting the ability to control for other potential confounders. Finally, we examined a single cohort including only Caucasian patients; thus, further studies are needed to investigate the reproducibility of our findings in other ethnic groups.

In conclusion, this study showed that the mean ambulatory BP levels were not significantly different between KTRs and age-, sex- and eGFR-matched CKD patients, except for nighttime DBP, which was found to be slightly higher in KTRs. Similarly, the ambulatory BP trajectories revealed a similar pattern in the two groups. BPV indices, as well as dipping profiles, were also not different between KTRs and CKD patients. The above results suggest that, in contrast to previous observations, KTRs have a similar ambulatory BP profile compared to CKD patients without kidney replacement therapy. Future studies are needed to examine longitudinal associations of office and ambulatory BP with hard renal and cardiovascular outcomes in KTRs in order to fully define the hypertension-associated risks and the optimal targets for treatment in this population.

Conflicts of interest

All authors have no conflicts of interest to declare.

Authors’ contributions

Conceptualization: PS, SM
Data curation: MK, EX, AA
Formal analysis: MEA, MT, EP, PS, MK, SM
Project administration: A Protogerou, A Papagianni, INB
Writing—original draft: MK, MEA, MT
Writing—review & editing: All authors
All authors read and approved the final manuscript.

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References


The Korean Organ Transplantation Registry (KOTRY): an overview and summary of the kidney-transplant cohort

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

Background: As the need for a nationwide organ-transplant registry emerged, a prospective registry, the Korean Organ Transplantation Registry (KOTRY), was initiated in 2014. Here, we present baseline characteristics and outcomes of the kidney-transplant cohort for 2014 through 2019.

Methods: The KOTRY consists of five organ-transplant cohorts (kidney, liver, lung, heart, and pancreas). Data and samples were prospectively collected from transplant recipients and donors at baseline and follow-up visits; and epidemiological trends, allograft outcomes, and patient outcomes, such as posttransplant complications, comorbidities, and mortality, were analyzed.

Results: From 2014 to 2019, there were a total of 6,129 registered kidney transplants (64.8% with living donors and 35.2% with deceased donors) with a mean recipient age of 49.4 ± 11.5 years, and 59.7% were male. ABO-incompatible transplants totaled 17.4% of all transplants, and 15.0% of transplants were preemptive. The overall 1- and 5-year patient survival rates were 98.4% and 95.8%, respectively, and the 1- and 5-year graft survival rates were 97.1% and 90.5%, respectively. During a mean follow-up of 3.8 years, biopsy-proven acute rejection episodes occurred in 17.0% of cases. The mean age of donors was 47.3 ± 12.9 years, and 52.6% were male. Among living donors, the largest category of donors was spouses, while, among deceased donors, 31.2% were expanded-criteria donors. The mean serum creatinine concentrations of living donors were 0.78 ± 0.62 mg/dL and 1.09 ± 0.24 mg/dL at baseline and 1 year after kidney transplantation, respectively.

Conclusion: The KOTRY, a systematic Korean transplant cohort, can serve as a valuable epidemiological database of Korean kidney transplants.

Keywords: Cohort studies, Kidney transplantation, Registries, Republic of Korea

Introduction

Solid-organ transplantation is the best treatment modality for organ failure in terms of quality of life, medical cost, and long-term survival [1–4]. Allograft survival rates have also substantially improved with the development of effective immunosuppressants over the past number of decades. Maximization of patient and allograft survival necessitates

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proper management of chronic complications, such as cardiovascular disease and malignancy, as well as quality of life. However, the incidence and prognosis of chronic complications as well as organ-transplantation outcomes may differ according to ethnic and regional differences. For instance, while the leading cause of death among Western kidney-transplant recipients is cardiovascular disease, a major cause of death among recipients from certain Asian countries is infectious disease, with a lower-than-expected incidence of cardiovascular disease [5,6]. In Korean organ-transplant patients, further data is required to determine outcomes and prognoses related to ethnic and regional characteristics.

In Korea, since the legislation of organ transplantation in 1999, a centralized organ-procurement organization system and an organ-allocation system as well as a public organ-donation agency have been established. Therefore, deceased-donor organ donation in Korea is a transparent and systematic process. Although most organ transplantations in Korea are from living donors, the number of deceased-donor organ transplantations increased from 233 cases (1.09 per 1 million people) in 2000 to 1,989 cases (9.72 per 1 million people) in 2015 [7,8]. As the number of organ transplantations increased, the need for a nationwide organ-transplant registry became clear, and a prospective registry, the Korean Organ Transplantation Registry (KOTRY), was initiated in 2014 [9]. Previously, the Korean Society of Transplantation managed a retrospective version of the KOTRY, which included approximately 91.9% of all kidney transplants in Korea, from January 2009 to September 2012 [10]. Subsequently, a second retrospective KOTRY was introduced for kidney-transplant patients from October 2012 to March 2014. The current, prospective KOTRY includes five solid-organ-transplantation cohorts (kidney, liver, lung, heart, and pancreas) and 79 transplantation centers, including 40 kidney centers, 24 liver centers, five heart centers, five lung centers, and five pancreas centers, as of December 2019. In this report, we present the baseline characteristics and outcomes of the kidney-transplant cohort in the KOTRY for 2014 through 2019.

Methods

Study population

The organ recipients in both living- and deceased-donor organ transplantations and the organ donors in living-donor organ transplantations were enrolled in this cohort after informed consent was obtained. Recipients who were <19 years old and those undergoing simultaneous multiorgan transplantation, except for simultaneous pancreas and kidney transplantation, were excluded. However, patients in whom sequential multiorgan transplantation was performed were not excluded from the registry, and there was no age limit in liver transplantation. The individual Institutional Review Boards of participating hospitals approved this cohort study (No. H-1312-087-543), and this study was performed in accordance with the Declaration of Helsinki and the Declaration of Istanbul.

Study design and data collection

For each organ-transplant cohort in the KOTRY, medical data of recipients and donors were prospectively collected and entered into the iCReaT, a web-based data-capturing system developed by the Korean National Institute of Health. From these data, epidemiological trends, allograft-related outcomes, and patient outcomes—including posttransplant complications, comorbidities, and mortalities—were analyzed. For instance, data in the kidney-transplant cohort included demographics, comorbid conditions, laboratory data at baseline, discharge data, immunosuppressant use, laboratory data at follow-up, posttransplant complications, event notification, rejection, biopsy, and infections. Kidney-transplant donor data included demographics, comorbid conditions, laboratory data at baseline, discharge data, laboratory data at follow-up, and event notification. Follow-up data collection was performed first at 6 months after kidney transplantation and then subsequently on an annual basis. To analyze the effect of new-onset comorbidities on posttransplant outcomes, data on posttransplant comorbidities were collected at every follow-up visit for consideration of the number and timing of posttransplant comorbidities. Such comorbidities include cardiovascular events, stroke, malignancy, and fractures. Recently, the KOTRY has added case reports of kidney-transplant
recipients infected with coronavirus disease 19 (COVID-19), so we collected the treatment and outcomes data related to COVID-19 in kidney-transplant patients.

To enhance the quality of the data, clinical research coordinators in all participating centers received regular training. In addition, an electronic data-validation system was utilized to provide feedback to clinical research coordinators in each center. A central coordination unit moderated the study process, inspected the weekly registration status, and provided feedback to each participating center. To encourage the collection of follow-up data, newsletters that include details on patient enrollment and follow-up were periodically forwarded to the transplant physicians and surgeons of the participating centers. We also adopted a transfer system where, if an enrolled patient in a center was transferred to another center also participating in the KOTRY, the other center could collect the patient’s data. In addition, the importance of the collection of follow-up data of living donors was periodically communicated to all participating centers.

Sample collection

Blood samples for DNA analysis are collected before transplantation from both recipients and donors. Baseline serum samples from organ recipients were collected before transplantation and at 1 and 3 years after all transplantations, except for liver transplantations. In kidney transplantations, additional plasma samples have been collected from recipients at the same time points since 2017. Collection, quality control, and storage of blood samples were performed by an external company (LabGenomics, Seongnam, Republic of Korea).

Study outcomes

The primary outcomes in this study were graft loss and patient mortality. In the kidney-transplant cohort, graft loss was defined as maintenance dialysis performed for >3 months, retransplantation, or death with a functional graft. Causes of graft loss were classified as rejection, recurrent or de novo glomerulonephritis, postoperative complications, calcineurin-inhibitor toxicity, BK-virus nephropathy, noncompliance, primary graft failure, and others. Graft loss was defined as retransplantation or patient death in the liver-, heart-, and lung-transplant cohorts. In the pancreas-transplant cohort, graft loss was defined as insulin dependence or patient death. Causes of patient death were classified as cardiovascular disease, infection, malignancy, liver disease, sudden cardiac death, accident, suicide, and others.

Secondary outcomes included acute rejection, infection requiring hospitalization, malignancy, cardiac events, stroke, tuberculosis, and fractures in the kidney-transplant cohort. Acute rejection included clinical rejection and biopsy-proven rejection, and treatment methods as well as responses were also recorded. The pathogens causing infection were classified into bacteria, viruses (including cytomegalovirus), mycobacteria, fungi, Pneumocystis jirovecii, and others. The type of malignancy was classified according to the International Classification of Diseases, 10th revision. Cardiac events included acute myocardial infarction, angina (requiring therapeutic intervention or objective clinical findings), and congestive heart failure, and others. Stroke events included ischemic and hemorrhagic brain disease.

In the kidney- and liver-transplant cohorts, outcomes of living donors were collected, including death, cause of death, and surgical morbidities. In kidney-transplant donors, new-onset diseases, such as diabetes mellitus, hypertension, end-stage renal disease, stones in the urinary tract, and other comorbid conditions, were also included in the registry.

Statistical analyses

In the KOTRY cohort study, statistical analysis files are generated three times a year after a data-cleaning procedure. The participating center can request their own data at any time, and the latest validated statistical analysis files are released. If investigators were to request all centers’ data for research, the requested variables would be sent as a de-identified dataset after approval of the study proposal by the organ committee of the KOTRY.

Continuous variables were expressed as mean ± standard deviation values or medians with ranges. Categorical variables were described as numbers and percentages. The chi-square test or Fisher exact test was performed to evaluate differences in categorical variables. The Student t-test or analysis of variance was conducted to evaluate differences in continuous variables. Patient and graft survival, rejection-free survival, cardiac events, new-onset dia-
betes after transplantation (NODAT), malignancy, and infection were estimated using the Kaplan-Meier method and log-rank test. Significant variables in the univariate Cox regression analyses (p < 0.05) and the variables known to be clinically important in previous studies were entered into a multivariate Cox proportional hazards model to determine which factors were independently predicted several outcomes. Statistical significance was defined as p < 0.05.

Results

Baseline characteristics of registered kidney-transplant recipients

We summarized and analyzed the data of kidney-transplant recipients and donors registered in the KOTRY from 2014 to 2019. There were 6,129 registered kidney transplants, of which 3,973 were living-donor kidney transplants (LDKTs) and 2,156 were deceased-donor kidney transplants (DDKTs) (Fig. 1A). The mean age of the registered recipients was 49.4 ± 11.5 years, with the largest age group being those in their 50s. The mean age of the LDKT group was 47.9 ± 11.7 years, and that of the DDKT group was 52.1 ± 10.6 years. Among all registered recipients, 3,656 (59.7%) were male and 2,473 (40.3%) were female. The proportions of males totaled 59.0% in the LDKT group and 60.9% in the DDKT group, and the distribution was similar year by year. The most common causes of end-stage renal disease were glomerular diseases (1,986 cases, 32.4%), followed by diabetes (1,507 cases, 24.6%) and hypertension (932
cases, 15.2%). Although glomerular diseases were the most common cause of end-stage renal disease, diabetes as a cause exhibited an increasing trend, year by year (Fig. 1B).

Among the recipients, 5,140 (83.9%) underwent dialysis before kidney transplantation, including 4,411 (72.0%) who underwent hemodialysis and 729 (11.9%) who underwent peritoneal dialysis. Among 3,973 LDKT recipients, 918 (23.1%) underwent preemptive kidney transplantation (Fig. 1C, D). The median duration of dialysis before kidney transplantation was 0.5 years (interquartile range, 0.2–2.0 years) for LDKTs and 6.9 years (interquartile range, 4.2–9.6 years) for DDKTs. At the time of transplantation, 1,911 recipients (31.2%) had diabetes mellitus (31.8% in the LDKT group and 30.0% in the DDKT group), with an increasing trend, year by year. At the time of transplantation, 702 recipients (11.5%) had cardiovascular disease; the proportion was higher in the DDKT group (334, 15.5%) than in LDKT group (368, 9.3%).

The baseline and clinical characteristics of kidney-transplant patients are summarized in Table 1.

### Perioperative clinical characteristics of kidney-transplant recipients

A total of 1,469 recipients (24.0%) received desensitization therapy prior to transplantation. The most common reason for desensitization was ABO blood-type incompatibility (1,069 cases, 17.4%), followed by positive human leukocyte antigen (HLA) crossmatch results (434 cases, 7.1%; 129 cases of positive complement–dependent cytotoxicity crossmatch results and 305 cases of positive flow–cytometric crossmatch results) and positive results for donor-specific antibodies (424 cases, 6.9%). Basiliximab was the most commonly used induction agent, and antithymocyte globulin (ATG) induction was used more frequently in the DDKT group than in the LDKT group (p < 0.001).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total (n = 6,129)</th>
<th>LDKT (n = 3,973)</th>
<th>DDKT (n = 2,156)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>6129</td>
<td>3973</td>
<td>2156</td>
<td></td>
</tr>
<tr>
<td>Age (yr)</td>
<td>49.4 ± 11.5</td>
<td>47.9 ± 11.7</td>
<td>52.1 ± 10.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male sex</td>
<td>3,656 (59.7)</td>
<td>2,343 (59.0)</td>
<td>1,313 (60.9)</td>
<td>0.14</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>23.1 ± 3.6</td>
<td>23.2 ± 3.7</td>
<td>23.0 ± 3.3</td>
<td>0.18</td>
</tr>
<tr>
<td>Causes of ESRD</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1,507 (24.6)</td>
<td>993 (25.0)</td>
<td>514 (23.8)</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>932 (15.2)</td>
<td>528 (13.3)</td>
<td>404 (18.7)</td>
<td></td>
</tr>
<tr>
<td>Glomerular disease</td>
<td>1,986 (32.4)</td>
<td>1,345 (33.9)</td>
<td>641 (29.7)</td>
<td></td>
</tr>
<tr>
<td>Tubulointerstitial disease</td>
<td>20 (0.3)</td>
<td>14 (0.4)</td>
<td>6 (0.3)</td>
<td></td>
</tr>
<tr>
<td>Polycystic kidney disease</td>
<td>295 (4.8)</td>
<td>197 (5.0)</td>
<td>98 (4.5)</td>
<td></td>
</tr>
<tr>
<td>Hereditary disease</td>
<td>80 (1.3)</td>
<td>56 (1.4)</td>
<td>24 (1.1)</td>
<td></td>
</tr>
<tr>
<td>Obstructive uropathy</td>
<td>26 (0.4)</td>
<td>21 (0.5)</td>
<td>5 (0.2)</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>66 (1.1)</td>
<td>30 (0.8)</td>
<td>36 (1.7)</td>
<td></td>
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<tr>
<td>Unknown</td>
<td>1,217 (19.9)</td>
<td>789 (19.9)</td>
<td>428 (19.9)</td>
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</tr>
<tr>
<td>Mode of dialysis before KT</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hemodialysis</td>
<td>4,411 (72.0)</td>
<td>2,688 (67.7)</td>
<td>1,723 (79.9)</td>
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<tr>
<td>Peritoneal dialysis</td>
<td>729 (11.9)</td>
<td>298 (7.5)</td>
<td>431 (20.0)</td>
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<tr>
<td>KT</td>
<td>69 (1.1)</td>
<td>69 (1.7)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Preemptive</td>
<td>920 (15.0)</td>
<td>918 (23.1)</td>
<td>2 (0.1)</td>
<td></td>
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<tr>
<td>Duration of dialysis before KT (yr)a</td>
<td>2.3 (0.3–7.2)</td>
<td>0.5 (0.2–2.0)</td>
<td>6.9 (4.2–9.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>History of previous KT</td>
<td>472 (7.7)</td>
<td>276 (6.9)</td>
<td>196 (9.1)</td>
<td>0.01</td>
</tr>
<tr>
<td>Desensitization before KT</td>
<td>1,469 (24.0)</td>
<td>1,423 (35.8)</td>
<td>46 (2.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ABO-incompatible KT</td>
<td>1,069 (17.4)</td>
<td>1,069 (26.9)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Smoking, current or former</td>
<td>1,419 (23.2)</td>
<td>956 (24.1)</td>
<td>463 (21.5)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
### Table 1. Continued

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total (n = 6,129)</th>
<th>LDKT (n = 3,973)</th>
<th>DDKT (n = 2,156)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>History of diabetes</td>
<td>1,911 (31.2)</td>
<td>1,265 (31.8)</td>
<td>646 (30.0)</td>
<td>0.19</td>
</tr>
<tr>
<td>History of hypertension</td>
<td>5,474 (89.3)</td>
<td>3,538 (89.1)</td>
<td>1,936 (89.8)</td>
<td>0.04</td>
</tr>
<tr>
<td>History of cardiovascular disease</td>
<td>702 (11.5)</td>
<td>368 (9.3)</td>
<td>334 (15.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>History of tumor</td>
<td>415 (6.8)</td>
<td>238 (6.0)</td>
<td>177 (8.2)</td>
<td>0.001</td>
</tr>
<tr>
<td>HBsAg, positive</td>
<td>378 (6.2)</td>
<td>218 (5.5)</td>
<td>160 (7.4)</td>
<td>0.01</td>
</tr>
<tr>
<td>HCV Ab, positive</td>
<td>16 (0.3)</td>
<td>11 (0.3)</td>
<td>5 (0.2)</td>
<td>0.21</td>
</tr>
<tr>
<td>HLA mismatch</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>0</td>
<td>618 (10.1)</td>
<td>305 (7.7)</td>
<td>313 (14.5)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>298 (4.9)</td>
<td>241 (6.1)</td>
<td>57 (2.6)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>857 (14.0)</td>
<td>666 (16.8)</td>
<td>191 (8.9)</td>
<td></td>
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<tr>
<td>3</td>
<td>1,586 (25.9)</td>
<td>1,152 (29.0)</td>
<td>434 (20.1)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>1,136 (18.5)</td>
<td>601 (15.1)</td>
<td>535 (24.8)</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>1,103 (18.0)</td>
<td>670 (16.9)</td>
<td>433 (20.1)</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>455 (7.4)</td>
<td>316 (8.0)</td>
<td>139 (6.4)</td>
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</tr>
<tr>
<td>Unknown</td>
<td>76 (1.2)</td>
<td>22 (0.6)</td>
<td>54 (2.5)</td>
<td></td>
</tr>
<tr>
<td>Induction therapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ATG</td>
<td>1,334 (21.8)</td>
<td>629 (15.8)</td>
<td>705 (32.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Basiliximab</td>
<td>4,890 (79.8)</td>
<td>3,379 (85.1)</td>
<td>1,511 (70.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Bortezomib</td>
<td>2 (0.03)</td>
<td>2 (0.1)</td>
<td>-</td>
<td>0.55</td>
</tr>
<tr>
<td>Calcineurin inhibitor</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>5,909 (96.4)</td>
<td>3,791 (95.4)</td>
<td>2,118 (98.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cyclosporin</td>
<td>181 (3.0)</td>
<td>159 (4.0)</td>
<td>22 (1.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Antimetabolite drug</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mycophenolate</td>
<td>5,681 (92.7)</td>
<td>3,687 (92.8)</td>
<td>1,994 (92.5)</td>
<td>0.45</td>
</tr>
<tr>
<td>Mizoribine</td>
<td>52 (0.8)</td>
<td>42 (1.1)</td>
<td>10 (0.5)</td>
<td>0.005</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>2 (0.03)</td>
<td>2 (0.1)</td>
<td>0 (0.0)</td>
<td>0.12</td>
</tr>
<tr>
<td>Steroid</td>
<td>6,019 (98.2)</td>
<td>3,910 (98.4)</td>
<td>2,109 (98.0)</td>
<td>0.13</td>
</tr>
<tr>
<td>eGFR at discharge (mL/min/1.73 m$^2$)</td>
<td>68.2 ± 24.7</td>
<td>72.7 ± 22.8</td>
<td>59.7 ± 25.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Delayed graft function</td>
<td>218 (4.2)</td>
<td>21 (0.6)</td>
<td>197 (10.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Acute rejection within 6 mo after KT</td>
<td>867 (16.5)</td>
<td>561 (16.8)</td>
<td>306 (15.9)</td>
<td>0.12</td>
</tr>
<tr>
<td>Infection requiring hospitalization within 6 mo after KT</td>
<td>1,114 (21.2)</td>
<td>617 (18.5)</td>
<td>497 (25.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Donor</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (yr)</td>
<td>47.3 ± 12.9</td>
<td>46.7 ± 11.8</td>
<td>48.5 ± 14.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male sex</td>
<td>3,221 (52.6)</td>
<td>1,726 (43.4)</td>
<td>1,495 (69.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Body mass index (kg/m$^2$)</td>
<td>23.9 ± 3.4</td>
<td>24.2 ± 3.2</td>
<td>23.3 ± 3.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cold ischemic time (min)</td>
<td>136.3 ± 136.1</td>
<td>61.6 ± 39.9</td>
<td>289.3 ± 135.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>History of diabetes</td>
<td>303 (4.9)</td>
<td>46 (1.2)</td>
<td>257 (11.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>History of hypertension</td>
<td>946 (15.4)</td>
<td>407 (10.2)</td>
<td>539 (25.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Serum creatinine before KT (mg/dL)</td>
<td>1.05 ± 0.99</td>
<td>0.78 ± 0.62</td>
<td>1.55 ± 1.31</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Values are presented as number only, mean ± standard deviation, number (%), or median (interquartile range). The chi-square test was performed to evaluate differences in categorical variables, and the Student t-test or analysis of variance test was conducted to evaluate differences in continuous variables. ATG, antithymocyte globulin; DDKT, deceased-donor kidney transplantation; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; HBsAg, hepatitis B surface antigen; HCV Ab, hepatitis C virus antibody; HLA, human leukocyte antigen; KT, kidney transplantation; LDKT, living-donor kidney transplantation.
steroids, tacrolimus, and mycophenolate mofetil were the predominantly used maintenance immunosuppressant. Annual trends in the proportion of ABO- and HLA-incompatible kidney transplantation, complications after kidney transplantation, and usage of maintenance immunosuppressant were represented in Supplementary Fig. 1-3 (available online).

**Posttransplant outcomes of registered kidney-transplant recipients**

Delayed graft function after kidney transplantation occurred in 10.3% of DDKTs and 0.6% of LDKTs. The mean serum creatinine concentration of the recipients was 1.22 ± 0.55 mg/dL at 1 year after kidney transplantation (1.19 ± 0.52 mg/dL in the LDKT group and 1.27 ± 0.6 mg/dL in the DDKT group, respectively), and the distribution of serum creatinine concentration did not significantly differ year by year. The mean estimated glomerular filtration rate (eGFR) at 1 year after transplantation was 62.9 ± 21.5, 63.4 ± 19.0, and 62.1 ± 25.1 mL/min/1.73 m² in all kidney transplantations, LDKTs, and DDKTs, respectively.

The overall 1-year patient survival rate was 98.4% for all recipients (99.3% in the LDKT group and 97.0% in the DDKT group), and the 3- and 5-year patient survival rates were 97.4% and 95.8% for all recipients (98.7% and 97.8% in the LDKT group and 95.2% and 92.8% in the DDKT group), respectively (Fig. 2A, B). Upon multivariate Cox regression analysis, older recipient age, a history of cardiovascular disease, bortezomib use, cyclosporine rather than tacrolimus use at discharge, no antimetabolite drugs used at discharge, a higher serum creatinine concentration at discharge, and DDKT rather than LDKT were significantly associated with death after kidney transplantation (Table 2). Supplementary Table 1 (available online) presents the causes of patient death, and the most common cause of death was...

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**Figure 2. Patient and graft survival of kidney-transplant recipients in KOTRY.** (A, B) Patient survival of kidney recipients. (C, D) Graft survival of kidney recipients. KOTRY, Korean Organ Transplantation Registry.
death was infection, followed by cardiovascular disease and malignancy. The overall 1-year graft survival rate was 97.1% for all recipients (98.4% in the LDKT group and 94.9% in the DDKT group), and the 3- and 5-year graft survival rates were 94.3% and 90.5% for all recipients (96.2% and 93.2% in the LDKT group and 91.3% and 86.1% in the DDKT group), respectively (Fig. 2C, D). No antimetabolite drugs used at discharge, a higher serum creatinine concentration at discharge, and episodes of acute T-cell-mediated or antibody-mediated rejection were significantly associated with graft loss after kidney transplantation upon multivariate Cox regression analysis (Table 3). The 1-year death-censored graft survival rate was 98.5% for all recipients (99.0% in the LDKT group and 97.5% in the DDKT group), and the 3- and 5-year death-censored graft survival rates were 96.5% and 93.6% for all recipients (97.1% and 94.9% in the LDKT group and 95.5% and 91.4% in the DDKT group), respectively.

During a mean follow-up period of 3.8 years, biopsyproven acute rejection episodes were confirmed after kidney transplantation in 17.0% of all recipients (16.1% in the LDKT group and 18.4% in the DDKT group) (Fig. 3A), of which 57 (0.9%) led to graft failures. Upon multivariate Cox regression analysis, younger recipient age, older donor age, HLA-incompatible transplantation, and a higher number of HLA mismatches were significantly associated with rejection after transplantation (Table 4). Cardiac events occurred after transplantation in 4.3% of all recipients (3.2% in the LDKT group and 6.2% in the DDKT group) (Fig. 3B), and NODAT developed in 18.6% of all recipients (19.0% in the LDKT group and 18.1% in the DDKT group) (Fig. 3C). Upon multivariate Cox regression analysis, a history of previous transplantation, diabetes, and a history of cardiovascular disease were significantly associated with cardiac events after transplantation (Table 5), and recipient age and body mass index were significantly associated with NODAT. Malignant tumors were detected after transplantation in 3.8% of all recipients (4.0% in the LDKT group and 3.5% in the DDKT group) (Fig. 3D). A history of tumors and the use of mechanistic target of rapamycin (mTOR) inhibitors, such as sirolimus and everolimus, were significantly associated with malignancy after kidney transplantation upon multivariate Cox regression analysis. The types of malignant tumor and cardiac events are summarized in Supplementary Table 2 (available online); the most common type of malignant tumor was thyroid cancer, followed by kidney cancer, breast cancer, and gastrointestinal cancer. Infection episodes requiring hospitalization were most frequent in the first 6 months after transplantation, and bacterial infection was the most common type of infection, followed by viral infection (Fig. 3E, F). Upon multivariate Cox regression analysis, older donor age, a higher recipient body mass index, ATG rather than basiliximab induction, and transplantation from a deceased donor rather than a living donor were significantly associated with viral infection after transplantation (Table 6), while female recipient sex, HLA- and ABO-incompatible kidney transplantation, a history of cardiovascular disease, and nonuse of anti-

---

**Table 2. Risk factors for patient death after kidney transplantation by multivariate Cox regression**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Adjusted HR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recipient age</td>
<td>1.047 (1.017–1.078)</td>
<td>0.002*</td>
</tr>
<tr>
<td>History of cardiovascular disease, vs. no</td>
<td>2.525 (1.460–4.364)</td>
<td>0.001*</td>
</tr>
<tr>
<td>Bortezomib use, vs. no</td>
<td>11.559 (5.233–87.708)</td>
<td>0.02*</td>
</tr>
<tr>
<td>Tacrolimus, vs. cyclosporin</td>
<td>0.234 (0.089–0.617)</td>
<td>0.006*</td>
</tr>
<tr>
<td>Use of antimetabolite drug, vs. no</td>
<td>0.180 (0.090–0.360)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Serum creatinine at discharge</td>
<td>1.476 (1.247–1.747)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Living donor, vs. deceased donor</td>
<td>0.218 (0.098–0.483)</td>
<td>&lt;0.001*</td>
</tr>
</tbody>
</table>

CI, confidence interval; HR, hazard ratio.

Adjusted for recipient age and sex, donor age and sex, number of previous transplants, dialysis modality, desensitization, recipient body mass index, recipient smoking history, recipient history of diabetes, recipient history of hypertension, history of cardiovascular disease, history of tumor, usage of statins, number of human leukocyte antigen mismatches, antithymocyte globulin induction, bortezomib use, tacrolimus (vs. cyclosporine) at discharge, antimetabolite drug at discharge, mechanical target of rapamycin inhibitor at discharge, recipient serum creatinine concentration at discharge, donor type (living vs. deceased), donor history of diabetes, donor history of hypertension, donor serum creatinine concentration at baseline, acute T-cell–mediated rejection, and acute antibody-mediated rejection. Antimetabolite drugs include mycophenolate, mizoribine, and azathioprine.

*p < 0.05.
metabolite drugs were significantly associated with nonviral infection after transplantation (Table 7).

Summary of the registered kidney-transplant donors

The mean age of registered kidney-transplant donors was 47.3 ± 12.9 years, with the largest age group being those in their 50s. The mean ages of living and deceased donors were 46.7 ± 11.8 and 48.5 ± 14.7 years, respectively. The age range of living donors was 19 to 76 years, and that of deceased donors was 0 to 81 years (Fig. 4A, B). Among all registered kidney donors, 3,221 (52.6%) were male and
Table 3. Risk factors for graft loss after kidney transplantation by multivariate Cox regression

<table>
<thead>
<tr>
<th>Factor</th>
<th>Adjusted HR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recipient age</td>
<td>0.981 (0.972–0.991)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Donor age</td>
<td>1.015 (1.006–1.023)</td>
<td>0.001*</td>
</tr>
<tr>
<td>HLA-incompatibility, vs. no</td>
<td>1.599 (1.159–2.206)</td>
<td>0.004*</td>
</tr>
<tr>
<td>No. of HLA mismatches</td>
<td>1.154 (1.083–1.230)</td>
<td>&lt;0.001*</td>
</tr>
</tbody>
</table>

CI, confidence interval; HR, hazard ratio. Adjusted for recipient age and sex, donor age and sex, number of previous transplants, dialysis modality, desensitization, recipient body mass index, recipient smoking, recipient history of diabetes, recipient history of hypertension, history of cardiovascular disease, history of tumor, usage of statins, number of human leukocyte antigen mismatches, antithymocyte globulin induction, bortezomib use, tacrolimus (vs. cyclosporine) at discharge, antimetabolite drug at discharge, mechanistic target of rapamycin inhibitor at discharge, recipient serum creatinine concentration at discharge, donor type (living vs. deceased), donor history of diabetes, donor history of hypertension, donor serum creatinine concentration at baseline, acute T-cell-mediated rejection, and acute antibody-mediated rejection. Antimetabolite drugs include mycophenolate, mizoribine, and azathioprine. *p < 0.05.

Table 4. Risk factors for rejection after kidney transplantation by multivariate Cox regression

<table>
<thead>
<tr>
<th>Factor</th>
<th>Adjusted HR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recipient age</td>
<td>0.981 (0.972–0.991)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Donor age</td>
<td>1.015 (1.006–1.023)</td>
<td>0.001*</td>
</tr>
<tr>
<td>HLA-incompatibility, vs. no</td>
<td>1.599 (1.159–2.206)</td>
<td>0.004*</td>
</tr>
<tr>
<td>No. of HLA mismatches</td>
<td>1.154 (1.083–1.230)</td>
<td>&lt;0.001*</td>
</tr>
</tbody>
</table>

CI, confidence interval; HLA, human leukocyte antigen; HR, hazard ratio. Adjusted for recipient age and sex, donor age and sex, number of previous transplants, dialysis modality, desensitization, recipient body mass index, recipient smoking, recipient history of diabetes, recipient history of hypertension, history of cardiovascular disease, history of tumor, usage of statins, number of human leukocyte antigen mismatches, antithymocyte globulin induction, bortezomib use, tacrolimus (vs. cyclosporine) at discharge, antimetabolite drug at discharge, mechanistic target of rapamycin inhibitor at discharge, recipient serum creatinine concentration at discharge, donor type (living vs. deceased), donor history of diabetes, donor history of hypertension, donor serum creatinine concentration at baseline, acute T-cell-mediated rejection, and acute antibody-mediated rejection. Antimetabolite drugs include mycophenolate, mizoribine, and azathioprine. *p < 0.05.

Table 5. Risk factors for cardiac events after kidney transplantation by multivariate Cox regression

<table>
<thead>
<tr>
<th>Factor</th>
<th>Adjusted HR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>History of previous transplanta</td>
<td>8.642 (1.322–56.492)</td>
<td>0.02*</td>
</tr>
<tr>
<td>tion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>4.448 (1.009–19.609)</td>
<td>0.049*</td>
</tr>
<tr>
<td>History of cardiovascular disease</td>
<td>7.384 (1.619–33.665)</td>
<td>0.01*</td>
</tr>
</tbody>
</table>

CI, confidence interval; HR, hazard ratio. Adjusted for recipient age and sex, donor age and sex, number of previous transplants, dialysis modality, desensitization, recipient body mass index, recipient smoking, recipient history of diabetes, recipient history of hypertension, history of cardiovascular disease, history of tumor, usage of statins, number of human leukocyte antigen mismatches, antithymocyte globulin induction, bortezomib use, tacrolimus (vs. cyclosporine) at discharge, antimetabolite drug at discharge, mechanistic target of rapamycin inhibitor at discharge, recipient serum creatinine concentration at discharge, donor type (living vs. deceased), history of donor diabetes, history of donor hypertension, and donor serum creatinine concentration at baseline. *p < 0.05.

Table 6. Risk factors for viral infection after kidney transplantation by multivariate Cox regression

<table>
<thead>
<tr>
<th>Factor</th>
<th>Adjusted HR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Donor age</td>
<td>1.026 (1.018–1.034)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Body mass index</td>
<td>1.041 (1.013–1.069)</td>
<td>0.003*</td>
</tr>
<tr>
<td>ATG induction, vs. basiliximab</td>
<td>1.418 (1.145–1.757)</td>
<td>0.001*</td>
</tr>
<tr>
<td>Living donor, vs. deceased donor</td>
<td>0.703 (0.543–0.909)</td>
<td>0.007*</td>
</tr>
</tbody>
</table>

ATG, antithymocyte globulin; CI, confidence interval; HR, hazard ratio. Adjusted for recipient age and sex, donor age and sex, number of previous transplants, dialysis modality, desensitization, recipient body mass index, recipient smoking, recipient history of diabetes, recipient history of hypertension, history of cardiovascular disease, history of tumor, usage of statins, number of human leukocyte antigen mismatches, ATG induction, bortezomib use, tacrolimus (vs. cyclosporine) at discharge, antimetabolite drug at discharge, mechanistic target of rapamycin inhibitor at discharge, recipient serum creatinine concentration at discharge, donor type (living vs. deceased), history of donor diabetes, history of donor hypertension, and donor serum creatinine concentration at baseline. Antimetabolite drugs include mycophenolate, mizoribine, and azathioprine. *p < 0.05.

2,907 (47.4%) were female. The proportion of male donors was 43.4% in LDKTs and 69.4% in DDKTs. In LDKTs, donations from spouses were the most common (1,518 cases, 38.2%), followed by those from siblings (921 cases, 23.2%), offspring (672 cases, 16.9%), parents (629 cases, 15.8%), and unrelated donors (133 cases, 3.3%) (Fig. 4C). The total number of deceased donations was 2,156, of which donation after circulatory death occurred in 78 cases (3.6%), and 31.2% of donors belonged to the expanded-criteria donors (Fig. 4D). At 1 year after kidney donation, there were no mortalities among the 2,140 LDKT donors who were followed up with. The mean serum creatinine concentration of the living donors at baseline was 0.78 ± 0.62 mg/dL (range, 0.09–1.75 mg/dL), and that at 1 year after kidney donation was 1.09 ± 0.24 mg/dL (range, 0.25–1.88 mg/dL). The mean eGFRs at baseline and at 1 year after donation among living kidney donors were 97.6 ± 27.7 and 65.5 ± 13.8 mL/min/1.73 m², respectively.

Discussion

In this study, we introduced the basic design and current
status of the KOTRY, which consists of five organ-transplant cohorts. Furthermore, the baseline characteristics and outcomes of the kidney-transplant cohort in the KOTRY were summarized.

The number of patients with end-stage renal disease in Korea increased to more than 100,000 in 2019, doubling since 2010 [11]. Despite several risks, such as rejection, infection, cardiovascular disease, and malignancy, kidney transplantation remains a preeminent treatment for kidney failure, with the number of kidney-transplant recipients growing continuously [7,8,10,12]. The Korean Network for Organ Sharing (KONOS) was founded in 2000 to manage aspects of organ transplantation nationwide, such as patient registration, approval of living-donor organ transplantation, and allocation of deceased-donor organs to patients on a waiting list. However, the KONOS database does not contain comprehensive posttransplant data, including treatment outcomes and long-term prognoses. For this reason, the Korean Society for Transplantation and the KONOS launched the KOTRY under the sponsorship of the Korea Centers for Disease Control and Prevention Agency in April 2014. The KOTRY consists of five organ-transplant cohorts (kidney, liver, heart, lung, and pancreas), for which baseline and posttransplant data of organ donors and recipients are recorded [9,10]. Annual KOTRY reports have been published every year since 2015, and the input data have proven reliable to date.

Several other countries have similar nationwide, integrated databases for systematic management of the information related to organ transplants and donations. These systems include the Scientific Registry of Transplant Recipients in the United States [13], the Australia and New Zealand Dialysis and Transplant Registry and the Australia and New Zealand Organ Donor Registry [14], the Collaborative Transplant Study [15], the China Liver Transplant Registry [16], the Japan Renal Transplantation Registry [17], the Thai Transplant Registry [5], and others [18–21]. As most transplant centers that conduct kidney transplantation in Korea have been included in the KOTRY and as all large-volume transplant hospitals have joined the KOTRY, the KOTRY has expanded to contain more than half of all kidney-transplant patients registered in the KONOS each year. Therefore, the KOTRY kidney cohort can be considered a nationally representative cohort of Korean kidney transplants. However, cautious interpretation is required because data were collected only from patients who agreed to participate in the KOTRY study. Additionally, KOTRY had an inherent limitation of being a multicenter registry study in terms of inter-center and inter-clinician differences in clinical practice for kidney transplantation.

Despite the relatively short follow-up duration of our report, it identified the independent risk factors for mortality of Korean kidney-transplant patients, including older age, a history of cardiovascular disease, bortezomib use, cyclosporine rather than tacrolimus usage at discharge, no usage of antimetabolite drugs at discharge, a higher serum creatinine concentration at discharge, and DDKT rather than LDKT. Older recipient age, cardiovascular disease, lower graft function, and DDKT are well-known risk factors for patient death in kidney transplant in previous studies [22–24], and Gonzalez-Molina et al. [25] reported that treatment with mycophenolate mofetil and the use of tacrolimus instead of cyclosporine reduced the risk of patient death by 43%. In addition, although there are scarce data of the effect of bortezomib use on mortality in kidney transplantation, several previous studies have reported a higher incidence of adverse events, such as infectious disease, gastrointestinal and hematologic toxicity for bortezomib use in kidney transplantation [26–28]. Independent

### Table 7. Risk factors for nonviral infection after kidney transplantation by multivariate Cox regression

<table>
<thead>
<tr>
<th>Variable</th>
<th>Adjusted HR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female recipient, vs. male</td>
<td>1.814 (1.510–2.180)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cause of desensitization</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HLA incompatible, vs. no</td>
<td>1.479 (1.154–1.895)</td>
<td>0.002*</td>
</tr>
<tr>
<td>ABO incompatible, vs. no</td>
<td>1.330 (1.045–1.693)</td>
<td>0.02*</td>
</tr>
<tr>
<td>History of cardiovascular disease, vs. no</td>
<td>1.635 (1.312–2.036)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Mycophenolate + mizoribine + azathioprine, vs. no</td>
<td>0.689 (0.486–0.978)</td>
<td>0.04*</td>
</tr>
</tbody>
</table>

CI, confidence interval; HLA, human leukocyte antigen; HR, hazard ratio.

Adjusted for recipient age and sex, donor age and sex, number of previous transplants, dialysis modality, cause of desensitization (HLA incompatible/ABO incompatible vs. no), recipient body mass index, recipient smoking, recipient history of diabetes, recipient history of hypertension, history of cardiovascular disease, history of tumor, usage of statins, number of HLA mismatches, antithymocyte globulin induction, bortezomib use, tacrolimus (vs. cyclosporine) at discharge, antimetabolite drug at discharge, mechanistic target of rapamycin inhibitor at discharge, recipient serum creatinine concentration at discharge, donor type (living vs. deceased), history of donor diabetes, history of donor hypertension, and donor serum creatinine concentration at baseline. Antimetabolite drugs include mycophenolate, mizoribine, and azathioprine.

* p < 0.05.
risk factors for graft loss were as follows: no antimetabolite drugs used at discharge, a higher serum creatinine concentration at discharge, and episodes of acute T-cell-mediated or antibody-mediated rejection. These findings are in parallel with several other studies [23,29–31]. Moreover, age, HLA-incompatible transplantation, and a higher number of HLA mismatches were associated with rejection after transplantation, in agreement with results from previous reports [32–34]. Our study indicated that episodes of viral or nonviral infection requiring hospitalization were associated with older age, deceased rather than living donors, female sex, HLA-incompatible and ABO-incompatible kidney transplantation, and ATG rather than basiliximab induction, in accordance with previous studies [32,33,35–37]. Because a compromised capacity to repair injury in older kidneys could lead to accelerated immune response and acute rejection, the risks of rejection might be higher in older donor kidney transplantation [38]. Older donor age is also associated with the occurrence of delayed graft function and could be a risk factor for viral infection [39]. Interestingly, nonuse of antimetabolite drugs at discharge was associated with nonviral infection after transplantation, which may reflect a discontinuation of antimetabolite drugs because of infection episodes during hospitalization. In addition, the association of usage of mTOR inhibitors with malignancy after kidney transplantation may reflect the tendency for patients with a history of tumors or at high risk of malignancy to be prescribed such treatments [40].

Maintaining the KOTRY will enable the analysis of longer-term outcomes of patients and grafts as well as the identification of prognostic factors for transplantation. Furthermore, KOTRY data may contribute to the scientific progress of organ transplantation worldwide by collaboration with transplant cohort studies in other countries.
and participation in international comparison studies. In addition, it is expected that these data will provide scientific evidence not only for the development of national policies to improve the availability and efficiency of organ transplantation but also for the research and development of cutting-edge transplantation techniques. In terms of living kidney donors, data about complications and prognosis, including changes in renal function after donation, are being collected in the KOTRY. These data can provide objective information of the postdonation clinical course and assist in the development of future guidelines and decision-making for living-donor selection and management.

The KOTRY, as a systematic and nationwide transplant cohort, can serve as a valuable epidemiological database of Korean kidney transplants. The KOTRY kidney-transplant cohort will provide nationwide, real-world data that can be leveraged to improve kidney transplantation in Korea. We believe that the KOTRY kidney cohort will contribute to improvements in patient and graft survival, enhancement of the quality of life of transplant recipients, and the development of treatment guidelines tailored to the national situation.

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**Conflicts of interest**

All authors have no conflicts of interest to declare.

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Authors’ contributions

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Formal analysis: HJJ, TYK, JHR, JCJ, JY
Investigation: TYK, MKJ, DWC, SJNC, MSK, JHR, CA, JY
Methodology: MSK, JCJ, CA, JY
Writing–original draft: HJJ, JY
Writing–review & editing: All authors
All authors read and approved the final manuscript.

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References


Background: Hypernatremia is a common electrolyte disorder in children and elderly people and has high short-term mortality. However, no high-quality studies have examined the correction rate of hypernatremia and the amount of fluid required for correction. Therefore, in this study, we will compare the efficacy and safety of rapid intermittent bolus (RIB) and slow continuous infusion (SCI) of electrolyte-free solution in hypernatremia treatment.

Methods: This is a prospective, investigator-initiated, multicenter, open-label, randomized controlled study with two experimental groups. A total of 166 participants with severe hypernatremia will be enrolled and divided into two randomized groups; both the RIB and SCI groups will be managed with electrolyte-free water. We plan to infuse the same amount of fluid to both groups, for 1 hour in the RIB group and continuously in the SCI group. The primary outcome is a rapid decrease in serum sodium levels within 24 hours. The secondary outcomes will further compare the efficacy and safety of the two treatment protocols.

Conclusion: This is the first randomized controlled trial to evaluate the efficacy and safety of RIB correction compared with SCI in adult patients with severe hypernatremia.

Keywords: Brain edema, Hypernatremia, Hypotonic solutions, Therapeutics
Introduction

Hypernatremia is a serum sodium (sNa) level exceeding 145 mmol/L, which is common in hospitalized patients [1]. It occurs mainly in children, the elderly, and critically ill patients and is known to occur in 3% of hospitalized patients and 9% of critically ill patients [2,3]. Hypernatremia occurs due to 1) water loss (diabetes insipidus), 2) hypotonic fluid loss (osmotic diarrhea), or 3) hypertonic fluid gain (Na+-containing fluids) [4].

Sodium and its associated anions are major determinants of extracellular tonicity and osmotic pressure, and they influence the movement of water across cell membranes [5-7]. In other words, hypernatremia indicates hypertonic hyperosmolality and causes water outflow, resulting in cell dehydration [4]. Therefore, the symptoms and signs of hypernatremia mainly indicate dysfunction of the central nervous system, presenting with hyperventilation, muscle weakness, lack of consciousness (lethargy), and coma [1,8,9]. Hypernatremia has been associated with mortality rates of 40% to 60% and prolonged intensive care unit stays, although that high risk of mortality could also be attributed to the severity of illness and comorbidities [4].

Most physicians think that too rapid a correction of hypernatremia can cause cerebral edema, seizures, and irreversible brain damage [1,4,10-15]. The recommendation for correcting acute hypernatremia has been decreased to 1 mmol/L per hour, and chronic hypernatremia should be corrected at <0.5 mmol/L per hour (approximately 10 mmol/L/day) [16-18]. However, those correction rates were based on retrospective pediatric studies [11,19]. No evidence-based guidelines suggest an appropriate sodium correction rate for hypernatremia in adults. Moreover, previous studies in adults have suggested that rapid correction rates (>0.5 mmol/L per hour) are not associated with a high risk of hypernatremia-related mortality or neurologic damage [16]. In fact, several studies in adults have shown that an excessively slow correction rate causes higher mortality and vice versa [20,21].

According to the European and American guidelines for hypernatremia, an infusion of 10 mL/kg during 1 hour or 3 mL/kg per hour of electrolyte-free water is recommended to prevent the overcorrection of hypernatremia [22,23]. In a randomized controlled trial published previously, 10 mL/kg during 1 hour was applied as a method of re-lowering the dosage in cases of excessively rapid correction of hypernatremia [24,25]. However, the rapid intermittent bolus (RIB) administration of electrolyte-free water has never been applied in treating hypernatremia. We hypothesize that RIB administration of electrolyte-free water in hypernatremia can increase the incidence of a rapid decrease of sNa levels and thereby increase the survival time compared with the slow continuous infusion (SCI) method. Therefore, our purpose in this study will be to evaluate the efficacy and safety of RIB and SCI with electrolyte-free water in patients with hypernatremia. In addition, we aim to determine the best method for treating hypernatremia in adult patients.

Methods

Study design

This study is a prospective, investigator-initiated, multicenter, open-label, randomized controlled study with two experimental groups. We comply with the Standard Protocol Items: Recommendation for Interventional Trials (SPIRIT) 2013 Statement, which defines standard protocol items for clinical trials [26]. The algorithm for this study is shown in Fig. 1. The SPIRIT and study schedule are shown in Fig. 2 and 3. After registration, clinical follow-up will be conducted after 2 days of treatment with electrolyte-free water.

Study participants and measurements

This study will be performed in three general hospitals in Korea (Hallym University Dongtan Sacred Heart Hospital, Seoul National University Bundang Hospital, and SMG-SNU Boramae Medical Center). Patients older than 18 years with severe hypernatremia (glucose-corrected sNa of ≥155 mmol/L) [27] who visit the emergency room or are hospitalized will be screened for enrollment. The subsequent evaluation will be performed as follows: 1) completion of questionnaire about medical and drug history, including the use of diuretics, lithium, amphotericin, foscarnet, and demeclocycline; 2) physical examination of all body systems; 3) height and weight measurements; 4) blood pressure and pulse rate measurements; 5) verification of the cause of emergency room visit or admission; 6)
surgery status and surgical procedure; and 7) calculated Acute Physiology and Chronic Health Evaluation score. Participants who meet all the inclusion criteria do not need to be screened for exclusion criteria, and those who submit written consent will be included in this study (Table 1). The study will be conducted in accordance with the Declaration of Helsinki. All participants will provide signed, written, informed consent stating that their participation is voluntary and can be withdrawn at any time. This study was approved by the Institutional Review Boards (IRBs) of Hallym University Dongtan Sacred Heart Hospital (No. 2021-03-007-001), Seoul National University Bundang Hospital (No. B-2104-680-003), and SMG-SNU Boramae Medical Center (No. 30-2021-120). The trial protocol has been registered at https://www.clinicaltrials.gov (identifier No. NCT04949139; registered on 1 July 2021).

Acute and chronic hypernatremia is defined when the symptoms of hypernatremia have developed in less than and more than 48 hours, respectively. Hospital-acquired hypernatremia is defined as persistent hypernatremia for 48 hours as assessed by serologic tests during a hospital stay. The sNa levels will be measured every 6 hours for 2 days. The sNa will be measured using the following indi-

---

**Figure 1. Study algorithm.**

---

**Figure 2. Schedule of enrollment, interventions, and assessments according to the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guideline.**

U/S ratio, uNa + uK/SNa; GCS, Glasgow Coma Scale.

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### Table 1. Inclusion and exclusion criteria

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inpatients and ER patients aged &gt;18 years</td>
<td>Arterial hypotension requiring inotropes or vaspressors (systolic blood pressure &lt; 90 mmHg and mean arterial pressure &lt; 70 mmHg)</td>
</tr>
<tr>
<td></td>
<td>Anuria or bilateral urinary outlet obstruction</td>
</tr>
<tr>
<td></td>
<td>Uncontrolled diabetes mellitus (HbA1c &gt; 9%) or glucose of &gt;500 mg/dL at baseline or uncontrolled diabetic ketoacidosis or uncontrolled hyperosmolar hyperglycemic syndrome</td>
</tr>
<tr>
<td>Severe hypernatremia: glucose-corrected serum sodium ≥ 155 mmol/L</td>
<td>Decompenated LC: known LC with ascites or diuretics use or hepatic encephalopathy or varix</td>
</tr>
<tr>
<td></td>
<td>Patients who are pregnant or breastfeeding</td>
</tr>
<tr>
<td></td>
<td>If the following features occur within 30 days prior to randomization</td>
</tr>
<tr>
<td></td>
<td>History of cardiac surgery excluding PCA, acute myocardial infarction, sustained ventricular tachycardia, ventricular fibrillation, acute coronary syndrome, and admission for heart failure</td>
</tr>
<tr>
<td></td>
<td>Uncontrolled increase of intracranial pressure</td>
</tr>
</tbody>
</table>

ER, emergency room; HbA1c, glycosylated hemoglobin; LC, liver cirrhosis; PCA, percutaneous coronary angioplasty.

*Glucose-corrected serum (Na+) = measured (Na+) + 2.4 × (glucose [mg/dL] – 100 [mg/dL])/100 mg/dL.*

Figure 3. Study schedule.

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; CBC, complete blood count; Chol, cholesterol; Cr, creatinine; CRP, C-reactive protein; E’, electrolyte; ER, emergency room; GCS, Glasgow Coma Scale; Glu, glucose; HDL, high-density lipoprotein; LDL, low-density lipoprotein; Osm, osmolality; P, phosphorus; R, randomization; tCO₂, total CO₂; sNa, serum sodium; TG, triglyceride; U/A, urinalysis; UCr, urine creatinine; UE’, urine electrolyte; uK, urine potassium; uNa, urine Na; Uosm, urine osmolality.

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ER, emergency room; HbA1c, glycosylated hemoglobin; LC, liver cirrhosis; PCA, percutaneous coronary angioplasty.

*Glucose-corrected serum (Na+) = measured (Na+) + 2.4 × (glucose [mg/dL] – 100 [mg/dL])/100 mg/dL.*
rect ion-selective electrodes: Seoul University Bundang Hospital will use AU5800 (Beckman Coulter, Pasadena, CA, USA) and Dimension Vista 1500 (Siemens Healthineers, Erlangen, Germany); SMG-SNU Boramae Medical Center will use Modular DP (Roche Diagnostics, Indianapolis, IN, USA) and Unicel DxC 800 (Beckman Coulter); and Hallym University Dongtan Sacred Heart Hospital will use AU5800 (Beckman Coulter). Serum creatinine will be measured using the isotope dilution mass spectrometry-traceable method with a Toshiba TBA 200FR Analyzer (Toshiba, Tokyo, Japan). The estimated glomerular filtration rate will be calculated using the Chronic Kidney Disease Epidemiology Collaboration equation [28]. The Glasgow Coma Scale (GCS) will be assessed before treatment and after 24 and 48 hours of treatment. All types and volumes of fluid administered during those 48 hours will be monitored.

Randomization

An independent statistician generated the randomization sequence using a computer-generated list of random numbers, which is stratified by center with a 1:1 allocation using random block sizes of 2, 4, 6, and 8. A research coordinator will be responsible for screening emergency room patients and inpatients with severe hypernatremia and enrolling participants to each group based on the randomized sequence. The allocation sequence will be concealed from the researchers and study coordinators by using opaque, sequentially numbered envelopes. Eligible participants will be randomly allocated in a 1:1 manner to either the RIB or SCI protocol for electrolyte-free fluid in accordance with the predefined randomization list. Although the patients and their physicians will be aware of the interventions administered, the analysts will be blinded to the intervention.

Practical treatment guidelines for physicians according to the serum sodium level

Except in cases of compromised circulation, hypotonic solutions are an appropriate treatment for cases of severe hypernatremia [1,11]. Therefore, we designed our study protocol using electrolyte-free, 5% dextrose water. After randomization, the subjects will receive either RIB or SCI treatment for hypernatremia correction. According to previous studies, every 1-mmol/L decrease in the sNa level requires 3 mL/kg of electrolyte-free water in elderly female patients and 4 mL/kg of electrolyte-free water in young male patients [29]. Therefore, our goal is to decrease the sNa level by 2 mmol/L at each sample time (0, 3, 6, 12, 18, and 24 hours) to reach the maximum recommended decrease of 12 mmol/L/day. Based on that calculation, elderly female patients (≥65 years), others (male patients ≥ 65 years or female patients < 65 years), and young male patients (<65 years) in the RIB group will be infused for 1 hour with 6 mL/kg, 7 mL/kg, and 8 mL/kg of 5% dextrose water, respectively. Participants in the SCI group will be infused with 5% dextrose water at a minimum rate of 1.35 mL/kg per hour (elderly female patients) according to previous literature [30]. Others and young male patients will be infused at a rate of 1.57 mL/kg per hour and 1.8 mL/kg per hour in accordance with the intended sNa decrease rate set for the RIB group. Because hypernatremia commonly results from a net water loss [1], we will adjust the infusion volume of electrolyte-free water by calculating the U/S ratio ([urine Na + urine potassium]/sNa), a measure of urinary electrolyte-free water clearance [31].

Our treatment goals are to decrease the sNa level from the initial level by 6 to 11 mmol/L within the first 24 hours and by 12 to 23 mmol/L or to an absolute sNa level of ≤150 mmol/L within 48 hours. Overcorrection is defined as a decrease of ≥12 mmol/L within 24 hours or ≥24 mmol/L within 48 hours. When overcorrection develops, the sNa level should not be raised again, but active treatment should be discontinued. Intravenous or per oral furosemide will be used if volume overload is detected by any of the following symptoms and signs: dyspnea, peripheral edema, pulmonary edema, and pleural effusion. In addition to sodium correction, potassium and magnesium should be corrected. If the sNa level decreases by less than 6 mmol/L after 24 hours, 2 μg of intravenous desmopressin can be repeatedly administered according to the judgment of the physician. If maintenance fluid is administered at more than 3 L/day (120 mL/hour) and that is judged to affect sNa correction, the maintenance fluid can be limited to less than 3 L/day. The following cases are exceptions: (1) fluids and transfusion for the correction of hypotension are not counted as maintenance fluid; (2) if sNa is decreased by less than 6 mmol/L after 24 hours, maintenance fluid can be administered at more than 3 L/day; (3) in the case of ongoing nonrenal loss (e.g., nasoga-
tric tube drain, percutaneous catheter drainage, diarrhea, ileus), additional fluid can be administered according to the judgment of the physician regardless of the maintenance fluid. The treatment goal, overcorrection strategy, use of furosemide in volume overload and desmopressin in undercorrection of sNa, and cause-specific treatment of hypernatremia will be the same in both groups. For safety reasons, participants will be dropped from the study in the following cases: (1) volume depletion-weight loss of ≥1 kg per day, deterioration of consciousness, or arterial hypotension that requires inotropes (systolic blood pressure < 90 mmHg and mean arterial pressure < 70 mmHg); and (2) uncontrolled volume overload with worsening pulmonary edema despite diuretics.

**Rapid intermittent bolus group (Fig. 4A)**

**First 3 hours**
Subjects with severe hypernatremia will be divided into three groups by age and sex, and the correction rate for initial treatment will be set differently for each group: elderly female patients (≥65 years), others (male patients ≥ 65 years or female patients < 65 years), and young male patients (<65 years) will receive an intravenous infusion of 6 mL/kg, 7 mL/kg, and 8 mL/kg of 5% dextrose water, respectively, in 1 hour. Upon sampling 3 hours after initial treatment, repeated infusions at that rate are recommended until the sNa level has decreased by ≥6 mmol/L from the initial level.

**Between 3 and 24 hours**
When undercorrection (defined as a decrease of <6 mmol/L in the sNa level from the initial level at 6, 12, 18, or 24 hours) develops, the correction rate should be adjusted according to the U/S ratio at 0 hours. If the U/S ratio is <0.5, an infusion of 6/7/8 mL/kg of 5% dextrose water in 1 hour every 3 hours is recommended. If the U/S ratio is ≥0.5, the infusion of 5% dextrose water will also be adjusted according to the U/S ratio at 24 hours. If the U/S ratio at 24 hours is <0.5, a single infusion of 6/7/8 mL/kg of 5% dextrose water in 1 hour is recommended. When target correction (defined as a decrease of 12–23 mmol/L in the sNa levels from the initial level) develops, the infusion of 5% dextrose water should also be adjusted according to the U/S ratio at 24 hours. If the U/S ratio is ≥0.5, 5% dextrose water should be discontinued. If the decrease in sNa levels is ≥24 mmol/L or if the absolute sNa level is <150 mmol/L, 5% dextrose water should be discontinued.

**Slow continuous infusion group (Fig. 4B)**

**First 3 hours**
The subjects will be divided into three groups and corrected at different rates, similar to the RIB group. It is recommended that intravenous infusions of 5% dextrose water be provided at 1.35 mL/kg per hour, 1.57 mL/kg per hour, and 1.8 mL/kg per hour in elderly female patients (≥65 years), others (male patients, ≥65 years or female patients, <65 years), and young male patients (<65 years), respectively. Sampling should be done 3 hours after initial treatment, repeated infusions at that rate are recommended until the sNa level has decreased by ≥6 mmol/L from the initial level.

**Between 3 and 24 hours**
When undercorrection (defined as a decrease of <6 mmol/L in the sNa level from the initial level at 6, 12, 18, or 24 hours) develops, the correction rate should be adjusted according to the U/S ratio at 0 hours. If the U/S ratio is <0.5, a continuous infusion of 5% dextrose water at twice the previous rate (2.70/3.14/3.60 mL/kg per hour) is recommended. When overcorrection (defined as a decrease of ≥12 mmol/L in the sNa level) or an absolute sNa level of <150 mmol/L occurs, 5% dextrose water should be discontinued.

**Between 24 and 48 hours**
When undercorrection (defined as a decrease of <12 mmol/L in the sNa level from the initial level at 30, 36, 42, or 48 hours) occurs, the correction rate should be adjusted according to the U/S ratio at 24 hours. If the U/S ratio is <0.5, a single infusion of 6/7/8 mL/kg of 5% dextrose water in 1 hour is recommended. If the U/S ratio is ≥0.5, a single infusion of 6/7/8 mL/kg of 5% dextrose water in 1 hour is recommended. When target correction (defined as a decrease of 12–23 mmol/L in the sNa levels from the initial level) develops, the infusion of 5% dextrose water should also be adjusted according to the U/S ratio at 24 hours. If the U/S ratio is ≥0.5, 5% dextrose water should be discontinued. If the decrease in sNa levels is ≥24 mmol/L or if the absolute sNa level is <150 mmol/L, 5% dextrose water should be discontinued.
**Figure 4. Treatment.** (A) Rapid intermittent bolus with 5% dextrose water in patients with severe hypernatremia. (B) Slow continuous infusion with 5% dextrose water in patients with severe hypernatremia.

sNa, serum sodium; q, quaque; uK, urine potassium; uNa, urine Na; U/S ratio, uNa + uK/sNa; ↓, decrease.

\[
\text{U/S ratio} = \frac{(uNa + uK)}{sNa}
\]
mended. If the U/S ratio is \( \geq 0.5 \), a continuous infusion of 5% dextrose water at the previous rate (1.35/1.57/1.80 mL/kg per hour) is recommended. When target correction (defined as a decrease of 6–11 mmol/L in the sNa level from the initial level) develops, it will be also corrected according to the U/S ratio at 0 hours. If the U/S ratio is <0.5, continuous infusion of 5% dextrose water at the previous rate (1.35/1.57/1.80 mL/kg per hour) is recommended. If the U/S ratio is \( \geq 0.5 \), 5% dextrose water should be discontinued. When overcorrection (defined as a decrease of \( \geq 12 \) mmol/L in the sNa level) or an absolute sNa level of <150 mmol/L occurs, 5% dextrose water should be discontinued.

**Between 24 and 48 hours**

When undercorrection (defined as a decrease of <12 mmol/L in the sNa level from the initial level at 30, 36, 42, or 48 hours) occurs, the correction rate should be adjusted according to the U/S ratio at 24 hours. If the U/S ratio is <0.5, continuous infusion of 5% dextrose water at twice the previous rate (2.70/3.14/3.60 mL/kg per hour) is recommended. If the U/S ratio is \( \geq 0.5 \), continuous infusion of 5% dextrose water at the previous rate (1.35/1.57/1.80 mL/kg per hour) is recommended. When target correction (defined as a decrease of 6–11 mmol/L in the sNa level from the initial level) develops, it will be also corrected according to the U/S ratio at 24 hours. If the U/S ratio is <0.5, continuous infusion of 5% dextrose water at the previous rate (1.35/1.57/1.80 mL/kg per hour) is recommended. If the U/S ratio is \( \geq 0.5 \), 5% dextrose water should be discontinued. When overcorrection (defined as a decrease of \( \geq 24 \) mmol/L in the sNa level or an absolute sNa level of <150 mmol/L) occurs, 5% dextrose water should be discontinued.

**Outcome measures**

The primary outcome is the incidence of a rapid decrease in the sNa level and aspects of efficacy, as follows: decrease in sNa of \( \geq 6 \) mmol/L or an absolute sNa level of \( \leq 150 \) mmol/L within the first 24 hours. The secondary outcomes are the 28-day survival rate after treatment for hypernatremia with 5% dextrose water, difference in sNa levels 6 hours after the initial test, volume of 5% dextrose water infused during 48 hours, and incidence of the target correction rate (defined as a decrease of \( \geq 12 \) mmol/L in the sNa level or an absolute sNa level of \( \leq 150 \) mmol/L within 48 hours). Additional outcomes are the target correction rate, incidence of undercorrection, length of hospital stay, incidence and number of desmopressin uses, incidence of overcorrection, incidence of cerebral edema documented via brain computed tomography (CT) at 48 hours, incidence of osmotic demyelinating syndrome via International Classification of Diseases 10 code or brain magnetic resonance imaging, and GCS at baseline (pretreatment), 24 hours, and 48 hours.

**Clinical and laboratory evaluations**

The physical examination, laboratory evaluations, and medication review will be performed before commencement of the study. The laboratory evaluations will comprise a complete blood count; tests for serum electrolytes, calcium, phosphate, blood urea nitrogen, creatinine, glucose, total CO\(_2\), total protein, albumin, uric acid, and C-reactive protein; liver function testing (aspartate transaminase, alanine aminotransferase, alkaline phosphatase, and total bilirubin); lipid profile; serum osmolality; and urine analysis, urine electrolytes, urine creatinine, and urine osmolality. The sNa level will be measured every 6 hours (after being measured at 0, 3, and 6 hours) for 2 days. Levels of urine sodium and potassium will be measured at 0 and 24 hours. The GCS score will be estimated at 0, 24, and 48 hours. Brain CT will be conducted at 48 hours in patients who develop overcorrection.

**Safety issues**

All serious side effects will be reported to the investigator and the ethics committee. In this study protocol, safety information about each patient should be collected within 48 hours after treatment. Safety concerns in the treatment of hypernatremia are caused by undercorrection and overcorrection, and we will check for those at every sample time point. Interventions will be performed as follows: if the sNa level is decreased by more than 12 mmol/L within 24 hours or more than 24 mmol/L within 48 hours at any sample time point, the ongoing active treatment will be discontinued, but the sNa level should not be raised. If the decrease in sNa levels is <6 mmol/L after 24 hours, 2 \( \mu \)g of intravenous desmopressin can be administered according to the judgment of the physician. When signs and symptoms of
volume overload are observed, such as dyspnea, peripheral edema, pulmonary edema, or pleural effusion, intravenous or oral administration of furosemide will be considered.

Sample size calculation

In the literature, a low hypernatremia correction rate in the first 24-hours (<0.25 mmol/L per hour or 6 mmol/L per day) can be significant predictors of 30-day mortality [20]. Therefore, as a surrogate marker for 30-day survival, a rapid decrease in the sNa level (≥0.25 mmol/L per hour or 6 mmol/L per day) was chosen as the primary study outcome. A previous study reported that 33% of hypernatremic patients being treated with the SCI method of electrolyte-free solution achieved a rapid decrease in their sNa levels within the first 24 hours [20]. However, no information is available on the incidence of a rapid decrease in sNa levels with RIB treatment. We expect the frequency of rapid decrease of sNa to increase by 1.8 times in the RIB group compared with the SCI group. Therefore, we expect the proportions of participants who achieve a rapid decrease in their sNa levels to be 55% and 30% in the RIB and SCI groups, respectively. We calculated the required sample size for an estimated dropout rate of 15%, a two-sided level of significance of $\alpha = 0.05$, a power of 80%, and one interim analysis and thus determined that 83 participants will be needed in each group to find significant differences between the two groups using the chi-square test. Therefore, a total of 166 participants will be enrolled. We considered one interim analysis at the time when half of the subjects have completed the study. The O’Brien-Fleming alpha spending function will be used to test the primary outcomes in the first interim analysis and final analysis.

Statistical analyses

The analysis of outcomes will be conducted on both the intention-to-treat (ITT) and per-protocol (PP) bases because a considerable dropout rate can be expected due to our sophisticated electrolyte-free water infusion protocol. The ITT population is defined as all participants for whom the primary endpoint will be available, and those participants will be analyzed in accordance with the groups to which they were randomly allocated, regardless of deviation from the protocol. In the ITT analysis, all outcomes will be counted until the infusion protocol is well-adhered to. The PP analysis will include only the participants who complete the study without major protocol deviations to evaluate the primary, secondary, and additional outcomes. Continuous variables will be expressed as means and standard deviations, and categorical variables will be expressed as frequencies or percentages for baseline characteristics and laboratory findings.

The incidence of a rapid decrease in sNa levels within 24 hours, 28-day survival, target correction rate, a decrease of ≥12 mmol/L in sNa level or an absolute sNa level of ≤150 mmol/L within 48 hours, additional treatment, use of desmopressin, cerebral edema, osmotic demyelination syndrome, and in-hospital mortality will be compared between the two groups using the chi-square test, Fisher exact test, odds ratios with logistic regression, and absolute risk with a Poisson regression. The differences in sNa levels at 3 hours, volume of 5% dextrose water in 48 hours, number of additional treatments, hospital stay, and number of desmopressin uses will be analyzed between the two groups using Student t test, Mann-Whitney U test, mean differences with linear regression, and a mixed model to analyze the effects of repeated sNa levels and the overall change in sNa level from baseline with fixed effects for time, group, and interactions between time and group. The marginal effect of sNa and overall change in sNa from baseline by group will be plotted. In the interim analysis, if the critical value is 2.96 ($p = 0.003$), early termination will be performed; if not, participant recruitment will be continued. A value of $p < 0.05$ will be considered statistically significant. Statistical analyses will be performed using IBM SPSS version 27.0 (IBM Corp., Armonk, NY, USA), STATA version 14.0 (StataCorp LP, College Station, TX, USA), and R version 3.5.3 (R Foundation for Statistical Computing, Vienna, Austria; https://www.r-project.org).

Data and safety monitoring

The paper data sheets and signed consents will be stored in locked cabinets, and electronic databases will be stored on secure servers with password protection. Unexpected side effects during treatment will be reported to the IRBs according to the procedures of the three participating hospitals. All revised procedures will be submitted to the IRBs of all three hospitals and ClinicalTrials.gov. The data will
Discussion

Recently, several cohort studies have suggested that rapid correction of hypernatremia did not increase the mortality rate or even that slow correction could increase mortality [20,21,32]. Nonetheless, the current recommendation is to reduce sNa by <0.5 mmol/L per hour (<10 mmol/L per day) to prevent cerebral edema, seizure, and brain damage during the treatment of hypernatremia [1,13–15]. In acute hypernatremia, the correction rate can be increased to 1 mmol/L of sNa per hour [33]. However, those correction rates reflect studies in children [11,19]. No previous, large-scale, prospective, randomized controlled studies have examined the correction rate for hypernatremia in adults. This is thus the first clinical trial to provide qualified evidence about administering electrolyte-free water to patients with severe hypernatremia. Additionally, our results will allow a protocolized approach to the management of hypernatremia to be established.

In acute hypernatremia, which develops within 48 hours, cerebral edema does not occur even upon immediate correction because the accumulated electrolytes can rapidly move out of brain cells [33,34]. In hypernatremia of >48 hours or unknown duration, rapid correction can lead to brain edema because several days are required to remove osmolytes from brain cells [34,35]. Therefore, expert opinion suggests a decrease rate of <0.5 mmol/L per hour, with an absolute change of <10 mmol/L per day to prevent brain damage [1,13–15]. However, some studies have indicated that rapid correction of hypernatremia was not associated with increasing disease-related mortality or cerebral edema and that excessively slow rates of correction were associated with increased short-term mortality [16,20,21,32]. Chauhan et al. [16] found that rapid correction of >0.5 mmol/L per hour or >12 mmol/L was not associated with increased mortality or cerebral edema and that mortality rates were consistently low with varying correction rates (>8, >10, and 12 mmol/L) at 24 hours. Bataille et al. [21] calculated the correction rate of hypernatremia as the mean rate, which implies that the difference in sNa between baseline and the last known hypernatremia was divided by the total time. Their correction rates were −0.1 ± 0.15 mmol/L per hour and −0.2 ± 0.22 mmol/L per hour, and the proportions of no improvement in hypernatremia were 44% and 21% in patients who died and survived, respectively. In children, the size of the cerebrum increases rapidly until age 6 years, and it continues to grow until age 15 years; therefore, the ratio of brain volume to cranial vault size reaches its maximum at 6 years. However, the brain size of adults gradually decreases after age 45 years and is the lowest at age 86 years [36–38]. Therefore, we inferred that rapid correction in adults might be tolerable [16].

However, the previous retrospective studies on hypernatremia had different definitions for rapid correction of sNa [16,20,21]. The correction rate calculated by dividing the difference in sNa levels by time [16,21] might also have differed from the actual correction rate or been inaccurate. Furthermore, it is difficult to determine in those studies whether electrolyte-free water was given by the RIB or SCI method, and it is also unclear whether hypernatremia was improved by administering electrolyte-free water or hypotonic solution or by treatment of the underlying disease.

In a randomized controlled trial (SALSA I) that we published previously [24,25,39], 10 mL/kg of electrolyte-free water was applied in 1 hour as a method of re-lowering therapy in excessively rapid hyponatremia correction, which complied with the European guidelines [23]. Because only one patient experienced pulmonary edema and pleural effusion during the study period, we hold that safety concerns about volume overload are negligible. Therefore, we adopted our previous RIB method in developing this infusion protocol. According to the literature, every 1 mmol/L decrease in sNa level requires 3 mL/kg of electrolyte-free water in elderly female patients and 4 mL/kg of electrolyte-free water in young male patients. We estimated a decrease of 2 mmol/L in sNa levels at every sample time by using 6/7/8 mL/kg infusions of electrolyte-free water, for a maximum sNa decrease of 12 mmol/L/day. The total amount of electrolyte-free water to be infused in the RIB group was converted to a continuous infusion rate for 24 hours for the SCI group. Therefore, we expect that the amount of electrolyte-free water infused into the patients in both groups will be similar. Because hypernatremia is commonly caused by a net water loss [1], we adjust the infusion volume of electrolyte-free water by calculating the U/S ratio, an indicator that conveniently reflects ongoing urinary clearance of electrolyte-free water [31]. In addition,
we plan to perform an interim analysis as a safety measure because the RIB method is a novel protocol.

The primary outcome of this study is the incidence of a rapid decrease in sNa levels. Prolonged hypernatremia can cause death by inducing brain damage, decreasing cardiac contractility, increasing peripheral insulin resistance, and impairing hepatic gluconeogenesis [40]. Therefore, the incidence of rapid correction is expected to be a good surrogate outcome of efficacy and safety.

This study has some limitations. First, differences in the expertise of doctors and nurses could cause protocol violations during the early period because of unfamiliarity with the protocol. Therefore, the protocol is designed in a simple way to prevent nonadherence among physicians. Second, mild hypernatremia is not covered by this study, which enrolls only patients whose absolute sNa levels are >155 mmol/L. However, the higher the sNa levels, the higher the incidence of neurologic symptoms due to high cell shrinkage. Therefore, targeting severe hypernatremia can maximize the efficacy of our rapid correction protocol. Third, this study uses only electrolyte-free water as the correction fluid, but various clinical situations can require a hypotonic solution (0.45% sodium chloride), which warrants further research.

In conclusion, the SALSA II study is the first prospective, multicenter, randomized, open-label, controlled clinical trial compared with SCI in adult patients with severe hypernatremia.

**Conflicts of interest**

All authors have no conflicts of interest to declare.

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**Authors’ contributions**

Conceptualization: SK, SHB
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Methodology: JYR, SY
Formal analysis: JL, JH
Visualization: KPK
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Important information
Articles should be prepared in the simplest form and submitted in the format of Microsoft Word (*.doc or *.docx). Manuscripts must be typed in English and double-spaced. All pages must be numbered consecutively starting from the title page. You may use automatic page numbering, but do NOT use other kinds of automatic formatting such as footnotes. Place text, references, tables and legends in one file with each table on a new page.

Please ensure that the following submission documents are also included, where applicable:
(1) A cover letter. It must include your name, address, telephone and fax numbers, e-mail address, and state that all authors have contributed to the paper and have never submitted the manuscript, in whole or in part, to other journals.
(2) A conflict of interest disclosure statement (see relevant section 4.2 below).
(3) All studies involving human subjects, human data or any material derived from human must be approved by the relevant review or ethics committee. Articles must include a statement on ethics approval, the name of the relevant committee that approved the study and the committee’s approval number. Manuscripts may be rejected at any time if the authors of the research fail to provide the approval number validated by the relevant committee (see relevant section 4.1 below).
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(5) Articles where human subjects can be identified in descriptions, photographs or pedigrees must be accompanied by a signed statement of informed consent to publish (in print and online) the descriptions, photographs and pedigrees from each subject who can be identified.
(6) The terms sex (when reporting biological factors) and gender (identity, psychosocial or cultural factors) should be correctly used. The sex and/or gender of study participants, the sex of animals or cells should be reported, and the methods used to determine sex and gender should be described. If the study was done involving an exclusive population, for example in only one sex, authors should justify why, except in obvious cases (e.g., ovarian cancer).
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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.
(10) All authors must register and update information about academic degree, affiliation, and position when they register or submit a journal online at https://www.editorialmanager.com/krcp.
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2. Types of Articles

2.1. Original Articles
These are expected to present major advances and important...
new research results. Section headings should include Abstract, Introduction, Methods, Results, Discussion, Conflicts of interest, Acknowledgments (if applicable), and References. The text should be limited to 4,000 words (excluding tables, figures and references) and 40 references.

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

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Articles in this section should provide insightful analysis and commentary about any important topic in medicine, research, ethics, or health policy. They may also address consensus statements, guidelines, statements from task forces, or recommendations. Most reviews are solicited by the editors, but unsolicited submissions may also be considered for publication. The text should be limited to 5,000 words (excluding tables, figures and references) and 50 references.

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

2.5. Editorials
These are manuscripts that are related to materials within the current issue; they raise challenging questions or explore controversies. The editor solicits such opinion pieces. The order of the submitted manuscript includes title page, integrated discussion, conflict of interest, acknowledgments (if applicable) and references. The text should be limited to 1,500 words and 10 references. A maximum of 2 figures or tables may be included.

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

3. Manuscript Preparation

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

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

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

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

3.5. References

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

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Entire Book:

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Website:

3.6. Tables

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

3.7. Figures

Figure legends should be submitted for all figures. They should be brief and specific, and placed on a separate sheet after the References section. Figures are numbered consecutively using Arabic numerals in the order of their citation in the text. Figures should be uploaded as separate files, not embedded in the manuscript file. Figures that are line drawing or photographs must be submitted separately in high-resolution EPS or TIF format (or alternatively in high-resolution JPEG format). Only high-resolution figure files (preferably 300 dpi for color figures and 1,200 dpi for line art and graphs) should be submitted. The files are to be named according to the figure number and format (e.g., Fig1.tif). Figures that are reproduced from other published sources require written permission from the authors and copyright holders.

3.8. Supplementary Digital Contents

Authors can submit supplementary digital contents to supplement the information provided in the print version of the manuscript. Supplementary materials will be published online-only. When uploading supplementary files through the online system, please use the “supplemental” file designation. Supplementary materials must be cited consecutively in the main body of the submitted manuscript and include the type of material submitted (e.g., “Supplementary Table 1”; “Supplementary Fig. 1”).
4. Ethical Considerations

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

4.2. Conflicts of Interest
The corresponding author must inform the editor of any potential conflicts of interest that could influence the authors’ interpretation of the data. Examples of potential conflicts of interest include financial support from or connections to pharmaceutical companies, political pressure from interest groups, and academically related issues. Conflict of interest statements will be published at the end of the text of the article, before the References section. Please consult the Committee on Publishing Ethics guidelines (http://www.publicationethics.org/) on conflict of interest. All sources of financial support for the study should be stated in Acknowledgments (see relevant section 3.4 above).

4.3. Authorship
Authorship credit should be based on 1) conception or design, or analysis and interpretation of data; 2) drafting the article or revising it; 3) providing intellectual content of critical importance to the work described; and 4) final approval of the version to be published. Authors should meet above four conditions. The title page should include a list of each author’s role for the submitted paper.

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Submitted manuscripts are considered with the understanding that they have not been published previously in print or electronic format (except in abstract or poster form) and are not under consideration in totality or in part by another publication or electronic medium. Authors must state that neither the manuscript nor any significant part of it is under consideration for publication elsewhere or has appeared elsewhere in a manner that could be construed as a prior or duplicate publication of the same, or very similar, work. When malpractices are found in an article submitted to KRCP, we will follow the flowchart by the Committee on Publication Ethics (COPE, https://publicationethics.org/resources/flowcharts) for settlement of any misconduct. Although the editors and referees make every effort to ensure the validity of published manuscripts, the final responsibility rests with the authors, not with KRCP, its editors, or the Korean Society of Nephrology.

5. Review Process
All submissions are sent to peer reviewers. Authors will usually be notified within 4 weeks by e-mail of whether the submitted article is accepted for publication, rejected, or subject to revision before publication. Revised manuscripts must be submitted online by the corresponding author. Failure to resubmit the revised manuscript within 3 months of the editorial decision is regarded as a withdrawal.

6. Visual Abstract Guidelines
Visual Abstracts are brief graphical summaries of Original Articles published online. They serve to summarize the work for readers and may be used in social media postings. Authors do not need to include a Visual Abstract with their initial submission but will be required to submit one at the revision stage for all original research articles. The submitted visual abstract will be reviewed along with the revised manuscript. If the submission of visual abstract is delayed, there is inevitable delay in publication. Please submit it within the specified time.

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Select one of the visual abstract templates provided (https://www.krcp-ksn.org/file/KRCP_Visual_Abstracts_v1.0.pptx). There are multiple layouts to accommodate author preferences as well as graphical constraints. The visual abstract should
include a title, methods, outcome and a concluding sentence. Please fill in the template as it’s laid out and do not alter the basic components of the template.

Keep in mind the following:
• Avoid excessive detail and clutter and keep text to a minimum.
• Any descriptive text should be at least 12 pt font size.
• The visual abstract should be saved as an editable Power Point file as staff will add the article DOI and may edit the text for clarity.

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It is critical that you only use images for which you have permissions or rights. To avoid any potential problems, either use the copyright filter during an image search online or subscribe to an icon image bank. There are many image banks on the internet, which are free to use. The images used for visual abstract is recommended only open source, and the author is responsible for copyright issues of visual abstract. Researchers who frequently prepare visual abstracts may benefit from purchasing a subscription to access higher quality icons (e.g. Shutterstock, Getty Images, iStock, etc.).

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• Select bold, solid color icons
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• Graphics should be 440 pixels wide by 350-365 pixels tall.

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12. After acceptance

12.1. Article-in-press publication

After the manuscript is finally accepted, it will be published online in PDF format through the English editing, author proofing and final editorial correction process. The corresponding author should promptly and appropriately respond to this editing process. Online publication will take place within several weeks depending on the proof process. A Digital Object Identifier (DOI) is allocated, making it fully citable and searchable by title, author name(s), and the full text. Since our journal is officially published every 3 months interval, the volume, issue, and page will be finally allocated sequentially according to the order of accepted articles.

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OPTIMIZE TROUGH LEVEL
START LIFE–LONG JOURNEY
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.

- Biweekly dose
  - The usual dose of NESP in adult patients is 60-120 μg administered as a single intravenous injection once every two weeks. The dose should be adjusted in one of the degrees of anemia symptoms and the patient’s age, and should not exceed 200 μg as a single injection. The target of anemia correction is around 11 g/l of hemoglobin levels.

- Monthly dose
  - The usual dose of NESP in adult patients is 60-120 μg administered as a single intravenous injection once every two weeks. The dose should be adjusted in one of the degrees of anemia symptoms and the patient’s age, and should not exceed 200 μg as a single injection. The target of anemia correction is around 11 g/l of hemoglobin levels.

- Hemodialysis patients
  - The usual dose of NESP in adult patients is 30-120 μg administered as a single intravenous injection once every two weeks. The dose should be adjusted according to the degree of anemia symptoms and the patient’s age, and should not exceed 200 μg as a single injection. The target of anemia correction is around 11 g/l of hemoglobin levels.

- Hemodialysis patients with chronic kidney disease not on dialysis
  - The usual dose of NESP in adult patients is 30-120 μg administered as a single intravenous injection once every two weeks. The dose should be adjusted in one of the degrees of anemia symptoms and the patient’s age, and should not exceed 200 μg as a single injection. The target of anemia correction is around 11 g/l of hemoglobin levels.

- Patients who have been treated with an erythropoietin preparation
  - The dosage of NESP should be determined on the basis of the dose of the erythropoietin preparation that has been used. See the table (package insert).

- Patients who have been treated with an erythropoietin preparation once weekly or once every other week
  - The dosage of NESP should be determined on the basis of the dose of the erythropoietin preparation that has been used. See the table (package insert).

PRECAUTIONS
- See the package insert.

MANUFACTURED BY:
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포시가®로 환자를 지켜주세요

SGLT2i 중 최초 및 유일하게 만성 콩팥병 적응증 획득

당뇨 유무와 관계없이 만성 콩팥병 환자에서 신기능 악화, ESKD, 신장 또는 심혈관 질환으로 인한 사망위험 39% 감소

제 2형 당뇨환자에
알부민뇨 개선 및 악화감소

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이 약 1정 (약 260mg) 중
유효성분: 다파글리플로진프로판디올수화물 (별규) 12.3mg (다파글리플로진으로서 10mg)
첨가제: 무수유당(동물유래성분, 기원동물: 소, 사용부위: 우유), 미결정셀룰로오스, 스테아르산마그네슘, 오파드라이II노란색(85F92582), 이산화규소, 크로스포비돈

【효능·효과】
1. 제2형 당뇨병: 이 약은 제2형 당뇨병 환자의 혈당 조절을 향상시키기 위해 식사요법 및 운동요법의 보조제로 투여한다.
- 단독요법 - 병용요법

2. 만성 심부전: 좌심실 수축기능이 저하된 만성 심부전(NYHA class II-IV) 환자에서 심혈관 질환으로 인한 사망 및 심부전으로 인한 입원 위험성 감소

3. 만성신장병: 만성 신장병 환자에서 추정 사구체 여과율 (eGFR)의 지속적인 감소, 말기 신장병에 도달, 심혈관 질환으로 인한 사망 및 신장 관련 사망 위험성 감소

【용법·용량】
제2형 당뇨병
단독 요법 및 추가 병용 요법
이 약의 권장 용량은 단독 요법 및 인슐린 등 다른 혈당 강하제와의 추가 병용 요법에 대하여 1일 1회 10mg이다. 이 약을 인슐린 또는 설포닐우레아와 같은 인슐린 분비 촉진제와 병용하여 사용하는 경우, 저혈당의 위험을 줄이기 위해 더 낮은 용량의 인슐린 또는 인슐린 분비 촉진제를 고려할 수 있다.

초기 병용요법
이전 당뇨병 약물치료를 받은 경험이 없는 경우 메트포르민과 병용투여 시, 이 약의 초기 권장용량은 1일 1회 5mg 또는 1일 1회 10mg이다.

만성 심부전 및 만성신장병
이 약의 권장용량은 1일 1회 10 mg이다.

특수 집단
신장애 - eGFR 45mL/min/1.73m2 미만: 혈당조절 개선 목적으로 이 약을 투여하는 것은 권장되지 않는다.
- eGFR 25mL/min/1.73m2 미만: 만성 심부전 및 만성 신장병 환자에게 이 약의 투여를 시작하는 것은 권장되지 않는다.
- 투석 중인 환자: 이 약을 투여하지 않는다.

간장애
경증 또는 중등증의 간장애 환자에 대한 용량 조절은 필요하지 않다. 중증의 간장애 환자에 대하여, 시작 용량으로 5 mg이 권장된다. 내약성이 양호한 경우, 이 용량은 10mg으로 증가시킬 수 있다.

고령자 (≥ 65세)
연령에 근거한 용량 조절은 권장되지 않는다.

소아
만 18세 미만의 소아에 대한 다파글리플로진의 유효성과 안전성은 확립되지 않았다. 관련 자료가 없다.

【사용상 주의사항】
1. 다음 환자에는 투여하지 말 것
1) 이 약의 주성분 또는 첨가제에 대한 과민반응 병력이 있는 환자
2) 제1형 당뇨병 또는 당뇨병성 케톤산증 환자
3) 이 약은 유당 무수물을 함유한다. 갈락토오스 불내성(galactose intolerance), Lapp 유당 분해효소 결핍증(Lapp lactase deficiency) 또는 포도당-갈락토오스 흡수장애(glucose-galactose malabsorption) 등의 유전적인 문제 있는 환자에게는 투여하면 안된다.
4) 투석 중인 환자

2. 다음 환자에는 신중히 투여할 것
1) 체액량 감소 및 신기능 장애가 있는 환자에서의 투여
이 약은 증상성 저혈압이나 크레아티닌의 급격하고 일시적인 changes로 나타날 수 있는 혈관 내 혈량 저하를 유발할 수 있다. 외국의 시판후 조사에서 이 약을 포함한 SGLT-2 저해제를 투여한 환자에서 급성 신장손상이 보고되었으며, 일부는 입원과 투석을 필요로 하였다. 신기능 장애(eGFR 60mL/min/1.73m2 미만), 고령자, 루프계 이뇨제 등을 사용하고 있는 환자에서 혈량 저하 또는 저혈압 위험이 증가할 수 있다. 이러한 특징을 가진 환자에 대해 이 약의 투여를 시작하기 전 체액량 상태 및 신장 기능에 대한 평가가 필요하며, 투여를 시작한 후 저혈압 증상 및 징후와 신기능에 대해 모니터링 한다.

혈당 조절에 대한 이 약의 유효성은 신장 기능에 따라 다르다. 중등도의 신장애가 있는 환자에서 혈당 조절 유효성이 감소하며 eGFR 45mL/min/1.73m2 미만인 제2형 당뇨환자에서 혈당조절 목적이만으로 이 약을 투여하는 것은 권장되지 않는다(용법·용량 항 참조). 중등도의 신장애 환자에서, 이 약을 투여한 피험자들은 위약을 투여한 피험자들에 비해 크레아티닌, 인, 부갑상샘 호르몬(PTH) 상승 및 저혈압의 이상반응을 나타내는 비율이 더 높았다.

이 약은 eGFR 25 mL/min/1.73 m2 미만인 환자에게 투여를 시작한 경험이 제한적이다.

eGFR 25mL/min/1.73m2 미만인 만성 심부전 환자 및 만성 신장병 환자에서 이 약의 투여를 시작하는 것은 권장되지 않는다(용법·용량 항 참조).

【투여방법】
이 약은 음식 섭취와 관계없이, 1일 1회 하루 중 언제라도 경구 투여할 수 있다. 정제는 통째로 삼켜야 한다.

strong and sustained BP control

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(based on ATACAND® 16 mg)

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REFERENCE

Atacand®
AstraZeneca

KR-9036 | Exp. 2023-08 (Prep.2021-08)
[제품명] 솔리리스

[조성] 1바이알(30mL)중 에 kull리주맙 300mg

[효능·효과] 1) 발작성 야간 혈색소뇨증(PNH : Paroxysmal Nocturnal Hemoglobinuria)을 감소시키기 위한 발작성 야간 혈색소뇨증(PNH : Paroxysmal Nocturnal Hemoglobinuria) 환자의 치료. 수혈 이력과 관계없이, 높은 질병 활성을 의미하는 임상 증상이 있는 환자의 용혈에 임상적 이익이 확립되었다.
2) 비정형 용혈성 요독 증후군(aHUS : atypical Hemolytic Uremic Syndrome) 보체 매개성 혈전성 미세혈관병증을 억제하기 위한 비정형 용혈성 요독 증후군(aHUS : atypical Hemolytic Uremic Syndrome) 환자의 치료.
3) 전신 중증 근무력증(Generalized Myasthenia Gravis) 항아세틸콜린 수용체 항체 양성인 환자의 불응성 전신 중증 근무력증(Refractory gMG: Refractory Generalized Myasthenia Gravis)의 치료.
4) 시신경 척수염 범주 질환 (Neuromyelitis optica spectrum disorder) 항아쿠아포린-4(AQP-4) 항체 양성인 환자의 시신경 척수염 범주질환(NMOSD: Neuromyelitis optica spectrum disorder)의 치료.

[용법·용량] 심각한 감염에 대한 위험을 줄이기 위해서 환자들은 최신의 백신 접종 지침(Advisory Committee on Immunization Practices(ACIP) recommendation)에 따라 백신 접종을 해야 한다. 이 약은 정맥투여되어야 하며 급속정맥투여(IV push) 또는 일시정맥투여(IV bolus)로 투여해서는 안된다.

[사용상의 주의사항] 1. 경고 중대한 수막구균 감염 작용기전으로 인하여 이 약의 사용은 중대한 수막구균 감염(패혈증 그리고/또는 뇌수막염)에 대한 환자의 감수성을 증가시킨다. 이 약의 투여 환자에게서 치명적이고 생명을 위협하는 수막구균 감염이 발생하였다. 수막구균 감염은 어느 혈청군에 의해서도 발생할 수 있지만, 이 약의 투여 환자들은 흔하지 않은 혈청군(X 등)에 의한 질환이 발생할 수 있다. 감염의 위험성을 낮추기 위하여, 이 약의 치료가 지연됨으로 인한 위험성이 수막구균 감염 발생의 위험성보다 큰 경우를 제외하고는 모든 환자들은 반드시 이 약의 투여 시작 최소한 2주 전에 수막구균 백신을 투여 받아야 한다. 만약 접종 받지 않은 환자가 긴급히 이 약의 치료를 받아야 하면, 최대한 빨리 수막구균 백신을 투여 받도록 한다. 수막구균 백신 접종 이후 2주 이내 이 약을 투여할 경우, 4가 수막구균 백신 접종 이후 2주 동안 적절한 예방적 항생요법으로 치료 받아야 한다. 흔한 병원성 수막구균 혈청군을 예방하기 위하여 가능하다면 혈청군 A, C, Y, W135, B에 대한 백신이 권장된다. 환자들은 백신 사용을 위한 최신의 백신 접종 지침(Advisory Committee on Immunization Practices(ACIP) recommendation)에 따라 백신을 접종 혹은 재접종 받아야 한다. 백신 접종은 보체를 더욱 활성화시킬 수 있다. 결과적으로, PNH, aHUS, 불응성 gMG 및 NMOSD를 포함한 보체 매개 질환을 가진 환자들은 용혈(PNH의 경우)이나 혈전성 미세혈관병증(TMA; aHUS의 경우) 또는 중증 근무력증의 악화(불응성 gMG의 경우) 또는 재발(NMOSD의 경우)과 같은 그들의 기저 질환의 징후 및 증상이 증가하는 경험을 할 수 있다. 따라서, 지침에 따른 백신 접종 이후 질환의 증상에 대해 면밀히 관찰되어야 한다. 백신 접종은 수막구균 감염 위험을 줄일 수 있지만, 완전히 없애지는 않는다. 적절한 항생제 사용에 대한 공식 지침(예: 국내 성인 세균성 수막염의 임상진료지침 권고안 등)을 고려하여야 한다. 수막구균 감염의 초기 징후나 증상이 나타나는지 면밀히 관찰하고, 감염이 의심되면 즉시 검사받아야 한다. 환자는 이러한 징후와 증상 및 즉시 치료를 받는 절차에 대해 안내 받아야 하며, 담당 의사는 반드시 환자와 이 약의 치료의 위험과 이익을 상의해야 한다. 수막구균 감염은 초기에 발견하고 치료하지 않으면 급격히 치명적이고 생명을 위협하게 될 수 있다. 중대한 수막구균 감염을 치료받는 환자는 이 약의 투여를 중지하도록 한다.

2. 다음 환자에는 투여하지 말 것
   1) 이 약의 주성분, 뮤린 단백질 또는 기타 구성성분에 과민반응이 있는 환자
   2) 치료되지 않은 중대한 수막구균(Neisseria meningitidis) 감염 환자
   3) 수막구균(Neisseria meningitidis) 백신을 현재 접종하지 않은 환자 또는 백신 접종 이후 2주 동안 적절한 예방적 항생요법으로 치료를 받지 않은 환자(이 약의 치료를 늦추는 것이 수막구균 감염을 일으키는 것보다 중대하지 않은 경우)

3. 다음 환자에는 신중히 투여할 것
   1) 기타 전신 감염: 작용기전으로 인하여 이 약의 치료는 활성 전신 감염이 있는 환자들에게 주의하여 투여하여야 한다. 이 약은 말단 보체 활성을 차단하므로 환자들은 감염, 특히 Neisseria균 및 피낭성 세균(encapsulated bacteria) 감염에 대한 감수성이 증가할 수 있다. 파종성 임균 감염을 포함하는 N. meningitidis 외의 Neisseria 종에 의한 중대한 감염이 보고되었다. 잠재적인 중대한 감염과 그 증상 및 징후에 대한 인식을 높이기 위하여 환자용 정보 안내서의 정보를 환자에게 제공해야 한다. 임질 예방에 관해 환자에게 조언해야 하고 위험성이 있는 환자는 정기적인 검사를 권고한다. 더욱이, 면역력이 약화된 환자와 호중구 감소 환자에서 아스페르길루스 감염이 발생하였다. 이 약을 투여 받는 소아는 폐렴연쇄상구균(Streptococcus pneumonia)과 인플루엔자 간균 B형(Haemophilus influenza type b(Hib))에 의한 중대한 감염을 일으킬 위험이 증가할 수 있다. 폐렴연쇄상구균(Streptococcus pneumonia)과 인플루엔자 간균 B형(Haemophilus influenza type b(Hib))에 의한 감염을 예방하기 위해 최신의 백신 접종 지침에 따라 백신 접종을 받도록 한다. 전신 감염이 있는 환자에게 이 약을 투여할 때는 주의하도록 한다. 에 kull리주맙에 안정되고 유지 요법을 받는 환자에게 추가적인 백신 접종이 필요한 경우, 이 약 투여에 따른 백신 접종 시기를 신중히 고려해야 한다.

4. 약물이상반응
   판 후 보고 및 완료된 임상시험에서 보고된 약물이상반응(발생률 1% 이상 발췌): 매우 흔하게(≥1/10) – 두통, 흔하게(≥1/100 ~ <1/10) - 폐렴, 상기도감염, 비인두염, 기관지염, 요로 감염, 구강 헤르페스, 백혈구감소증, 빈혈, 불면, 현기증, 미각이상, 고혈압, 기침, 입인두통, 설사, 구토, 구역, 복부통증, 발진, 탈모, 소양증, 관절통, 근육통, 열, 피로감, 인플루엔자 유사질환모든 임상시험에서, 가장 중대한 이상반응은 수막구균 패혈증이었고, 이는 이 약으로 치료받은 환자에서 수막구균 감염증의 흔한 증상이었다. 수막구균 패혈증의 징후와 증상에 대해 환자에게 알리고 즉시 의료 조치 받을 것을 환자에게 권고해야 한다. Neisseria gonorrhoeae, Neisseria sicca / subflava, Neisseria spp unspecified로 인한 패혈증을 포함하여 Neisseria 종의 다른 사례들이 보고되었다.
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카리메트 산과목
[ 효능 · 효과] 고혈압증증, [생제 · 용법] 1. 당뇨병이 있는 목사당증달성시달로 1회 15mg을 2ml수로 정려한 후 카라길 20ml에 섞어 주사하여 카라길로 한다. 2. 카라길까지 섞어 주사하여 카라길로 한다. 3. 카라길임에 30% 당뇨병을 섞어 주사하여 카라길로 한다. 4. 카라길임에 30% 당뇨병을 섞어 주사하여 카라길로 한다.
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환자의 주요 증상들로는 막사구체신염, 막사구체신염, 저산소증
마찬가지로 마찬가지로
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(1 mg/kg once every 2 weeks1)
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(1 mg/kg once every 2 weeks1)
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