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Kidney and heart cross-talk

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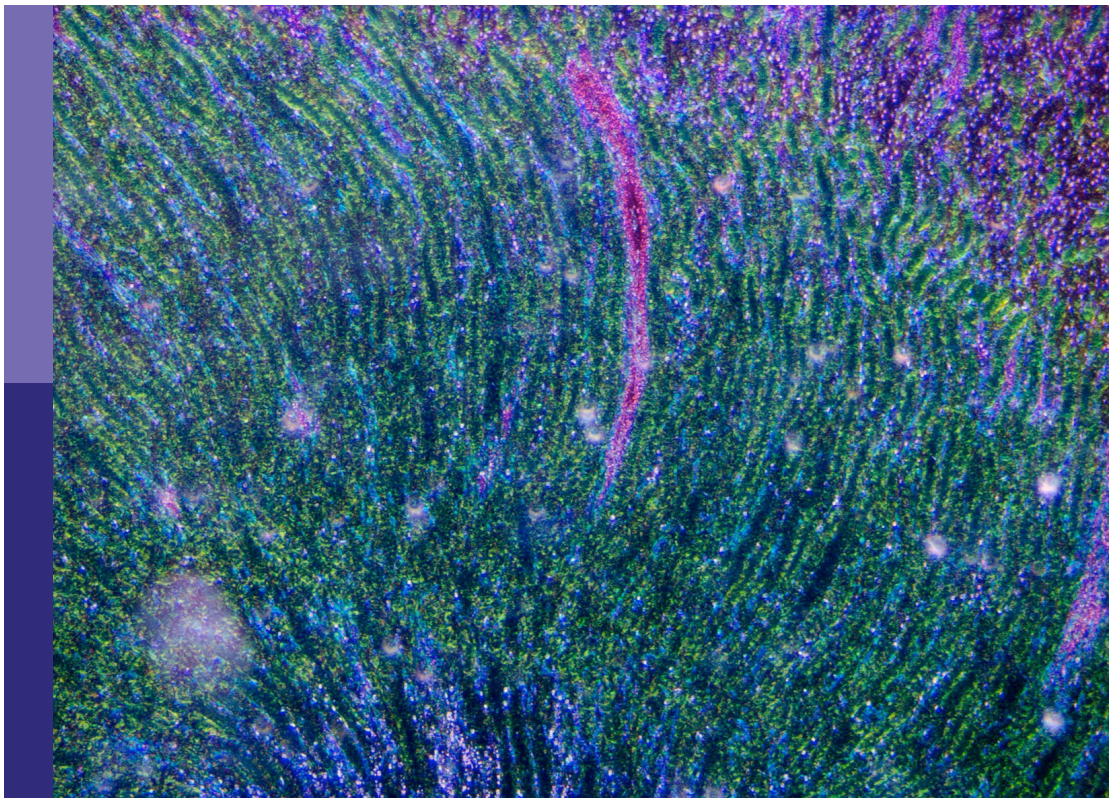

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Kidney and heart cross-talk

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Editorial: Kidney and heart cross-talk

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Editorial on the Research Topic
Kidney and heart cross-talk

Two organs, one fate: the intricate interplay between the heart and kidneys is not a simple equation, but a complex, bidirectional symphony in which dysfunction in one precipitates deterioration in the other. This reality highlights the strong connection between chronic kidney disease (CKD) and cardiovascular disease (CVD). Patients with CKD face a cardiovascular risk that is significantly higher than that of the general population. CKD and CVD share common underlying mechanisms, including chronic inflammation, endothelial dysfunction, oxidative stress, metabolic dysregulation, and changes in gut microbiota. These factors contribute to the markedly increased cardiovascular risk in patients with CKD. However, management of this risk is often fragmented, indicating the need for a multidisciplinary and integrated approach.

Our Research Topic has compiled key studies that explore these shared mechanisms, offering new perspectives on emerging biomarkers, therapeutic strategies, and physiological interactions. For instance, Kaysi et al. demonstrated how pulmonary and systemic congestion in hemodialysis patients impacts cardiovascular mortality, emphasizing the importance of proactive volume management (1). Similarly, Rajnochova Bloudickova et al. highlighted the need for more effective risk stratification in kidney transplant recipients, while Zhao et al. assessed the diagnostic value of high-sensitivity cardiac troponin T in dialysis patients with myocardial infarction, underscoring the role of biomarkers in early diagnosis (2).

Systemic inflammation is another critical factor in the simultaneous involvement of the heart and kidneys. Orsi et al. analyzed multisystem inflammatory syndrome in children with associated proximal tubular injury, demonstrating how inflammation can have multi-organ effects (3). Meanwhile, Kim et al. showed that uncontrolled hypertension in kidney transplant recipients increases the risk of graft failure, reinforcing the importance of strict blood pressure monitoring. The link between hypertension and renal dysfunction is well-documented, as elevated blood pressure contributes to glomerular injury, worsening kidney function, and subsequently increasing cardiovascular morbidity (4).

Early diagnosis of cardiovascular complications in patients with CKD is another crucial aspect. Su et al. developed a risk model for the early detection of acute myocardial infarction in nephropathic patients, which improved the predictive ability over traditional models. Kwon et al. demonstrated that components of the metabolic syndrome influence the risk of adverse renal outcomes in patients with atrial fibrillation, suggesting an integrated approach to the management of comorbidities. Wu et al. investigated the relationship between early-stage renal insufficiency and cardiac structural and functional abnormalities in a large population of asymptomatic Asians, indicating that even minor renal alterations may have significant cardiac implications. Finally, Molina Andújar et al. examined the impact of cardiac surgery-associated acute kidney injury on one-year major adverse kidney events, emphasizing the need for more effective preventive strategies in patients undergoing cardiovascular interventions (5).

These studies underscore the crucial role of various pathophysiological factors in the cardiorenal syndrome. Chronic inflammation and oxidative stress accelerate endothelial damage and disease progression, while mitochondrial dysfunction compromises energy metabolism, exacerbating both heart and kidney failure. Endothelial dysfunction and vascular calcification increase the risk of major cardiovascular events, while gut microbiota alterations contribute to systemic inflammation and organ damage. Managing pulmonary and systemic congestion in hemodialysis patients is essential to reducing mortality and improving quality of life.

A growing body of research suggests that mitochondrial dysfunction plays a pivotal role in cardiorenal syndrome. The inability of mitochondria to maintain cellular energy production leads to increased oxidative stress, which further exacerbates endothelial damage and metabolic disturbances. These dysfunctions set off a cascade of events that contribute to both renal and cardiac deterioration. Additionally, alterations in calcium-phosphate metabolism have been linked to vascular calcification, a major risk factor for cardiovascular mortality in patients with CKD.

Despite advancements in research, managing cardiovascular risk in patients with CKD remains challenging. The lack of an effective multidisciplinary approach and the underutilization of advanced biomarkers limit the efficacy of preventive strategies. Moreover, risk stratification often occurs only after cardiovascular symptoms appear, diminishing the impact of early intervention. Personalized therapies remain an ongoing challenge, as many cardiovascular treatments fail to account for the specificities of CKD.

To improve clinical outcomes, an innovative approach is required that includes closer collaboration among specialists, extensive use of biomarkers to refine diagnosis, and new therapeutic strategies such as SGLT2 inhibitors and finerenone to mitigate cardiovascular risk in nephropathic patients. Optimizing dialysis and transplantation management, incorporating cardiovascular risk considerations, is equally essential to enhance prognosis. Furthermore, therapeutic approaches targeting chronic inflammation and oxidative stress should be integrated into standard treatment protocols to address the underlying molecular pathways contributing to cardiorenal syndrome.

Artificial intelligence and machine learning are also emerging as powerful tools for risk stratification and early diagnosis in patients with CKD. Predictive models utilizing large datasets can help identify high-risk individuals and personalize treatment plans, leading to improved outcomes. The integration of these technologies into clinical practice could revolutionize the way cardiovascular and renal risks are managed in the future.

These emerging insights present exciting new interventional possibilities and underscore the urgency of rethinking our cardiovascular approach to patients with CKD. Nephrology and cardiology can no longer exist in isolation. The future of cardiovascular medicine for CKD patients lies in a unified, integrative approach. Addressing CKD without taking the heart into account is like navigating a storm without a compass—eventually, the course will be lost.

Author contributions

NM: Conceptualization, Writing – review & editing, Formal analysis, Writing – original draft, Validation. MC: Writing – review & editing, Writing – original draft, Supervision. GD: Writing – review & editing, Visualization, Writing – original draft. EL: Conceptualization, Writing – original draft, Writing – review & editing.

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The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Impact of cardiac surgery associated acute kidney injury on 1-year major adverse kidney events

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Background: The incidence of acute kidney injury following cardiac surgery (CSA-AKI) is up to 30%, and the risk of chronic kidney disease (CKD) has been found to be higher in these patients compared to the AKI-free population. The aim of our study was to assess the risk of major adverse kidney events (MAKE) [25% or greater decline in estimated glomerular filtration rate (eGFR), new hemodialysis, and death] after cardiac surgery in a Spanish cohort and to evaluate the utility of the score developed by Legouis D et al. (CSA-CKD score) in predicting the occurrence of MAKE.

Methods: This was a single-center retrospective study of patients who required cardiac surgery with cardiopulmonary bypass (CPB) during 2015, with a 1-year follow-up after the intervention. The inclusion criteria were patients over 18 years old who had undergone cardiac surgery [i.e., valve substitution (VS), coronary artery bypass graft (CABG), or a combination of both procedures].

Results: The number of patients with CKD (eGFR < 60 mL/min) increased from 74 (18.3%) to 97 (24%) within 1 year after surgery. The median eGFR declined from 85 to 82 mL/min in the non-CSA-AKI patient group and from 73 to 65 mL/min in those with CSA-AKI (p = 0.024). Fifty-eight patients (1.4%) presented with MAKE at the 1-year follow-up. Multivariate logistic regression analysis showed that the only variable associated with MAKE was CSA-AKI [odds ratio (OR) 2.386 (1.31–4.35), p = 0.004]. The median CSA-CKD score was higher in the MAKE cohort [3

(2–4) vs. 2 (1–3), p < 0.001], but discrimination was poor, with a receiver operating characteristic curve (AUC) value of 0.682 (0.611–0.754).

Conclusion: Any-stage CSA-AKI is associated with a risk of MAKE after 1 year. Further research into new measures that identify at-risk patients is needed so that appropriate patient follow-up can be carried out.

KEYWORDS

score, chronic kidney disease (CKD), major adverse kidney events (MAKE), acute kidney injury (AKI), cardiac surgery

1 Introduction

Acute kidney injury (AKI) is a sudden loss of kidney function that, from start to finish, occurs in less than 7 days. It is well known from experimental models that, depending on the severity of AKI, some tubule cells are irreversibly lost and replaced by renal progenitor cells. Tubules regenerating after AKI may fail to differentiate and exhibit profibrotic paracrine activity before they become atrophic, so these mechanisms of loss and maladaptive repair imply post-AKI chronic kidney disease (CKD) and a reduction of kidney lifespan (1, 2). In addition, clinical data suggest that AKI at any stage is an independent risk factor for CKD and end-stage CKD (ESCKD) (3). Although the connection between AKI and CKD is well established, it was not until 2017 that the Acute Disease Quality Initiative (ADQI) reached a consensus and defined acute kidney disease (AKD) as disease developing in the period between 7 and 90 days after AKI, which led to the design of studies focusing on interventions in this period, with the aim of preventing CKD after AKI (1).

The incidence of AKI following cardiac surgery (CSA-AKI) is up to 30%, and 2%–5% of patients require renal replacement therapy (RRT) during an AKI episode. CSA-AKI increases the risk of death during admission, which can increase to 50% when there is a need for RRT (4). Given the high incidence of AKI in this controlled scenario, studies have focused on the incidence of *de novo* CKD [defined as eGFR < 60 mL/min] after cardiac surgery. In 2017, Legouis D et al. studied a cohort of 4,791 patients and found that the risk of CKD was higher in patients who had experienced CSA-AKI than in the AKI-free population (5).

Despite the link between AKI and CKD, information about AKI (even for those patients with a need for RRT) is not always provided in the discharge documentation, which makes it difficult for primary care doctors to improve their kidney function follow-up. This issue was recently reviewed by Ostermann et al. (6). Among the AKI patients who received RRT in intensive care units (ICUs) in the UK, the development of AKI and the need for RRT were mentioned in 85% and 82% of critical care discharge letters, respectively, and the monitoring of kidney function post discharge was recommended in only 36.3% of hospital discharge summaries (6).

Providing clinicians with tools to identify patients at risk of CKD after AKI should be a key priority. With this in mind, Legouis D et al. developed a prediction score for *de novo* CKD (defined as e GFR< 60 mL/min) 1 year after cardiac surgery that was found to have fair accuracy in a validation cohort [receiver operating characteristic curve (AUC) value of 0.78]. The score comprises preoperative eGFR by Modification of Diet in Renal Disease formula (MDRD) < 80 mL/min (1 point), age > 65 years (1 point), transplant or aortic surgery (2 points), aortic clamping time > 50 minutes (1 point), and AKI stage one (1 point) and AKI stage 2 or 3 (2 points) (7).

With the aim of including all clinically meaningful renal endpoints in AKI clinical trials, the concept of major adverse kidney events (MAKE) was introduced. This composite endpoint comprises persistently impaired renal function (i.e., a 25% or greater decline in eGFR), new hemodialysis, and death. It has been proposed as a way to improve the capacity to understand AKI and provide a means of comparing different interventions (8).

The aim of our study was to assess the incidence of MAKE 1 year after cardiac surgery and its risk factors and, as a secondary objective, to evaluate the utility of the score developed by Legouis D et al. (CSA-CKD score) in the prediction of MAKE 1 year after surgery, and in so doing to shed light on potential tools for the identification of at-risk patients that require particular follow-up.

2 Materials and methods

We conducted a unicentric retrospective study of patients admitted to Hospital Clínic de Barcelona for cardiac surgery with cardiopulmonary bypass (CPB) from January 2015 to December 2015, with a 1-year follow-up after the intervention. The inclusion criteria were patients over 18 years old who had undergone cardiac surgery [i.e., valve substitution (VS), coronary artery bypass graft (CABG), or a combination of both procedures] and who were in need of a CPB. Patients with chronic kidney diseases at any stage were included. However, patients who were already undergoing chronic dialysis therapy, renal transplant recipients, and those who had had an AKI immediately prior to surgery were not included in the study. In addition, patients who had undergone emergent surgeries, intra-aortic balloon pump (IABP) users, patients who died during surgery or admission, and patients with endocarditis were

excluded. The Ethics Committee of our institution approved the study (Reg. HCB/2019/0959)

2.1 Data collection

Clinical, epidemiological, and laboratory variables were collected from our institution's Electronic Health Records (EHR), SAP®. For each patient, data on medical history, surgery characteristics, intraoperative variables, 24-hour monitoring period in the intensive care unit (ICU), and renal function evolution until discharge and at the 1-year follow-up were collected. Data pertaining to the duration and type of RRT for those patients who required it were also recorded.

Baseline variables included sex, age, medical history, anthropometric variables, Charlson Index Comorbidity Score, creatinine and hemoglobin values before surgery, smoking status, and ejection fraction. Surgical variables included the type of surgery, need for transfusion, ischemia time, extracorporeal circulation time, furosemide or ultrafiltration requirements, and the use of vasopressors, vasodilators, or inotropic drugs. Variables recorded during the first 24 hours included renal function, need for transfusion, use of vasopressors, vasodilators, or inotropic drugs, and need for iodinated contrast media. Information on MAKE was collected 1 year after surgery.

Leicester score (LS), Cleveland Clinic score (CCS), and Euroscore II were calculated for each patient using the information collected during pre-anesthetic visits and/or patient admission reports. CSA-CKD scores were calculated using information from the reports on patient admission and discharge.

Data on new AKI episodes occurring in the first year after discharge from cardiac surgery were extracted from the EHR.

2.2 Definitions

CSA-AKI was defined in accordance with the Kidney Disease Improving Global Outcomes (KDIGO) criteria, i.e., as an increase in serum creatinine (sCr) of ≥ 0.3 mg/dL within 48 hours or of ≥ 1.5- to 2-fold from baseline within 1 week after surgery. Owing to the nature of this study, urinary output criteria were not included. Moderate AKI was defined as a 2.0- to 2.9-fold increase in sCr from baseline, and severe AKI was defined as a 3-fold increase in sCr from baseline or an increase of 0.5 mg/dL if the sCr level was ≥ 4.0 mg/dL at baseline or at the beginning of RRT. The baseline sCr level for CSA-AKI measurements was taken as the value obtained 24 hours before surgery. The duration of AKI was regarded as being from the AKI diagnosis until the sCr level returned to baseline (± 0.3 mg/dL).

MAKE within 1 year of cardiac surgery discharge was defined as persistent renal function decline (i.e., a > 25% decline in eGFR), a new requirement for hemodialysis, or death. Baseline and 1-year eGFR values were calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula. The baseline eGFR for the 1-year MAKE assessment was taken as the value obtained in the pre-anesthetic chart or, if this was not available, as the value obtained 24 hours before surgery.

2.3 Statistics

The study variables are expressed as mean ± standard deviation (SD) if normally distributed, and as medians and interquartile ranges (IQRs) if not. Categorical variables are expressed in terms of absolute values (n) and relative frequency (%). p-values less than 0.05 were considered significant. Variables associated with a risk of MAKE after 1 year were assessed by logistic regression in univariate analysis, and those with statistical significance or clinical relevance were included in the multivariate analysis. We determined the overall performance of the CSA-CKD score by calculating the AUC and carrying out the Hosmer–Lemeshow goodness-of-fit test to assess its discrimination and calibration, respectively. A p-value above 0.05 indicated acceptable calibration. The statistical analysis was conducted using SPSS software, v.25 (SPSS Inc, Chicago, IL, USA).

3 Results

3.1 Characteristics of the population

A total of 404 patients met the inclusion criteria and completed the 1-year follow-up period. Baseline characteristics are depicted in Table 1. The majority of patients (63.4%) were men, and the median age at the time of surgery was 69 years (IQR 61–76 years). Hypertension was the most prevalent comorbidity, followed by diabetes and obesity (presenting in 76.5%, 35.4%, and 30.7% of patients, respectively). Peripheral vascular disease was diagnosed in only 8.9% of patients. The median baseline sCr was 0.9 mg/dL (IQR 0.73–1.05 mg/dL), and 18.3% of the patients had an eGFR of < 60 mL/min. Anemia (hemoglobin level < 120 g/L) was present in 18.6% of patients before cardiac surgery. The most common procedure was VS (46%), followed by CABG (37.4%). Intraoperative variables and AKI scores/surgical risk are included in Supplementary Material Table 1. It should be noted that 78 out of the 404 patients (19.3%) had a cardiopulmonary bypass time of over 120 minutes.

One hundred and forty-seven (36.4%) patients had CSA-AKI, which for the majority of patients was stage 1 (63.3%) and started within the first 24 hours after surgery. The median duration of AKI (i.e., the time from AKI diagnosis until sCr levels returned to baseline value ± 0.3 mg/dL) was 3 days (IQR 1–6 days), and 10 patients (2.5%) required RRT. Additional information pertaining to patients' CSA-AKI characteristics is provided in Supplementary Material Table 2. The median sCr level at discharge was 0.86 mg/dL (IQR 0.69–1.04 mg/dL), and the median eGFR was 84 mL/min (IQR 64–95 mL/min). Twenty-nine out of 147 patients with AKI (19.7%) had persistent renal dysfunction decline at discharge (i.e., a > 25% decline in eGFR) but none of these patients was receiving RRT.

3.2 Renal function and MAKE 1 year after cardiac surgery

In the overall cohort, sCr levels and eGFR at 1 year were similar to those at baseline [0.93 mg/dL (IQR 0.78–1.10 mg/dL), 78 mL/

TABLE 1 Baseline characteristics.

N = 404	N (%)/median (IQR)/mean ± SD
Sex (% men)	256 (63.4)
Age (years) ≥ 75	69 (61–76) 122 (30.2)
History of smoking	188 (46.5)
Diabetes Diabetes with insulin therapy	143 (35.4) 38 (9.4)
Hypertension	309 (76.5)
Charlson Comorbidity Index score	4 (3–5)
BMI ($kg/m^{2)}$ BMI ≥ 30	28.25 ± 4.47 124 (30.7)
Anemia Hemoglobin (g/L) Hematocrit (%)	75 (18.6) 134 (123–144) 39 (36–42)
Peripheral vascular disease	36 (8.9)
Low ejection fraction (< 40%)	40 (9.9)
Creatinine (mg/dL) eGFR(mL/min) eGFR< 60 mL/min CKD SIII CKD SIV	0.9 (0.73–1.05) 81 (66–92) 74 (18.3) 63 (15.6) 10 (2.5)
Previous cardiac surgery	43 (10.6)
Procedure	Valve surgery: 186 (46) CABG: 151 (37.4) Valve + CABG: 67 (16.6)

BMI, body mass index; eGFR, estimated glomerular filtration rate; CKD, chronic kidney disease; IQR, interquartile range; SD, standard deviation; CABG, coronary artery bypass grafting.

min (IQR 61–90 mg/dL)], but when the cohort was divided between those who had AKI and those who did not, the eGFR declined from 85 to 82 mL/min and from 73 to 65 mL/min ($p = 0.024$) in the non-AKI and AKI groups, respectively (Table 2 and Figure 1). The number of patients with CKD (eGFR < 60 mL/min) increased from 74 (18.3%) to 97 (24%) within 1 year after surgery.

Fifty-eight (14.36%) patients had experienced MAKE within 1 year after surgery. Incidences of MAKE included a decline by ≤ 25% in eGFR in 54 patients, the need for RRT in two patients, and the death of two patients (Figure 2). The association of CSA-AKI with MAKE was assessed in a univariate logistic regression analysis, including any-stage CSA-AKI, long CSA-AKI, and CSA-AKI with the need for RRT, and the three forms of CSA-AKI were statistically associated with the outcome (Table 3).

A univariate analysis of baseline characteristics was performed to identify baseline risk factors that could be also associated with the risk of MAKE within 1 year after surgery so that these could be included in the multivariate analysis. Among the included baseline variables, patients who were associated with MAKE 1 year after surgery were over 75 years of age [odds ratio (OR) 2.12 (1.2–3.74), $p = 0.01$], or having arterial hypertension [OR 2.42 (1.07–5.59), $p = 0.034$], or preoperative anemia [OR 2.27 (1.22–4.25), $p = 0.01$]. As for renal function, an eGFR of < 60 mL/min was considered almost statistically significant [OR 1.85 (0.98–3.52), $p = 0.059$] (Table 4). Relatedly, median Charlson Comorbidity Index Scores was higher for patients who had experienced MAKE [4.5 (3–6)] than in those who had not [4 (3–5)].

A multivariate logistic regression analysis was performed with 1-year MAKE within 1 year after surgery as a dependent variable and any-stage CSA-AKI (with the statistically significant baseline variables being the patient having arterial hypertension, preoperative anemia, or being aged > 75 years) and CKD (with the statistically significant baseline variable being an eGFR of < 60 mL/min) as clinically relevant independent variables. In that analysis, the only variable that was still associated with MAKE 1 year after surgery was any-stage CSA-AKI [OR 2.386 (1.31–4.35), $p = 0.004$) Table 5.

3.3 CSA-CKD score

Because the CSA-CKD score study validation was performed in patients without pre-existing CKD (i.e., those with an eGFR of < 60 mL/min) to predict the likelihood of CKD after 1 year, we first assessed the performance of the score in the selected population with an eGFR of > 60 mL/min ($n = 329$). The number of patients with CKD after 1 year was 40 (12.16%) and the CSA-CKD score achieved a fair discrimination with an AUC of 0.737 (95% CI 0.657–0.817), which was similar to the original study validation cohort (AUC 0.78, 95% CI 0.72–0.83). Calibration was acceptable with a Chi-square test result of 2.444 and $p = 0.485$ (Figure 3).

We then assessed the performance of the CSA-CKD score in the overall cohort to assess the likelihood of MAKE after 1 year. The median CSA-CKD score was higher in patients who had experienced MAKE after 1 year [3 (2–4) vs. 2 (1–3), $p < 0.001$).

TABLE 2 Changes in sCr level and eGFR in the overall cohort, CSA-AKI, and no-CSA-AKI cohort.

	Overall cohort N = 404 median (IQR)	CSA-AKI *n* = 147 median (IQR)	No CSA- AKI *n* = 257 median (IQR)
Baseline sCr level (mg/dL)	0.9 (0.73–1.05)	0,97 (0.79–1.22)	0.86 (007–1.01)
1-year sCr level (mg/dL)	0,93 (0.78–1.10)	1.02 (0.86–1.28)	0.89 (0.76–1.08)
Baseline eGFR (mL/min)	81 (66–92)	73 (54–87)	85 (71–95)
1-year eGFR (mL/min)	78 (61–90)	65 (51–83)	82 (68–93)

IQR, interquartile range; CSA-AKI, cardiac surgery associated acute kidney injury; eGFR, estimated glomerular filtration rate.

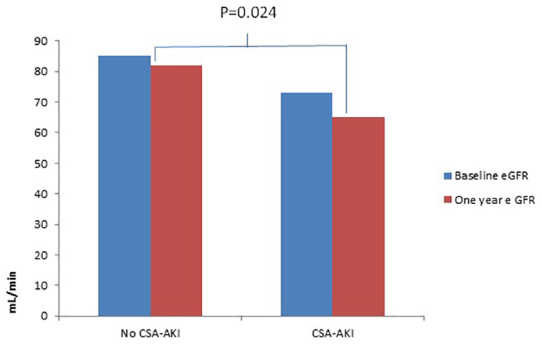

FIGURE 1
Differences in eGFR at 1-year follow-up between patients who had CSA-AKI and those who did not. CSA-AKI, cardio surgery associated acute kidney injury; e GFR, estimated glomerular filtration rate.

Discrimination fell, with an AUC of 0.682 (0.611–0.754), but calibration was similar (p = 0.489) (Figure 4).

3.4 Risk of 1 year new-AKI episodes

During the 1-year follow-up visit, only 14 patients presented with a registered new AKI episode. Although experience of CSA-AKI was more common in patients who presented with a second AKI during the 1-year follow-up visit (57.1% vs 35.6%), no statistically significant association was found (Table 6).

4 Discussion

In this retrospective unicentric study, we evaluated the risk of MAKE after CSA-AKI in a Spanish cohort, and the utility of the CSA-CKD score in the prediction of MAKE after discharge. Any-stage CSA-AKI was the only variable associated with the outcome when analyzed in a multivariate analysis with baseline characteristics of the patients. The CSA-CKD score had acceptable discrimination (AUC 0.737) for the prediction of CKD (eGFR < 60), but the AUC decreased to 0.682 for the prediction of MAKE after 1 year.

GFR generally declines at a rate of 1 mL/min/year (9), but in our cohort we observed median declines of 3 mL/min/year and 8 mL/min/year in patients who did not and did experience CSA-AKI, respectively. Patients who undergo cardiac surgery are at an increased risk of losing kidney function, probably because of their comorbidities (for example, we found that a high percentage of patients who underwent cardiac surgery had diabetes and were hypertensive), but this risk is significantly increased when CSA-AKI occurs (p = 0.024). In that regard, Reyden et al. studied a cohort of 29,330 patients who underwent primary isolated CABG in Sweden, with a mean follow-up period of 4.3 years, and found that the risk of end-stage chronic kidney disease (ESCKD) was significantly increased for any-CSA-AKI stage compared with non-CSA-AKI patients, also when stratified by preoperative renal function (10).

Previous studies have focused on the risk of CKD (an eGFR of < 60 mL/min) in this population 1 year after cardiac surgery, but recent evidence shows that defining worsened renal function as a decline of ≤ 25% in eGFR can help to identify patients that can develop CKD in later years, or patients who already have CKD and whose episodes of CSA-AKI could accelerate the decline of their renal function (8). Legouis et al. studied a cohort of 4,791 patients and observed that patients without pre-existing CKD (regardless of their AKI stage) were associated with a risk of *de novo* CKD after fully recovering from an AKI episode after cardiac surgery, and, based on this finding, they developed a CSA-CKD score to identify at-risk patients (5, 7). It is important to note that excluding patients with an eGFR of < 60 mL/min prevents clinicians from identifying patients who can rapidly progress to ESKD and who may benefit from nephrology follow-up. This is particularly important in cardiac surgery as the percentage of patients with pre-existing CKD is increasing, alongside increased rates of patient comorbidity. For instance, in our cohort almost 20% of the

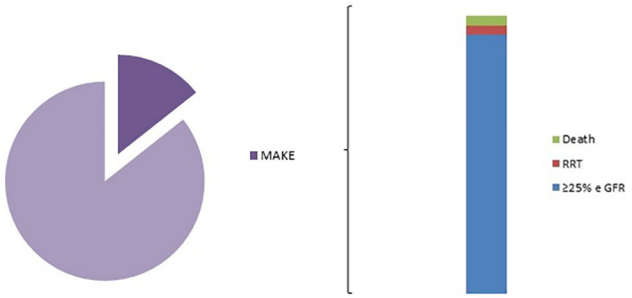

FIGURE 2
MAKE distribution. MAKE, major adverse kidney events. RRT, Renal Replacement Therapy; e GFR, estimated glomerular filtration rate.

TABLE 3 Univariate analysis of CSA-AKI as a risk factor for 1-year MAKE.

	Total (N = 404)	MAKE (*n* = 58)	No MAKE (*n* = 346)	OR (95% CI)	*p*-value
Any-stage CSA-AKI (%)	147 (36.4)	34 (58,6)	113 (32.7)	2.921 (1.654 to 5.159)	< 0.001
Long CSA-AKI (>3 days)(%)	58 (14.4)	20 (34.5)	38 (11)	4.266 (2.254 to 8.072)	< 0.001
RRT CSA-AKI (%)	10 (2.5)	4 (6.9)	6 (1.7)	4.198 (1.147 to 15.36)	0.003

CSA-AKI, cardiac surgery associated acute kidney injury; OR, odds ratio; RRT, renal replacement therapy.

patients had pre-existing CKD. Another study, conducted by Ishami et al., included 29,388 individuals who underwent cardiac surgery. They found that a creatinine increase, defined as either none (0%) or as class I (1%-24%), II (25%-49%), III (50%-99%), or IV (100%) was associated, in a graded manner, with an increased risk of incident CKD, CKD stage progression, and mortality (11). This study also gives more weight to the categories of CKD than to the percentage of GFR decline itself. To our knowledge, the present study is the first that focuses on the impact of CSA-AKI on MAKE, with a special focus on the relative reduction of eGFR in line with current AKI research.

Interestingly, the risk of MAKE in our cohort was not associated with age or sex. This is always a major concern when studying eGFR decline, because the CKD-EPI formula includes not only sCR levels but also age and sex (12). Moreover, we did not find differences in the risk of MAKE between the diabetic and non-diabetic populations, which could be explained by the high comorbidity of the whole cohort, which had a median Charlson Comorbidity Index of 4.

Providing information about AKI episodes is key not only to attempts to change the natural history of AKI to CDK transition, but also to the introduction of strategies that identify patients at increased risk to determine which patients may benefit from a nephrology or primary-care follow-up. In that regard, patients in which sCr levels do not return to baseline levels at discharge could be considered candidates for specialist follow-up. However, we must take into account that hyperfiltration after AKI, changes in distribution volume, and loss of muscle mass during long hospital admissions may also decrease creatinine values, and therefore that a large percentage of patients could be lost (13, 14). Interestingly, low sCr levels have been associated with higher mortality rates as a result of malnutrition. On the contrary, when using cystatine C, a biomarker that is independent of muscle metabolism, there is a linear rather than a U–shaped association between eGFR and adverse events (13). The use of cystatin-C may not always be possible, but the measurement of creatinine clearance could be a way to identify patients with persistent kidney dysfunction after CSA-AKI (15). Studies of biomarkers in AKI have mainly been conducted by intensivists and have focused on short-term outcomes. In this field, only a secondary analysis of the Sapphire study for NephroCheck® ([TIMP-2]×[IGFBP7]), known as the cell cycle arrest biomarker, showed that a result of >2 was equivalent to

TABLE 4 Univariate analysis of baseline risk factors for 1-year MAKE.

N (%)/median (IQR)/mean+/-SD	MAKE (*n* = 58)	No MAKE (*n* = 346)	OR (95% CI)	*p*-value
Male sex	34 (58.6)	222 (64.4)	0.791 (0.449–1.395)	$p = 0.418$
Age ≥ 75 years	26 (44.8)	96 (27,7)	2.116 (1.198–3.736)	$p = 0.010$
Smoking status	28 (48.3)	160(46.2)	1.080 (0.616–1.894)	$p = 0.788$
Diabetes	23 (39.7)	120 (34.7)	1.238 (0.699–2.190)	$p = 0.464$
Hypertension	51 (87.9)	259 (74.9)	2.4247(1.071–5.593)	$p = 0.034$
BMI ≥ 30	17 (29,3)	107 (30.9)	0.94 (0.503–1.755)	$p = 0.845$
Anemia	7 (12.1)	57 (16.5)	2.27 (1.217–4.246)	$p = 0.01$
Peripheral vascular disease	6 (10.5)	30 (8,7)	1.215 (0.482–3.063)	$p = 0.679$
EF < 40%	8 (13.8)	32 (9.2)	1,57 (0.684–3.601)	$p = 0.287$
EGFR< 60 mL/min **CKD SIII** **CKD SIV**	16 (27.6) 13 (22.4) 3 (5.2)	59 (17,1) 52 (15) 7 (2)	FG<60: 1.853 (0.977–3.516)	$p = 0.059$
Past cardiac surgery	7 (12.1)	36 (10.2)	1.178 (0.497–2.790)	$p = 0.709$
Procedure: **VS** **CABG** **VS +CABG**	 35 (60.3) 16 (27.6) 7 (12.1)	 151 (43.6) 135 (39) 60 (17.3)	CABG: 0.595 (0.322–1.101)	$p = 0.098$

IQR, Interquartile range; MAKE, major adverse kidney events; OR, odds ratio; BMI, body mass index; EF, ejection fraction; CKD, chronic kidney disease; VS, valve substitution; CABG, coronary artery bypass graft.

TABLE 5 Multivariate analysis of risk factors associated to 1-year MAKE.

	OR	95% CI	*p*-value
Age > 75 years	1,657	0.914–3.006	0.096
AHT	1.895	0.811–4.430	0.140
Anemia	1.799	0.932–3.473	0.080
Any-stage CSA-AKI	2.386	1.31–4.346	0.004
Baseline eGFR < 60 mL/min	1.112	0.557–2.223	0.763

AHT, arterial hypertension; CSA-AKI, cardiac surgery associated acute kidney injury; MAKE, major adverse kidney events; eGFR, estimated glomerular filtration rate.

AKI stage progression on the risk of ESKD or death at 9 months (16).

Tools such as the CSA-CKD scoring system developed by Legouis et al. show promise as simple ways to identify patients at risk of kidney disease progression (7). In our study, we first tried to assess if the score had fair discrimination for CKD, as was first described in its original study. We found that the AUC value for CKD in patients without pre-existing CKD was 0.737 (95% CI 0.657–0.817), similar to the validation cohort of the original study (0.78 [95% CI 0.72–0.83]). On the other hand, when analyzing AUC for MAKE in the overall population, the AUC value decreased to 0.682 (95% CI 0.611–0.754). In our study we used the CKD-EPI formula, since it is currently the formula with the most international endorsement. Legouis et al. used the MDRD formula for the estimation of basal GFR in patients without CKD, but it has been proven that this formula has worse precision for eGFRs of 60–90 mL/min, and in that scoring system patients received 1 point for eGFR < 80 ml/min. We believe that multicenter studies are needed to create a new scoring system that focuses on MAKE and uses CKD-EPI as the formula for eGFR estimation (17, 18).

However, after patients at risk of MAKE have been identified, there is still no robust data about the benefits of a specific nephrology follow-up compared to standard care. The first randomized controlled trial investigating this was published in 2021 (19). Patients who survived severe AKI stage 2 or 3 were enrolled and randomized to receive either comprehensive or standard care for 12 months. The comprehensive group comprised a multidisciplinary team that included nephrologists, nurses, nutritionists, and pharmacists. The primary outcome was feasibility and the secondary outcomes included incidence of MAKE, renal function, and albuminuria rate at 12 months. They accomplished the primary feasibility outcomes; for the secondary outcomes they found statistically significant differences only in albuminuria rate. However, blood pressure was better controlled in the comprehensive group.

Our study has some limitations. First, the albuminuria rate was not assessed because data were not available. It is known that post-AKI proteinuria is associated with kidney disease progression and, even in patients without changes in eGFR at 1 year, it is considered a sequela of AKI (20). Second, owing to the nature of this study, almost 7% of the original cohort were lost to follow-up and therefore could not be included in the final analysis. Third, the lack of association between CSA-AKI and new AKI episodes could also be due to the nature of the study, as only 14 new AKI episodes

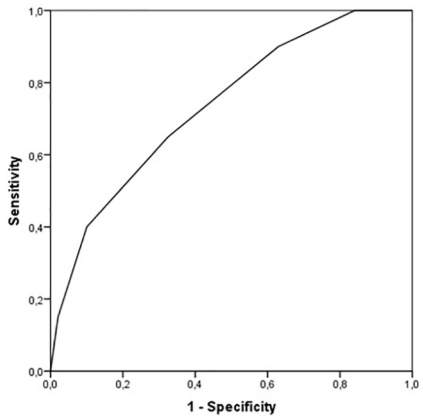

FIGURE 3
Receiver operating characteristic curve of CSA-CKD score for CKD. CSA-CKD, Cardiac surgery associated chronic kidney disease; CKD, chronic kidney disease.

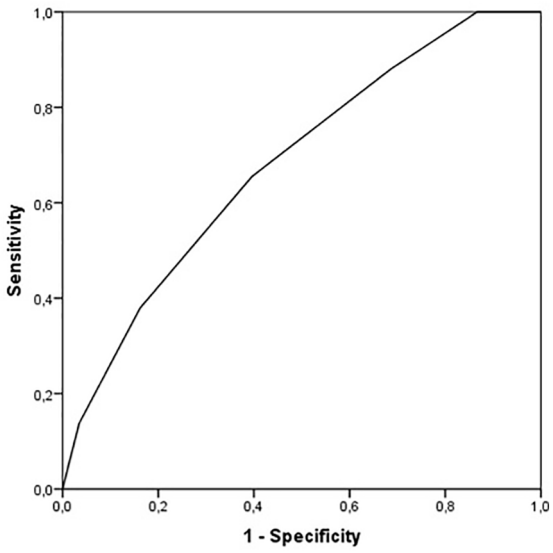

FIGURE 4
Receiver operating characteristic curve of CSA-CKD score for MAKE. MAKE, major adverse kidney events.

TABLE 6 Univariate analysis of CSA-AKI as a risk factor for new AKI during the 1-year follow-up visit.

	No 1-year AKI (*n* = 390)	1-year AKI (*n* = 14)	OR (95%CI)	*p*-value
Any-stage CSA-AKI	139 (35,6)	8 (57,1)	1,818 (0.499–6.624)	0.365
Long CSA-AKI (> 3 days)	54 (13.8)	4 (28,6)	1.154 (0.249–5.353)	0.855
RRT CSA-AKI	8 (2,1)	2 (14.3)	5.130 (0.79–33.3)	0.087

CSA-AKI, cardiac surgery associated acute kidney injury; RRT, renal replacement therapy; OR, odds ratio.

were registered because of the short and retrospective follow-up. Finally, this is a unicentric retrospective study that provides information about the increased risk of MAKE after CSA-AKI, but multicentric and prospective studies are needed to confirm our results and create a scoring system that tries to identify patients at risk of MAKE.

In conclusion, based on our results, any-stage CSA-AKI is associated with MA; however, the development of further scoring systems that help clinicians to identify at-risk patients is needed so that appropriate patient follow-up can be provided.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The Ethics Committee of our institution approved the study (Reg. HCB/2019/0959). Written informed consent from the patient or patient's legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

Author contributions

Research idea and study designs: AM and EP. Data acquisition: AM, VE, and AL. Data analysis and interpretation: AM. Supervision and mentorship: EP. IR, PM, CI, MB, ES, LQ, MC, GP, and EQ contributed important intellectual content during manuscript drafting. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneph.2023.1059668/full#supplementary-material

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Relation of early-stage renal insufficiency and cardiac structure and function in a large population of asymptomatic Asians: a cross-sectional cohort analysis

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Background: Few studies have addressed early-stage kidney disease and preclinical cardiac structural and functional abnormalities from a large-scale Asian population. Further, the extent to which measures of myocardial function and whether these associations may vary by testing various formulas of renal insufficiency remains largely unexplored.

Objective: To explore the associations among renal function, proteinuria, and left ventricular (LV) structural and diastolic functional alterations.

Design: A cross-sectional, retrospective cohort study.

Setting: Registered data from a cardiovascular health screening program at MacKay Memorial Hospital from June 2009 to December 2012.

Participants: Asymptomatic individuals.

Measurements: Renal function was evaluated in terms of estimated glomerular filtration rate (eGFR) by both MDRD and CKD-EPI formulas and severity of proteinuria, which were further related to cardiac structure, diastolic function (including LV e' by tissue Doppler), and circulating N-terminal pro-brain natriuretic peptide (NT-proBNP) level.

Results: Among 4942 participants (65.8% men, mean age 49.4 $\pm$ 11.2 years), the mean CKD-EPI/MDRD eGFR was 90.6 $\pm$ 15.7 and 88.5 $\pm$ 16.9 ml/min/1.73m^2, respectively. Lower eGFR, estimated either by the MDRD or CKD-EPI method,

and higher proteinuria were significantly associated with lower LV e' and higher NT-proBNP (all $p<0.05$) even after adjusting for clinical covariates. In general, lower eGFR estimated by CKD-EPI and MDRD displayed similar impacts on worsening e' and NT-proBNP, rather than E/e', in multivariate models. Finally, lower LV e' or higher composite diastolic score, rather than E/e', demonstrated remarkable interaction with eGFR level estimated by either CKD-EPI or MDRD on circulating NT-proBNP level ($p_{interaction} <0.05$).

Limitations: Proteinuria was estimated using a urine dipstick rather than more accurately by the urine protein-to-creatinine ratio. Also, pertaining drug history and clinical hard outcomes were lacking.

Conclusion: Both clinical estimate of renal insufficiency by eGFR or proteinuria, even in a relatively early clinical stage, were tightly linked to impaired cardiac diastolic relaxation and circulating NT-proBNP level. Elevation of NT-proBNP with worsening renal function may be influenced by impaired myocardial relaxation.

KEYWORDS

chronic kidney disease, echocardiography, left ventricular diastolic dysfunction, N-terminal pro-brain natriuretic peptide, proteinuria

Introduction

Chronic kidney disease (CKD) carries an unambiguous risk for a broad spectrum of cardiovascular diseases (CVD), among which heart failure (HF) remains the most common chronic clinical manifestation in patients with CKD (1, 2). The risk of HF rises in accordance with a decline in glomerular filtration rate (GFR) and is greatest in patients with end-stage renal disease requiring dialysis (3). It has been proposed that advanced CKD is characterized by accelerated atherosclerosis (4) and large arterial remodeling, secondary to pressure or volume overload (5), and possibly indolic uremic toxins (6, 7). These factors, when taken together, may lead to unfavorable cardiac remodeling from reduced arterial compliance, increased pulse pressure, and left ventricular hypertrophy (LVH) or fibrosis closely associated with a stiffened left ventricle and impaired diastolic relaxation (2, 8). As a consequence, based on the Frank–Starling law, an acute elevation of preload can cause increased left atrial pressure and pulmonary edema despite apparently preserved ventricular systolic function (9, 10).

A number of mechanisms illustrate the bidirectional interactions between myocardial dysfunction and kidney disease (11); however, it remains unclear whether this interplay may start to take place at a relatively early, clinically asymptomatic stage. Furthermore, various estimates of GFR have been proposed (e.g., CKD Epidemiology Collaboration [CKD-EPI] (12) and four-variable Modification of Diet in Renal Disease [MDRD] (13) formulas), although their impacts on cardiac structural and functional alterations in earlier stages of renal insufficiency have not been fully explored. On the other hand, assessment of diastolic dysfunction (DD) as precursor of HF (14, 15), albeit its complexity with diversity, can be readily assessed using non-invasive echocardiography (16, 17). However, the extent to what degree these indices may be affected and whether these estimates may be equally influenced by renal insufficiency at an earlier stage remains largely unexplored in large-scale Asian population. Here, we aimed to investigate the association between renal function and echocardiographic measurement of diastolic function in asymptomatic individuals.

Methods

Data source and study population

This cross-sectional study included asymptomatic participants in an ongoing cardiovascular health screening program from June 2009 through December 2012 at a tertiary-care teaching institute in Northern Taiwan. The primary aim of this program was to examine the hypothesis that certain demographic characteristics, behavioral factors, or biochemical data are associated with subclinical cardiac dysfunction in otherwise healthy individuals. All participants underwent a thorough evaluation, including general physical examination, baseline anthropometric measurements, blood sampling, and comprehensive echocardiography on the day of appointment. As described in our previous work (18), clinical symptoms, baseline comorbidities, smoking status, and exercise habits were obtained from a detailed structured questionnaire. This study was approved by the institutional review board of MacKay Memorial Hospital (14MMHIS202), and conducted in accordance with the Declaration of Helsinki. Informed consent was obtained from all participants.

Baseline comorbidities collected included diabetes, hypertension, dyslipidemia, and CVD. CVD constituted a group of diseases including coronary artery disease (CAD), stroke, and peripheral arterial disease. Laboratory parameters measured included hemoglobin, fasting blood sugar, lipid profile, renal function, N-terminal pro-brain natriuretic peptide (NT-proBNP), and urinalysis. All biochemical tests were conducted using a Hitachi 7170 Automatic Analyzer (Hitachi Corp., Hitachinaka, Ibaraki, Japan), and NT-proBNP was measured using an electrochemiluminescence immunoassay "ECLIA" assay (Roche Diagnostics GmbH, D-68298, Mannheim, Germany) in a standardized central laboratory. Renal function in terms of estimated glomerular filtration rate (eGFR) was calculated using CKD-EPI and four-variable MDRD equations, and was categorized as 30 to < 60, 60 to < 90, and ≧ 90 ml/min/1.73 m^2. For simplicity, eGFR is referred to as CKD-EPI eGFR if not otherwise specified. We defined proteinuria, measured with a dipstick, as negative, mild (trace to 1+), or severe (2+ to 3+). Test strips were measured using an automatic dipstick analyzer (CLINITEK Novus®, Siemens). Validation of results with quantitative urine albumin amount was good (Supplemental Figure 1). As per the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines, participants were further classified based on eGFR and proteinuria categories (19). Subjects with missing data for serum creatinine or dipstick proteinuria were excluded from analysis.

Echocardiographic evaluation

Conventional echocardiography and TDI were performed on all participants, based on the American Society of Echocardiography and European Association of Cardiovascular Imaging guidelines (20, 21) using a GE system (Vivid i, GE Vingmed Ultrasound, Norway) equipped with a 2- to 4-MHz transducer (3S-RS). LV and left atrial (LA) structural parameters measured included LV end-diastolic and end-systolic diameters, wall thickness, LA/LV volume by modified biplane Simpson's method, and LV mass by the Devereux formula (22). Maximum LA volume (LAVmax) was measured at ventricular end-systole just before opening of the mitral valve, while minimum LA volume (LAVmin) was measured at end-diastole, just before closure of the mitral valve. LV ejection fraction (LVEF) was calculated as 100 × (maximal LV volume − minimal LV volume)/maximal LV volume. LVEF was considered abnormal if < 50%. LV mass was further indexed to body surface area (BSA) as LV mass index (LVMI), and LAV was similarly indexed to BSA. LVH was defined as an LVMI greater than 115 g/m^2 in men and 95 g/m^2 in women (23).

The most important modalities to evaluate diastolic function are transmitral pulsed-wave Doppler flow and tissue Doppler mitral annular velocity profile (16, 17). The former helps to assess the presence and severity of DD, which alters the relationship between peak velocity flow in early diastole (E-wave) and that in late filling (A-wave), the time taken from the maximum E to baseline (deceleration time [DT]), and the interval between closure of the aortic valve and opening of the mitral valve (isovolumetric relaxation time [IVRT]). TDI measures the velocity of mitral annular motion, characterized by peak systolic velocity (s'), early diastolic velocity (e'), and late diastolic velocity (a') in apical four-chamber view. Average e' was taken as the average of septal e' and lateral e'. LV filling pressure was estimated using the E/e' ratio (average e'). DD was defined as E/e'> 15 or average e' <9 cm/s when E/e' is between 8 and 15 (24). Composite diastolic score was calculated based on TDI e' velocity, E/e' ratio, LAV index, and pulmonary artery pressure (16). Scores ranged from 0 to 2, where 0 was normal, 2 abnormal, and 1 in-between.

All echocardiographic images were performed blind to clinical information by an experienced technician, and stored digitally and reviewed offline using proprietary software (EchoPAC version 10.8, GE Vingmed Ultrasound, Norway). The reproducibility analysis has been reported in our previous article (18). We randomly selected 50 subjects for coefficient of variation analysis of a number of measured parameters (Supplemental Table 1). For instance, the intra-class correlation coefficients for LAVmax were 92% between analyzers (interobserver) and 98.5% for the same analyzer (intraobserver).

Statistical analysis

This study analyzed the relationship between degree of renal dysfunction and cardiac deformational functional changes. The cohort was divided into eGFR and proteinuria categories. Trend tests were performed for continuous variables across categories of eGFR and proteinuria using one-way analysis of variance (ANOVA) and for categorical ones using the Cochran–Armitage test. Continuous variables are presented as mean ± standard deviation (SD); discrete variables are described as counts and percentages.

Multivariate linear regression was performed for markers of DD and renal function. Model 1 was adjusted for baseline clinical features (age and gender). Model 2 was additionally adjusted for baseline comorbidities (hypertension, diabetes, and CVD), body mass index (BMI), systolic blood pressure (SBP), current smoking, and laboratory data (fasting glucose, high-density lipoprotein [HDL], and total cholesterol). Model 3 added proteinuria to model 2. As for sensitivity tests, key echocardiographic variables (LVMI, LVEF, and stroke volume [SV]) were separately added to models 2 and 3. The final results of multivariate analyses were summarized by β-coefficient and 95% confidence intervals (CI).

Because NT-proBNP is a powerful indicator of HF (25), we also tested whether associations between renal function and diastolic parameters vary with NT-proBNP as an *a priori* hypothesis; therefore, possible interactions was evaluated with or without interaction terms between renal function (i.e., eGFR and proteinuria categories) and diastolic parameters (i.e., average e', composite diastolic score, and LAV index) with NT-proBNP in factorial (two-way ANOVA in SPSS) and linear (ggplot2 package in R) designs.

All statistical analyses were carried out using Microsoft Excel 2013, IBM SPSS Statistics for Windows, Version 22.0 (IBM Corp. Released 2013. Armonk, NY), and R (R Core Team (2022). A two-sided p-value <0.05 was considered significant.

Role of the funding source

No funding was used for this study.

Results

Baseline demographics

Our study included 5526 asymptomatic participants, and 584 were excluded for lack of serum creatinine or urine dipstick test (Supplemental Tables 2; 3). Among 4942 enrollees, 65.8% were men, mean age was 49.4 ± 11.2 years, and mean CKD-EPI eGFR was 90.6 ± 15.7 ml/min/1.73 m^2 at enrollment (Table 1). Hypertension was the most prevalent systemic disease in this cohort, reported in 18.7% of the enrollees. All participants were categorized into three groups based on eGFR and into three groups based on proteinuria on a dipstick (Table 1). Great heterogeneity was observed between groups in terms of patient characteristics, baseline comorbidities, and laboratory data. As eGFR declined or proteinuria increased, there were trends of greater age, larger BMI, higher blood pressure, higher fasting glucose, higher uric acid, higher triglyceride, and higher NT-proBNP levels (all p for trends < 0.05).

Echocardiographic findings

On echocardiographic assessment, the systolic function of our participants was preserved (overall LVEF was 62.7 ± 5.4%) (Table 2). Overall E/A ratio was 1.2 ± 0.4, E/average e' 7.9 ± 2.6, septal e' 8.0 ± 2.2 cm/s, lateral e' 10.4 ± 2.9 cm/s, average e' 9.2 ± 2.4 cm/s, LVMI 76.9 ± 14.8 g/m^2, and NT-proBNP 46.9 ± 109.9 pg/ml. LVMI in our cohort did not meet the criteria for LVH. LV geometry differed significantly by renal function status with higher LVMI, LAV indices, and LV end-diastolic and end-systolic diameters among individuals with lower CKD-EPI eGFR (or higher proteinuria) when compared with their counterparts. In parallel with the severity of renal dysfunction, E/A ratio and e' gradually decreased, while peak A-wave velocity, DT, IVRT, E/e', and composite diastolic score all gradually increased (all p for trends < 0.05). Similar trends of altered cardiac structures and functions were observed across MDRD eGFR categories (Supplemental Table 4). Of note, participants in the worst categories (i.e., having eGFR between 30 and < 60 ml/min/1.73 m^2 or severe dipstick proteinuria) showed the lowest TDI-determined e' values (septal e' < 7 cm/s, lateral e' < 10 cm/s, and average e' < 9 cm/s), suggestive of highly abnormal diastolic relaxation (Table 2; Supplemental Table 4) (16).

Figure 1 illustrates the levels of average e', E/e', LVMI, and NT-proBNP across categories of eGFR and proteinuria. We demonstrated a graded pattern of average e', E/e', and LVMI with the severity of renal function. In Table 3, average e' is summarized by CKD-EPI/MDRD eGFR and proteinuria category. The levels of average e' did not meet the risk classification for prognosis of CKD and cardiovascular mortality as per the KDIGO guidelines (19).

Associations between cardiac diastolic function, renal insufficiency, and circulating NT-proBNP level

In several multivariate regression models adjusted for clinical risk factors, CKD-EPI eGFR was positively correlated with average e', and negatively correlated with NT-proBNP (Table 4) and maximum LAVi (Supplemental Table 5). CKD-EPI eGFR had no significant effect on LV filling E/e' and LVMI. The adjusted models remained significant with respect to markers of DD when CKD-EPI eGFR was replaced by MDRD eGFR (Table 4; Supplemental Table 5).

As shown in Figure 2, a significant interaction exists between renal function and diastolic markers with reference to NT-proBNP, (interaction p < 0.05). Individuals with lower average e' or higher composite diastolic score, rather than E/e', present with higher NT-proBNP levels across worsening eGFR category (or having severe proteinuria) (Figure 2; Supplemental Figure 2).

Discussion

This observational study had a large sample size, and describes the associations between renal function and several indices of DD in a cohort without prevalent HF. The majority (97%) of our study participants had a preserved renal function (eGFR of ≥ 60 ml/min/1.73 m^2). We demonstrated that in the condition of preserved LVEF, lower eGFR, estimated by either by MDRD or CKD-EPI formula, was significantly associated with lower LV e', greater maximum LAVi, and elevated NT-proBNP, suggesting that abnormal LV structure and diastolic relaxation may be present in subjects with early stages of kidney disease and progress as renal function declines. Instead, E/e' ratios, markers of LV filling pressures, had a lack of discriminatory power to detect subtle differences in diastolic function in subjects with mild renal impairment. Broadly, average e' was a more sensitive alternative for the assessment of LV DD in this population.

A noteworthy strength of our study was that we analyzed LV DD with risk stratification by two-dimensional information on GFR and proteinuria. Both markers are pivotal for kidney function, and combined assessment of these two factors is better than either one solely to characterize and to prognosticate CKD progression and relevant morbidities (26). Our study provided objective evidence to demonstrate that eGFR and proteinuria both present independent and synergistic effects on LV structure and DD, even in clinically asymptomatic stages. The pathophysiological mechanism linking renal dysfunction and LV abnormalities has been extensively explored in the past decade. Aside from conventional risk factors such as older age, diabetes, hypertension, smoking, and dyslipidemia (27), some CKD-specific nonconventional factors such as albuminuria (28), LVH (29), fibroblast growth factor 23 (30), deranged mineral metabolism (31), anemia (32) and inflammation (33) may all contribute to CVD. The term cardiorenal syndrome has been increasingly used to describe that severe dysfunction of these organs often occurs in combination rather than in isolation (34). Nevertheless, CKD is a clinical

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TABLE 1 Clinical characteristics of the entire cohort graded by eGFR and proteinuria.

	All (n = 4942)	CKD-EPI eGFR			*p* for trend	Proteinuria on Dipstick			*p* for trend
		≥ 90 (n = 2556)	60-89 (n = 2235)	30-59 (n = 151)		None (n = 3835)	Mild (n = 1030)	Severe (n = 77)	
Patient characteristics									
Age (year)	49.4 ± 11.2	45.3 ± 10.1	52.9 ± 10.4	65.3 ± 10.7	< 0.001	49.1 ± 11.2	49.8 ± 11.1	56.3 ± 12.3	< 0.001
Male gender	3254 (65.8%)	1448 (56.7%)	1696 (75.9%)	110 (72.8%)	< 0.001	2508 (65.4%)	693 (67.3%)	53 (68.8%)	0.21
Height (cm)	165.6 ± 8.5	165.1 ± 8.7	166.4 ± 8.3	164.2 ± 8.2	0.25	165.7 ± 8.6	165.6 ± 8.4	163.5 ± 9.1	0.02
Weight (kg)	67.4 ± 12.9	66.0 ± 13.7	68.8 ± 11.7	69.7 ± 12.4	0.001	67.2 ± 12.5	67.9 ± 14.0	71.5 ± 14.6	0.003
BMI (kg/cm^2)	24.4 ± 3.6	24.1 ± 3.8	24.7 ± 3.3	25.8 ± 3.8	< 0.001	24.3 ± 3.5	24.6 ± 4.1	26.6 ± 4.5	< 0.001
Body fat (%)	26.2 ± 6.7	26.8 ± 7.0	25.6 ± 6.3	27.0 ± 8.1	0.76	26.2 ± 6.6	26.4 ± 7.0	27.9 ± 8.4	0.03
SBP (mm Hg)	122.9 ± 17.2	120.2 ± 16.6	125.2 ± 16.9	134.9 ± 20.6	< 0.001	122.5 ± 16.5	123.2 ± 18.7	137.7 ± 22.8	< 0.001
DBP (mm Hg)	75.8 ± 10.9	74.4 ± 10.8	77.3 ± 10.7	78.9 ± 12.8	< 0.001	75.6 ± 10.6	76.1 ± 11.5	82.4 ± 13.9	< 0.001
Pulse rate (/min)	74.4 ± 10.2	74.9 ± 10.3	73.7 ± 9.9	76.9 ± 12.2	0.02	74.1 ± 10.0	75.3 ± 10.6	79.5 ± 13.4	< 0.001
Smoking	543 (11.0%)	284 (11.1%)	243 (10.9%)	16 (10.6%)	0.76	389 (10.1%)	144 (14.0%)	10 (13.0%)	0.001
Exercise	704 (14.2%)	353 (13.8%)	333 (14.9%)	18 (11.9%)	0.58	526 (13.7%)	170 (16.5%)	8 (10.4%)	0.13
Comorbidities									
Diabetes mellitus	334 (6.8%)	134 (5.2%)	164 (7.3%)	36 (23.8%)	< 0.001	226 (5.9%)	81 (7.9%)	27 (35.1%)	< 0.001
Hypertension	923 (18.7%)	318 (12.4%)	520 (23.3%)	85 (56.3%)	< 0.001	631 (16.5%)	253 (24.6%)	39 (50.6%)	< 0.001
Hyperlipidemia	404 (8.2%)	171 (6.7%)	201 (9.0%)	32 (21.2%)	< 0.001	291 (7.6%)	98 (9.5%)	15 (19.5%)	< 0.001
Cardiovascular disease	334 (6.8%)	113 (4.4%)	191 (8.5%)	30 (19.9%)	< 0.001	247 (6.4%)	76 (7.4%)	11 (14.3%)	0.03
Coronary artery disease	50 (1.0%)	14 (0.5%)	32 (1.4%)	4 (2.6%)	< 0.001	40 (1.0%)	8 (0.8%)	2 (2.6%)	0.99
Stroke	39 (0.8%)	14 (0.5%)	23 (1.0%)	2 (1.3%)	0.04	31 (0.8%)	7 (0.7%)	1 (1.3%)	0.91
Laboratory data									
Hemoglobin (g/dL)	14.3 ± 1.5	14.1 ± 1.6	14.6 ± 1.3	14.2 ± 1.8	0.65	14.3 ± 1.5	14.4 ± 1.6	14.5 ± 1.7	0.34
Fasting glucose (mg/dl)	101.2 ± 22.0	99.9 ± 23.0	102.0 ± 20.4	110.4 ± 26.3	< 0.001	99.6 ± 19.3	105.1 ± 27.7	126.8 ± 37.2	< 0.001
BUN (mg/dl)	11.9 ± 3.6	11.0 ± 3.1	12.6 ± 3.4	17.2 ± 5.8	< 0.001	11.7 ± 3.4	12.3 ± 3.9	14.0 ± 5.7	< 0.001
Uric acid (mg/dl)	5.9 ± 1.5	5.5 ± 1.4	6.2 ± 1.4	7.1 ± 1.8	< 0.001	5.9 ± 1.5	5.8 ± 1.5	6.4 ± 1.7	0.003
Creatinine (mg/dl)	0.92 ± 0.20	0.80 ± 0.14	1.02 ± 0.14	1.38 ± 0.24	< 0.001	0.9 ± 0.2	0.9 ± 0.2	1.1 ± 0.3	< 0.001
eGFR (MDRD)	88.5 ± 16.9	100.7 ± 13.0	77.1 ± 7.1	52.4 ± 7.4	< 0.001	89.2 ± 16.5	86.9 ± 17.5	77.2 ± 21.2	< 0.001
eGFR (CKD-EPI)	90.6 ± 15.7	102.9 ± 8.4	79.4 ± 7.6	50.8 ± 7.5	< 0.001	91.4 ± 15.2	88.9 ± 16.6	77.5 ± 21.0	< 0.001

(Continued)

TABLE 1 Continued

	All (n = 4942)	CKD-EPI eGFR			*p* for trend	Proteinuria on Dipstick			*p* for trend
		≥ 90 (n = 2556)	60-89 (n = 2235)	30-59 (n = 151)		None (n = 3835)	Mild (n = 1030)	Severe (n = 77)	
Total cholesterol (mg/dl)	201.6 ± 37.0	198.7 ± 36.1	204.7 ± 35.9	204.2 ± 58.3	0.08	201.4 ± 36.3	201.5 ± 38.7	210.2 ± 46.6	0.04
Triglyceride (mg/dl)	136.2 ± 107.1	130.4 ± 102.8	139.6 ± 78.4	181.9 ± 321.4	< 0.001	133.4 ± 92.8	141.1 ± 145.8	205.2 ± 132.4	< 0.001
LDL (mg/dl)	129.9 ± 33.2	126.8 ± 32.9	133.5 ± 32.7	129.8 ± 38.8	0.29	129.8 ± 33.0	130.1 ± 33.1	133.0 ± 42.7	0.40
HDL (mg/dl)	53.7 ± 15.1	54.8 ± 15.5	52.6 ± 14.7	49.0 ± 12.5	< 0.001	54.0 ± 15.1	52.7 ± 15.1	48.6 ± 14.5	0.002
Albumin (g/dl)	4.5 ± 0.3	4.5 ± 0.3	4.5 ± 0.3	4.4 ± 0.3	< 0.001	4.5 ± 0.3	4.5 ± 0.3	4.4 ± 0.5	< 0.001
Potassium (mEq/l)	4.0 ± 0.3	4.0 ± 0.3	4.0 ± 0.3	4.0 ± 0.4	0.02	4.0 ± 0.3	4.0 ± 0.3	3.9 ± 0.4	0.46
Sodium (mEq/l)	142.2 ± 1.9	142.0 ± 1.8	142.4 ± 1.9	142.0 ± 2.5	0.79	142.2 ± 1.9	142.3 ± 1.9	141.6 ± 2.6	0.03
Chloride (mEq/l)	103.9 ± 2.4	104.0 ± 2.2	103.9 ± 2.4	103.4 ± 3.1	0.01	104.0 ± 2.3	103.7 ± 2.5	102.8 ± 3.4	0.07
Phosphate (mg/dl)	3.6 ± 0.5	3.7 ± 0.5	3.6 ± 0.6	3.4 ± 0.6	< 0.001	3.6 ± 0.5	3.5 ± 0.6	3.5 ± 0.7	0.003
Calcium (mg/dl)	9.3 ± 0.4	9.2 ± 0.4	9.3 ± 0.4	9.4 ± 0.4	< 0.001	9.3 ± 0.4	9.3 ± 0.4	9.3 ± 0.6	0.31
NT-proBNP (pg/ml)	46.9 ± 109.9	35.5 ± 48.5	50.9 ± 100.7	173.5 ± 423.1	< 0.001	43.2 ± 59.3	54.1 ± 175.3	138.7 ± 428.8	< 0.001

eGFR, estimated glomerular filtration rate; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; BUN, blood urea nitrogen; LDL, low-density lipoprotein; HDL, high-density lipoprotein; NT-proBNP, N-terminal pro-brain natriuretic peptide.

TABLE 2 Echocardiographic findings of the entire cohort graded by eGFR and proteinuria.

	All (n = 4942)	CKD-EPI formula			*p* for trend	Proteinuria on Dipstick			*p* for trend
		≥ 90 (n = 2556)	60-89 (n = 2235)	30-59 (n = 151)		None (n = 3835)	Mild (n = 1030)	Severe (n = 77)	
Mitral E (cm/s)	69.2 ± 16.2	71.5 ± 16.2	66.9 ± 15.7	62.9 ± 19.2	< 0.001	69.3 ± 16.1	68.5 ± 16.7	67.9 ± 19.2	0.48
Mitral A (cm/s)	60.8 ± 19.2	57.9 ± 16.6	63.0 ± 20.7	77.0 ± 24.7	< 0.001	60.2 ± 19.2	61.7 ± 18.3	78.4 ± 23.8	< 0.001
E/A ratio	1.2 ± 0.4	1.3 ± 0.4	1.1± 0.4	0.9 ± 0.4	< 0.001	1.2 ± 0.4	1.2 ± 0.5	0.9 ± 0.3	< 0.001
DT (ms)	204.1 ± 39.0	200.4 ± 36.3	207.1 ± 40.5	221.9 ± 50.9	< 0.001	203.6 ± 38.4	204.5 ± 41.1	218.5 ± 42.5	0.002
IVRT (ms)	89.9 ± 15.2	87.9 ± 13.2	91.6 ± 16.1	99.2 ± 23.7	< 0.001	89.6 ± 14.5	90.9 ± 17.2	94.8 ± 18.1	0.01
Septal e' (cm/s)	8.0 ± 2.2	8.6 ± 2.2	7.5 ± 2.1	5.7 ± 1.7	< 0.001	8.1 ± 2.2	7.7 ± 2.3	6.4 ± 2.3	< 0.001
Lateral e' (cm/s)	10.4± 2.9	11.1 ± 2.9	9.7 ± 2.7	7.4 ± 2.2	< 0.001	10.5 ± 2.9	10.1 ± 3.0	8.4 ± 2.6	< 0.001
Average e' (cm/s)	9.2 ± 2.4	9.8 ± 2.4	8.6 ± 2.2	6.6 ± 1.8	< 0.001	9.3 ± 2.4	8.9 ± 2.5	7.4 ± 2.3	< 0.001
E/average e'	7.9 ± 2.6	7.6 ± 2.3	8.2 ± 2.6	10.2 ± 3.9	< 0.001	7.8 ± 2.5	8.1 ± 2.7	9.9 ± 3.4	< 0.001
PAP (mm Hg)	17.1 ± 5.3	16.8 ± 5.0	17.4 ± 5.6	18.3 ± 6.6	0.03	17.1 ± 5.2	16.9 ± 5.4	17.5 ± 5.4	0.63
LVMI (g/m^2)	76.9 ± 14.8	74.6 ± 14.1	78.7 ± 14.8	86.9 ± 16.1	< 0.001	76.5 ± 14.4	77.8 ± 15.7	86.4 ± 17.7	< 0.001

(Continued)

TABLE 2 Continued

	All (n = 4942)	CKD-EPI formula			*p* for trend	Proteinuria on Dipstick			*p* for trend
		≥ 90 (n = 2556)	60-89 (n = 2235)	30-59 (n = 151)		None (n = 3835)	Mild (n = 1030)	Severe (n = 77)	
IVS (mm)	9.0 ± 1.1	8.8 ± 1.1	9.2 ± 1.1	9.8 ± 1.2	< 0.001	9.0 ± 1.1	9.1 ± 1.2	9.6 ± 1.4	< 0.001
LVPW (mm)	9.0 ± 1.1	8.8 ± 1.0	9.2 ± 1.1	9.7 ± 1.0	< 0.001	9.0 ± 1.1	9.1 ± 1.1	9.6 ± 1.3	< 0.001
LVIDd (mm)	46.7 ± 3.6	46.3 ± 3.7	47.1 ± 3.5	48.1 ± 3.5	< 0.001	46.7 ± 3.6	46.7 ± 3.6	48.4 ± 4.1	< 0.001
LVIDs (mm)	29.3 ± 3.0	29.0 ± 2.9	29.5 ± 2.9	30.8 ± 3.9	< 0.001	29.3 ± 2.9	29.2 ± 3.0	30.6 ± 4.0	< 0.001
LVEDV (ml)	76.6 ± 14.3	75.0 ± 14.2	78.0 ± 14.1	82.4 ± 15.5	< 0.001	76.4 ± 14.2	76.7 ± 14.2	83.1 ± 17.2	< 0.001
LVESV (ml)	28.7 ± 7.5	28.0 ± 7.3	29.2 ± 7.3	32.7 ± 12.1	< 0.001	28.6 ± 7.4	28.7 ± 7.8	32.0 ± 11.4	< 0.001
LVEF (%)	62.7 ± 5.4	62.8 ± 5.3	62.7 ± 5.2	60.8 ± 8.2	< 0.001	62.7 ± 5.3	62.7 ± 5.6	61.9 ± 6.7	0.23
SV (ml)	47.9 ± 9.3	47.0 ± 9.2	48.8 ± 9.2	49.7 ± 10.5	0.001	47.8 ± 9.2	48.0 ± 9.4	51.1 ± 10.3	0.002
LAVmax/BSA (ml/m^2)	16.1 ± 5.8	15.9 ± 5.5	16.3± 6.0	17.4 ± 6.4	0.002	16.1 ± 5.8	16.1 ± 5.7	18.7 ± 7.0	< 0.001
LAVmin/BSA (ml/m^2)	10.1 ± 7.2	9.7 ± 7.1	10.2 ± 7.3	12.5 ± 8.5	< 0.001	9.9 ± 7.1	10.5 ± 7.5	12.9 ± 8.3	0.001
Composite diastolic score	0.12 ± 0.40	0.10 ± 0.36	0.13 ± 0.41	0.36 ± 0.66	< 0.001	0.11 ± 0.39	0.14 ± 0.43	0.26 ± 0.52	0.001

DT, deceleration time; IVRT, isovolemic relaxation time; PAP, pulmonary artery pressure; LVMI, left ventricular mass index; IVS, interventricular septum thickness; LVPW, left ventricular posterior wall thickness; LVIDd, left ventricular end-diastolic diameter; LVIDs, left ventricular end-systolic diameter; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; LVEF, left ventricular ejection fraction; SV, stroke volume; LAV, left atrial volume; BSA, body surface area.

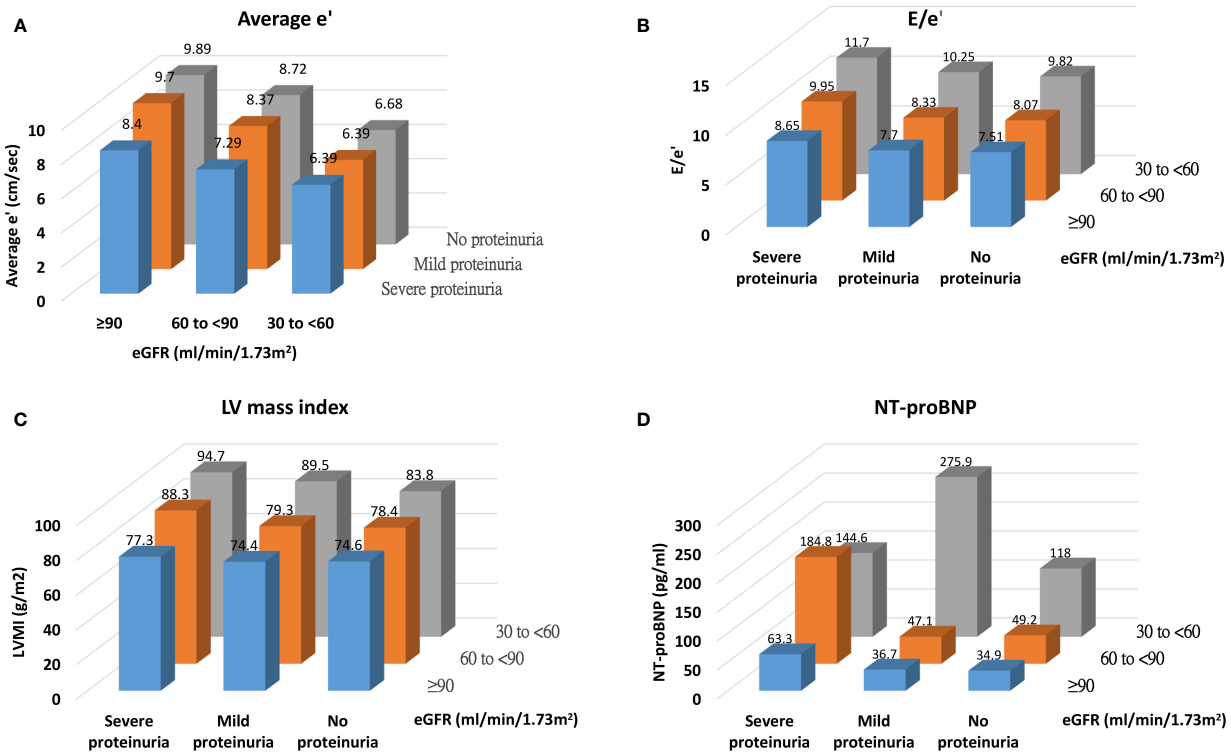

FIGURE 1
Distribution of cardiac structural and functional parameters [**(A)** average e', **(B)** E/e', **(C)** LV mass index, and **(D)** NT-proBNP] across categories of renal function.

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TABLE 3 Illustrations of average e′ of the entire cohort across graded MDRD/CKD-EPI eGFR and proteinuria categories.

	Average e′ (cm/s)		Proteinuria		
			Normal	Mildly to moderately increased	Severely increased
	CKD-EPI GFR		None	Mild	Severe
1	Normal or high	≥ 90	9.89	9.71	8.40
2	Mildly decreased	60–89	8.72	8.37	7.29
3a	Mildly to moderately decreased	45–59	6.68	6.39	6.39
	Average e′ (cm/sec)		Proteinuria		
			Normal	Mildly to moderately increased	Severely increased
	MDRD GFR		None	Mild	Severe
1	Normal or high	≥ 90	9.82	9.55	8.47
2	Mildly decreased	60–89	8.95	8.63	7.41
3a	Mildly to moderately decreased	45–59	6.80	6.41	6.35

Green, yellow, orange and red cells indicate low, moderately increased, moderate and high relative risks of cardiovascular mortality and prognosis of chronic kidney disease as per the KDIGO 2012 guidelines (19).

TABLE 4 Association of CKD-EPI and MDRD eGFR with markers of diastolic function and cardiac structure in multivariate-adjusted linear regression models.

Variables	CKD-EPI formula							
	Average e′		E/e′		LVMI†		NT-proBNP	
(per 10-ml/min/ 1.73m^2 increment)	Coef. (95% CI)	*p*-value	Coef. (95% CI)	*p*-value	Coef. (95% CI)	*p*-value	Coef. (95% CI)	*p*-value
Univariate	0.63 (0.59, 0.67)	< 0.001	−0.38 (−0.43, −0.33)	< 0.001	−2.11 (−2.39, −1.83)	< 0.001	−13.6 (−15.6, −11.6)	< 0.001
Multivariate								
Model 1	0.09 (0.05, 0.13)	< 0.001	−0.05 (−0.11, 0.00)	0.06	−0.17 (−0.57, 0.17)	0.32	−12.3 (−14.7, −9.9)	< 0.001
Model 2	0.06 (0.02, 0.10)	0.004	−0.04 (−0.10, 0.01)	0.11	−0.22 (−0.56, 0.11)	0.19	−12.3 (−14.9, −9.8)	< 0.001
Multivariate + Echo Data								
Model 2 + LVMI†	0.07 (0.03, 0.11)	0.002	−0.06 (−0.12, 0.00)	0.06	–	–	−12.9 (−15.8, −10.0)	< 0.001
Model 2+ LVEF	0.06 (0.02, 0.10)	0.01	−0.04 (−0.10, 0.01)	0.11	−0.23 (−0.57, 0.11)	0.18	−12.4 (−15.0, −9.8)	< 0.001
Model 2 + SV	0.06 (0.02, 0.10)	0.01	−0.04 (−0.10, 0.01)	0.11	0.12 (−0.17, 0.40)	0.42	−12.6 (−15.2, −10.1)	< 0.001
Multivariate + Echo Data + Proteinuria								
Model 3	0.05 (0.01, 0.09)	0.01	−0.04 (−0.09, 0.02)	0.17	−0.24 (−0.58, 0.10)	0.17	−12.0 (−14.5, −9.4)	< 0.001
Model 3 + LVMI†	0.06 (0.02, 0.11)	0.004	−0.05 (−0.11, 0.01)	0.09	–	–	−12.6 (−15.5, −9.7)	< 0.001

(Continued)

TABLE 4 Continued

Variables	CKD-EPI formula							
	Average e′		E/e′		LVMI†		NT-proBNP	
(per 10-ml/min/ 1.73m^2 increment)	Coef. (95% CI)	*p*-value	Coef. (95% CI)	*p*-value	Coef. (95% CI)	*p*-value	Coef. (95% CI)	*p*-value
Model 3 + LVEF	0.05 (0.01, 0.09)	0.01	−0.04 (−0.09, 0.02)	0.17	−0.25 (−0.58, 0.09)	0.15	−12.1 (−14.6, −9.5)	< 0.001
Model 3 + SV	0.05 (0.01, 0.09)	0.01	−0.04 (−0.09, 0.02)	0.17	0.14 (−0.15, 0.42)	0.35	−12.3 (−14.9, −9.7)	< 0.001
	MDRD formula							
Variables	Average e′		E/e′		LVMI†		NT-proBNP	
(per 10-ml/min/1.73m^2 increment)	Coef. (95% CI)	*p*-value	Coef. (95% CI)	*p*-value	Coef. (95% CI)	*p*-value	Coef. (95% CI)	*p*-value
Univariate	0.40 (0.36, 0.43)	< 0.001	−0.21 (−0.26, −0.17)	< 0.001	−1.16 (−1.42, −0.89)	< 0.001	−9.9 (−11.7, −8.0)	< 0.001
Multivariate								
Model 1	0.08 (0.05, 0.12)	< 0.001	−0.02 (−0.06, 0.02)	0.36	−0.35 (−0.08, −0.63)	0.012	−8.4 (−10.5, −6.4)	< 0.001
Model 2	0.04 (0.01, 0.07)	0.02	−0.03 (−0.07, 0.02)	0.26	−0.36 (−0.09, −0.64)	0.01	−8.5 (−10.6, −6.4)	< 0.001
Multivariate + Echo Data								
Model 2 + LVMI†	0.05 (0.01, 0.08)	0.03	−0.03 (−0.08, 0.02)	0.18	–	–	−9.1 (−11.4, −6.7)	< 0.001
Model 2+ LVEF	0.04 (0.01, 0.08)	0.01	−0.03 (−0.07, 0.02)	0.23	−0.37 (−0.09, −0.64)	0.008	−8.6 (−10.7, −6.5)	< 0.001
Model 2 + SV	0.04 (0.01, 0.07)	0.02	−0.03 (−0.07, 0.02)	0.23	0.19 (−0.04, 0.42)	0.11	−8.8 (−10.9, −6.7)	< 0.001
Multivariate + Echo Data + Proteinuria								
Model 3	0.04 (0.00, 0.07)	0.03	−0.02 (−0.06, 0.02)	0.38	−0.38 (−0.10, −0.65)	0.01	−7.9 (−10.0, −5.8)	< 0.001
Model 3 + LVMI†	0.04 (0.01, 0.08)	0.02	−0.03 (−0.08, 0.02)	0.26	–	–	−9.5 (−10.8, −6.1)	< 0.001
Model 3 + LVEF	0.04 (0.00, 0.07)	0.03	−0.02 (−0.07, 0.02)	0.36	−0.38 (−0.11, −0.66)	0.01	−8.0 (−10.1, −5.8)	< 0.001
Model 3 + SV	0.04 (0.00, 0.07)	0.04	−0.02 (−0.07, 0.02)	0.35	0.20 (−0.03, 0.43)	0.09	−8.2 (−10.3, −6.1)	< 0.001

Model 1 was adjusted for age + gender;
Model 2 was adjusted for age, gender, BMI, SBP, hypertension, diabetes, CVD, fasting glucose, total cholesterol, HDL, and smoking;
Model 3: Model 2 + proteinuria;
†Model 1 and Model 3 were not adjusted for BMI for LVMI.

continuum. Our study offered additional insight into heart–kidney interplay, which begins in the early stage of either disease when LVEF and GFR are preserved. To date, early detection of cardiorenal interaction is not easy in the clinically asymptomatic stage without the help of novel biomarkers (such as neutrophil gelatinase-associated lipocalin [NGAL], kidney injury molecule-1 [KIM-1], cystatin C, natriuretic peptides, and cardiac troponins) (35, 36).

On the other hand, NT-proBNP is of the natriuretic peptide family and has excellent *in vitro* stability (37) and diagnostic ability

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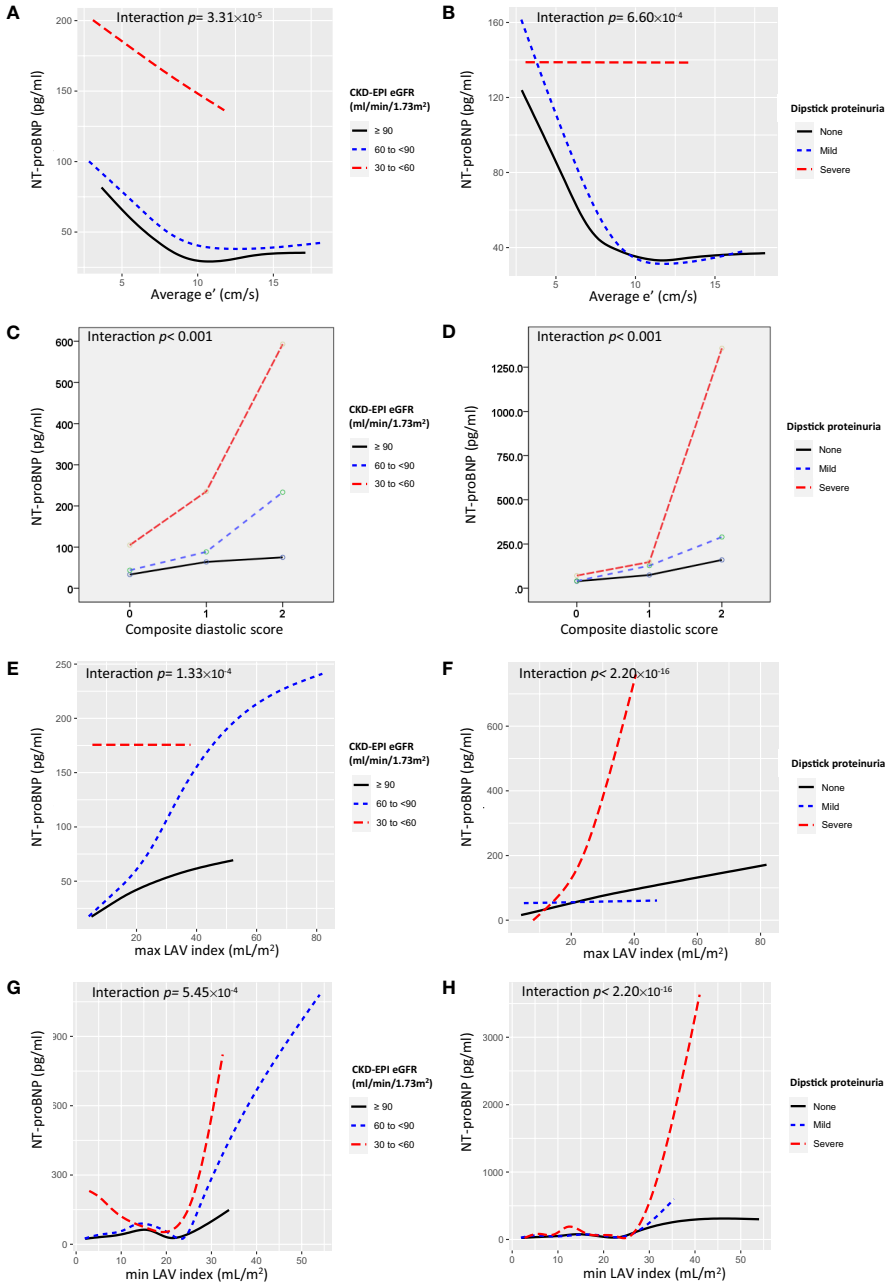

FIGURE 2
Interaction plots for NT-proBNP for the effects of **(A)** average e' and eGFR, **(B)** average e' and proteinuria, **(C)** composite diastolic score and eGFR, **(D)** composite diastolic score and proteinuria, **(E)** maximum LAV index and eGFR, **(F)** maximum LAV index and proteinuria, **(G)** minimum LAV index and eGFR, and **(H)** minimum LAV index and proteinuria.

in the assessment of asymptomatic LV dysfunction in patients at risk for HF development (25). NT-proBNP levels are positively correlated with the severity of DD (25, 38); however, interpretation should always consider subjects' age, gender (25), and renal function (39), and yet data regarding possible interactions between DD and renal function on NT-proBNP level in a large, asymptomatic Asian population remain unexplored. Using NT-proBNP as an indicator of LV DD, our interaction plots showed a marked increase in NT-proBNP in subjects in the severest categories of renal function (i.e., having eGFR between 30 and < 60 ml/min/1.73 m^2 or heavy dipstick proteinuria) in comparison with those having better renal function. Moreover, an even steeper elevation in NT-proBNP was noted in subjects in the worst renal function categories with parallel lower average e' (or in the category of composite diastolic score equal to 2 or higher LAV index), rather than E/e', suggesting that the interaction between heart and kidneys might grow vehemently and disproportionately as either organ begins to lose some function. Of note, although prior studies have reported the utilization of CKD-EPI equation as a more applicable and useful surrogate marker than MDRD for CKD in Asians (40, 41), in our study these two equations displayed similar trends in associations with cardiac diastolic markers.

This study has several limitations. First, although proteinuria or albuminuria is more accurately assessed in terms of urinary protein-to-creatinine or albumin-to-creatinine ratio (ACR), calculated by dividing the urine protein or albumin by urine creatinine during morning urine collection, the urine dipstick test is a simple, fast, and inexpensive tool to screen and diagnose urinary tract problems, including proteinuria. Standard reagent strip dipsticks are especially sensitive to albumin, and even a dipstick test result of trace or higher identifies ACR ≥ 300 mg/g with 100% sensitivity and 83.7% specificity (42). Our study showed a graded pattern of a series of LV measurements with the severity of dipstick results, suggesting that urinalysis is a useful first step to assess proteinuria. Second, the individuals of our cohort were included in a tertiary medical center, which might introduce selection bias. Third, our cohort did not record their drug-taking history. For example, β-blockers, renin–angiotensin–aldosterone system blockers, sodium–glucose cotransporter 2 inhibitors (SGLT2i), and glucagon-like peptide-1 receptor agonists (GLP1 RA) have cardioprotective and renoprotective effects, while non-steroidal anti-inflammatory drugs (NSAIDs) and contrast media may hamper renal function. However, this screening program was conducted between 2009 and 2012, when SGLT2i and GLP1 RA were unavailable. Still, certain missing drug information might elicit treatment bias. Lastly, our database did not contain clinical outcomes, and the correlations to outcomes might be more important than those to surrogate markers.

Conclusions

In conclusion, in this large cohort of participants with early CKD and without clinical HF, we found a strong association between renal function and LV structural and functional change during diastole. Average e', instead of E/A or E/e' ratios, was more sensitive to detect LV DD in this population. Heart–kidney crosstalk starts in the early asymptomatic stage. In this regard, renal function in terms of eGFR and dipstick proteinuria provide crude information on subjects' LV diastolic function, and prompt interventions might be needed to hinder the devastating cardiorenal crosstalk from the perspective of preventive medicine.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

This study was approved by the institutional review board of MacKay Memorial Hospital (14MMHIS202). The informed consent from the patients/participants was waived because of the retrospective nature of this study and the analysis used anonymous clinical data.

Author contributions

Authors' contributions: P-CW drafted the manuscript. K-TS, J-LL and T-CH collected data. C-LH and C-JW provided the original conception and design of the study. Y-HL, C-HS and H-IY modified the statistical models critically and provided technical and statistical support during the analyses. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The reviewer Y-WW declared a past co-authorship with the authors H-IY, C-JW, and C-LH to the handling editor.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneph.2023.1071900/full#supplementary-material

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Case Report: Multisystem inflammatory syndrome in children with associated proximal tubular injury

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Introduction: SARS-CoV-2 infection in the pediatric population can be associated with a multiorgan inflammatory syndrome called children's multisystem inflammatory syndrome (MIS-C). The kidneys can be affected by a broad spectrum of possible injuries, whose pathogenetic mechanisms are still unclear.

Case report: We report the case of a 5-year-old boy with severe cardiac involvement in the context of MIS-C. After two weeks of hospitalization, an abdominal ultrasound showed massive bladder "debris", followed by the onset of normoglycemic glycosuria. Over time, there was a progressive increase in glycosuria, and the presence of a mat of amorphous phosphate crystals was evidenced on urinary sediment. Together with the findings of hypo-uricemia, increased urinary uric acid, and globally increased urinary amino acids, a clinical picture of kidney proximal tubular damage with secondary Fanconi-like syndrome took shape.

Discussion: This case report describes the case of a patient with MIS-C with cardiac and kidney involvement characterized by proximal tubular damage, which slowly improved but still persisted at the 8-month follow-up. The pathogenesis of the damage is unclear and probably multifactorial.

KEYWORDS

MIS-C multisystem inflammatory syndrome in children, proximal tubule injury, bladder debris, Fanconi syndrome, kidney injury, SARS – CoV – 2

Introduction

Kidney dysfunction is a common consequence of SARS-CoV-2 infection (1, 2), having been reported in adults and, to a lesser degree, in children. Kidney consequences of COVID-19 can include a broad spectrum of damages, ranging from acute kidney injury (AKI) with glomerular or tubular injury to mild proteinuria and/or hematuria (3).

In children, SARS-CoV-2 infection can manifest as a multisystem inflammatory syndrome (MIS-C) that typically occurs 3–6 weeks after mild or asymptomatic COVID-19 disease (4). This rare disorder is characterized by a hyperinflammatory state with a range of clinical presentations that can involve multiple organs with a generalized increase in inflammatory biomarkers, such as C-reactive protein (CRP), ferritin, D-dimer, and lactate dehydrogenase (5, 6). Common manifestations include fever, rash, abdominal pain, and gastrointestinal symptoms, mimicking appendicitis in some children (4). Cardiological involvement is characterized by diminished left ventricular systolic function with or without coronary artery abnormalities, fluid overload or hypotension, and an increase in pro-brain natriuretic peptide and cardiac enzymes. The kidneys can be affected by a broad spectrum of possible injuries; the incidence of AKI ranges from 10% to 46% (7) and its pathogenetic mechanisms are still unclear and probably multifactorial (8, 9).

Here, we report a case of MIS-C with peculiar nephro-urological involvement and ultra-sonographic features characterized by proximal tubule dysfunction.

Case description

A previously healthy 5-year-old boy was admitted to hospital in February 2022 due to fever lasting for 6 days with spikes up to 40°C, accompanied by vomiting, diarrhea, and intense abdominal pain. Because of suspected intestinal adenitis with neutrophilic leukocytosis and markedly increased CRP (26 mg/dL n.l. < 0.46), the patient underwent a laparoscopic appendicectomy that showed an uninjured appendix. Considering the recent paucisymptomatic SARS-CoV-2 infection confirmed by an antigenic pharyngo-nasal swab test and the persistent fever unresponsive to antibiotics, further investigations were carried out. Blood tests revealed the presence of a hypochloremic metabolic alkalosis and increased blood urea nitrogen (max value 60mg/dl), troponin I, and NT-Pro-BNP, while other parameters were normal, including urine examination (see Table 1). On admission, Creatinine was 0.4 mg/dL. It then progressively decreased and stabilized at 0.2-0.25 mg/dL, together with the decrease in blood urea nitrogen values. The echocardiogram demonstrated diffuse hypokinesia with a reduced left ventricular ejection fraction (LVEF 35%), a right ventricle with volumetric overload, and a left coronary artery ectasia. The case was suggestive of MIS-C; therefore, steroids (methylprednisolone 30mg/kg), immunoglobulins (IGIV 1gr/kg), and immunosuppressive therapy with anti-IL-1 receptor antagonist (Anakinra 200mg twice daily) were started. In addition, supportive therapy with furosemide was administered and, on day 14, an ACE inhibitor drug (enalapril 0.05mg/kg) was added due to persisting high values of arterial blood pressure. Finally, anticoagulant therapy with heparin (2000 IU/day) was started and was later replaced by anti-platelet therapy (aspirin 75 mg/day) on day 11 (see Figure 1).

The therapy was well tolerated, and progressive clinical, laboratory, and instrumental improvements were observed. In particular, the echocardiograms showed a progressive normalization of LVEF and the left coronary artery (Figure 1).

On day 18, during an abdominal ultrasound performed as surgery follow-up, the presence of bladder debris was discovered (Figures 2A, B), despite the absence of other signs of urinary tract infection.

Thus, more examinations were performed. They showed a persistent normal renal function with normoglycemic glycosuria, confirmed by the urinary sediment and the 24-hour urine collection (glucose 1.1 g/24h n.l < 0.1), together with hypercalciuria (rCaU/CrU 0.66 n.l < 0.2) and mild proteinuria (0.18 g/24h n.l. < 0.15). In addition, the urinary sediment reported numerous amorphous phosphate crystals. Due to suspicions of Fanconi syndrome, further tests were performed: uricemia had decreased (1,6 mg/dl n.l. > 2) and hyperuricosuria was found together with a significant increase in all urinary amino acids excreted (see Table 1). During the ultrasound examination performed on day 29, a sharp decrease of multiple echoes of hyperechogenic corpuscular material in suspension was reported, with no morphological abnormalities of the kidneys and urinary tract (Figures 2C, D).

Thus, after a few days, the patient was discharged in good condition, with normal echocardiography and urinary exams. They were given instructions to continue with oral steroid therapy and antiplatelet and antihypertensive therapy, which were later stopped due to the normalization of blood pressure values. At the 8-month follow-up, no bladder debris was present upon ultrasound examination, while urinalysis showed an improvement of persistent proximal renal tubule damage characterized by increased amino acids, sodium chloride, and uric acid excretion.

Discussion

We have described the case of a child diagnosed with MIS-C with severe cardiac involvement, who experienced alterations in urinalysis consisting of normo-glycemic glycosuria, amino-aciduria, hyperuricosuria, and the presence of amorphous phosphate crystals. These findings, together with decreased uricemia, are consistent with proximal tubule damage, more precisely, a Fanconi-like syndrome tubulopathy that persists over months. MIS-C is thought to be an exaggerated immune response to SARS-CoV-2 infection, but the exact pathogenesis of multiorgan dysfunction is still unknown. Very few studies have described the incidence and characteristics of renal complications in MIS-C. AKI is frequently reported in children diagnosed with this disorder (7–10), but no studies have specifically reported acute tubular involvement.

The pathophysiology of renal dysfunction seems to be multifactorial. Hemodynamic, iatrogenic, viral, or immune-mediated causes could have all contributed to the development of both pre-renal and renal parenchymal effects (7). Firstly, the

TABLE 1 Patient's blood and urine tests data.

	Admission	+2 days from admission	+14 days from admission	+22 days from admission	+33 days from admission	8 months follow-up
Hemoglobine (g/dl)	10,5	10	12,6	–	12	12,4
White blood cells (n°/uL)	24350	12900	24030	–	12300	11200
Neutrophils (n°/uL)	21570	9040	13070	–	8040	4090
Lymphocytes (n°/uL)	1660	2200	9060	–	3090	5800
Platelets (n°/uL)	429000	500000	580000	–	324000	512000
Creatinine (mg/dL)	0,4	0,44	0,25	–	0,2	0,3
Blood urea nitrogen (mg/dL)	40	60	36	–	35	46
GOT (U/L)	40	30	40	–	30	27
GPT (U/L)	60	50	80	–	50	19
CRP (mg/dL) [n.l. < 0.46)]	17,87	6	neg	–	neg	neg
Procalcitonin (ng/ml) [n.l. < 0.5)]	48,87	15	–	–	–	–
Ferritin (ng/ml)	1277	428	968	–	–	15
NT-pro BNP (pgr/ml)	> 35000	13286	182	–	–	17
Troponin I (ng/ml) [n.l. <10]	neg	0,17	–	–	neg	neg
Albumin (mg/dl)	2400	3500	3664	–	3370	4065
D-dimer (mg/L FEU) [n.l. < 0.55)]	12,37	5,45	0,62	–	neg	neg
Uric acid (mg/dl) [n.l. > 2]	–	2,7	2,5	–	1,6	3,7
Proteinuria on 24h collection (g/24h) [n.l. < 0.15]	–	–	–	–	0,18	0,08
Glycosuria on 24h collection (g/24h) [n.l < 0.1]	–	–	–	–	1,1	0
Natriuresis on 24h collection (mEq/24h) [n.l < 150]	–	–	–	–	231,4	171
Chloruria on 24h collection (mEq/24h) [n.l < 125]	–	–	–	–	247,7	167,8
Uricuria (mg/dl)	–	–	–	–	170,2	114,4
Phosphaturia (mg/dl)	–	–	–	–	184,2	95,9
rCaU/CrU [n.l < 0.2]		–	–	–	0,66	0,15
Urinalysis	–	–	Glucose: tracks; proteins: absent	Glucose 1,8gr/L; proteins: absent	Glucose and proteins absent	Glucose and proteins absent
Urinary amino acids chromatography (umol/mmcrea)						
ALA [n.l 27 – 92]	–	–	–	–	281	178
ARG [n.l 0 - 7]	–	–	–	–	21	20
ASP [n.l 2 - 8]	–	–	–	–	47	–
CYS [n.l 4 - 11]	–	–	–	–	25	10
GLN [n.l 52 - 133]	–	–	–	–	486	210
GLY [n.l 91 - 246]	–	–	–	–	800	619
HIS [n.l 61 - 216]	–	–	–	–	729	293
LYS [n.l 10 - 68]	–	–	–	–	379	285

(Continued)

TABLE 1 Continued

	Admission	+2 days from admission	+14 days from admission	+22 days from admission	+33 days from admission	8 months follow-up
ORN [n.l 0 - 7]	–	–	–	–	8	6
SEU [n.l 38 - 93]	–	–	–	–	587	322
TAU [n.l 17 - 230]	–	–	–	–	278	285
THR [n.l 9 - 39]	–	–	–	–	518	257

GOT, Glutamic Oxaloacetic Transaminase; GPT, Glutamate Pyruvate Transaminase; CRP, C-Reactive Protein.

reduced cardiac ejection fraction and the capillary leakage due to the inflammatory state both lead to kidney hypoperfusion and consequent ischemic damage, ischemic tubular damage. Secondly, our patient experienced a subclinical AKI, with increased values of blood urea nitrogen; creatinine, albeit not enough to meet the KDIGO (Kidney Disease Improving Global Outcomes) criteria for AKI; and elevated serum urea/creatinine ratio. Moreover, the contribution of drug toxicity to kidney injury cannot be excluded. Diuretics and iACE could have also contributed to glomerular hypoperfusion and consequent pre-renal damage. However, iatrogenic kidney damage due to steroids, IL-1 receptor antagonists, or immunoglobulins is very unlikely and can be excluded. Finally, a possible contribution of immune overactivation or a direct kidney tropism of the SARS-CoV-2 virus leading to tubular injury and podocytopathy cannot be ruled out. SARS-CoV-2 virus is suggested to reach proximal tubule and podocytes through spike (S) glycoprotein and ACE-2 receptor binding, and the consequent transmembrane serine proteases (TMPRSSs) action, which facilitates membrane fusion (7, 11–13). In the human kidney, ACE-2 and TMPRSSs are expressed in the nephron and demonstrate high tropism, primarily in the proximal tubule apical membrane, along with other proteases necessary for SARS-CoV-2 (14, 15). The development of a hyperinflammatory state with similar aspects to cytokine release syndrome has been hypothesized, with a possible crucial role of IL-6 IL-2R (7) in worsening renal function.

Proximal tubule dysfunction in adults was investigated in a recent study by A. Werion et al. (12). They showed that the dysfunction occurs early during the course of SARS-CoV-2 infection, and it is characterized by low molecular weight proteinuria, defective handling of uric acid and phosphate, and aminoaciduria. Normoglycemic glycosuria was not evidenced in their cohort of patients. Moreover, the aminoaciduria they detected in 46% of patients tested was limited to neutral amino acids, while in our patient, a generalized aminoaciduria was found.

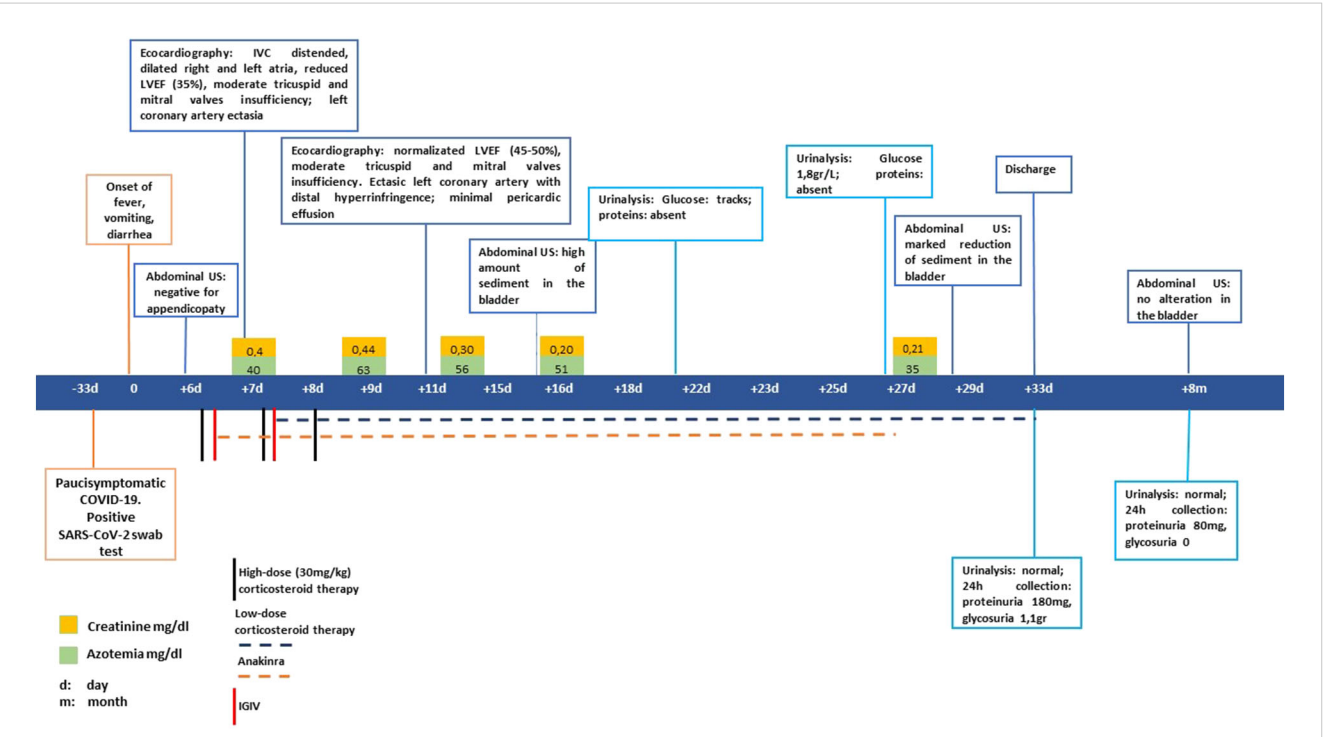

FIGURE 1
Timeline of clinical events, diagnostic examinations, and treatments of the patient.

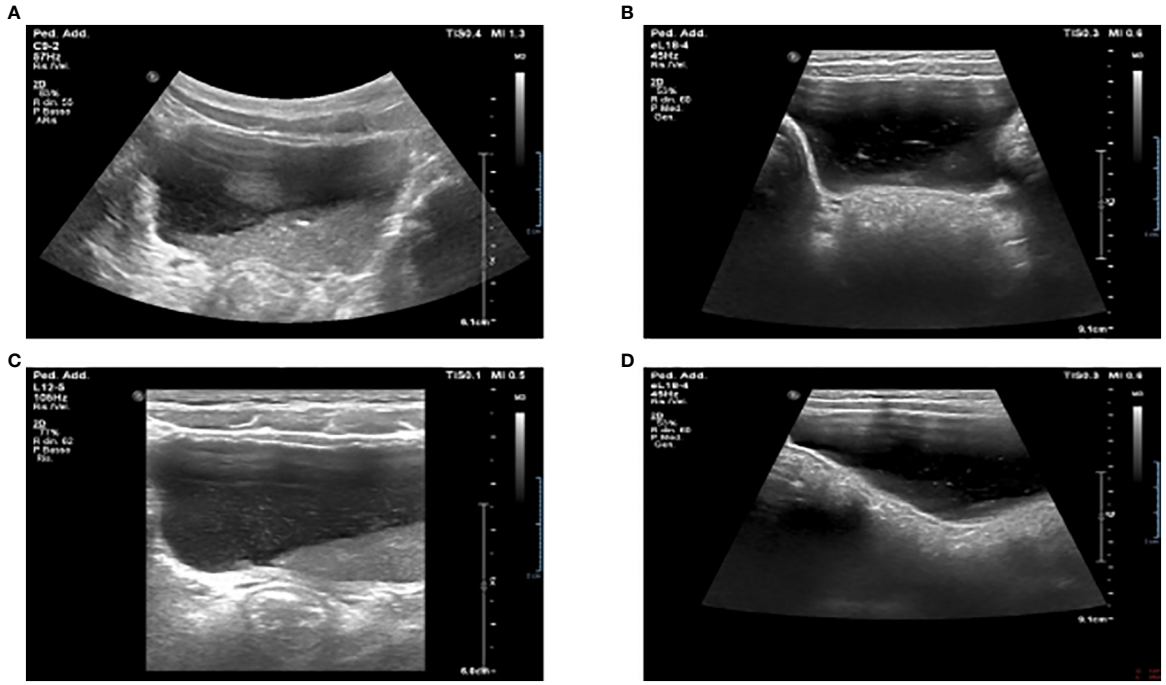

FIGURE 2
Ultrasound examination showing massive bladder debris in a 5-year-old child affected by MIS-C **(A, B)**. First incidental finding of massive sediment and floating bladder debris at abdominal ultrasound examination. **(C, D)**. Reduction of the debris after X days at ultrasound control examination.

Our patient did not present a clinical AKI, but the results obtained are coherent with an alteration of the proximal renal tubular structure. Because we chose not to perform a kidney biopsy, the exact etiology of the damage is unknown, and we can only speculate on the possible causes behind it. The abovementioned presence of bladder debris could be associated with a concomitant urinary tract infection (16), a clinical condition that was ruled out in our patient. Nevertheless, the significance of bladder debris in the alteration of urine analysis is still unclear and deserves further study (17). In our case, we ruled out the presence of urinary tract infection. Thus, the significance of bladder debris is attributable to an aspecific urine alteration with a massive presence of phosphate crystals.

Subclinical AKI, defined as the presence of kidney dysfunction not meeting the criteria for AKI, has been described in SARS-CoV-2 infection. Even if clinical data are still poorly known, especially in MIS-C, it seems to be correlated to a more severe course of the disease (18). Our patient experienced a subclinical AKI by presenting, at admission, serum creatinine values that were double those when discharged. These persisted for 10 days before starting to decrease. A few days after reaching the peak of serum creatine, abdominal US was performed with the incidental evidence of bladder debris and urinary alterations. Unfortunately, no urine examinations were performed before this because there was no suspicion of nephron-urological involvement. We, therefore, cannot determine exactly when kidney tubular injury arose.

Increasing evidence suggests that subclinical AKI and urinary alterations are clinically significant and independently associated with adverse outcomes (19, 20). It also underlines the important role of urinary biomarkers and urinary analysis in the recognition of precocious subclinical and clinical AKI (21, 22).

Regardless of the etiopathology of the tubular injury, this illustrative case aims to emphasize the relevance of urinary examinations in this clinical setting, with the ultimate goal of aiding the early recognition of clinical and subclinical AKI.

The primary goals of therapy in MIS-C are to reduce systemic inflammation, to give hemodynamic support in cases of cardiac dysfunction, and to treat singular organ involvement. Most widely used pharmacologic approaches consider IVIG and steroids, anakinra (IL-R1 antagonist), infliximab (TNF-alfa blocker), or tocilizumab (IL-6 antagonist) in cases of persistent inflammatory state and poor response to first-line therapy (23). If renal damage is present, the therapy is based, at first, on renal supportive care, optimizing hemodynamics through infusive therapy or diuretics, depending on the volemic status of the patient. Critical cases could require kidney replacement therapy (7).

In conclusion, we suggest considering possible renal involvement in cases of MIS-C, and in particular, assessing renal function and performing frequent urine tests in order to recognize AKI and dysfunction of the kidney proximal tubule as early as possible.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

Ethics statement

Written informed consent was obtained from the minor(s)' legal guardian/next of kin for the publication of any potentially identifiable images or data included in this article.

Author contributions

SO and EP contributed to the conception of the study and wrote the paper. MS, AA, GMG, CP, SV, SP, AF, FL, CB and EV reviewed the manuscript and contributed to the final draft. All authors contributed to the article and approved the submitted version.

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Conflict of interest

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Publisher's note

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Uncontrolled hypertension is associated with increased risk of graft failure in kidney transplant recipients: a nationwide population-based study

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Backgroud: Hypertension is highly prevalent in patients with kidney transplantation caused by transplantation-related immunologic or non-immunologic risk factors. However, whether a strict definition of hypertension (≥130/80 mmHg) and subdivided blood pressure (BP) groups are associated with an increased risk of graft failure after kidney transplantation using a nationwide large cohort study are still unknown.
Methods: Using Korean National Health Insurance Service data, we included 14,249 patients who underwent kidney transplantation from 2002 to 2016. Patients were categorized into five BP groups according to the 2021 Kidney Disease: Improving Global Outcomes practice guidelines for BP management: normal BP (<120/80 mmHg), elevated BP (120–129/ < 80 mmHg), incident hypertension (≥130/80 mmHg), and controlled or uncontrolled hypertension with anti-hypertensive medications.
Results: The primary outcome was graft failure, which occurred in 1934 (13.6%) participants during the 6-year follow-up. After adjusting for covariates, hypertension was associated with a higher risk of graft failure [Adjusted hazard ratio (AHR), 1.70; 95% confidence interval (CI), 1.48–1.96)] than no-hypertension. The AHR for graft failure was the highest in patients with uncontrolled hypertension (AHR, 2.13; 95% CI, 1.80–2.52). The risk of graft failure had a linear relationship with systolic and diastolic BP, and pulse pressure.
Conclusions: In this nationwide population-based study, hypertension ≥130/80 mmHg based on the 2021 KDIGO BP guidelines in kidney transplantion recipients, and elevated systolic and diastolic BP, and pulse pressure were associated with the risk of developing graft failure in kidney transplant recipients.

KEYWORDS
kidney, transplantation, hypertension, graft failure, risk

Introduction

Hypertension is highly prevalent in patients with kidney transplantation (1–3). Various factors affect blood pressure (BP) in kidney transplant recipients (KTR) including acute and chronic renal allograft dysfunction, retained native kidney, denervated transplanted kidney, and the regular use of calcineurin inhibitors and steroids (3–5). These factors may impair the

autoregulation of BP or result in sodium and water retention (6, 7). After kidney transplantation, increased blood pressure is associated with deleterious allograft and patient survival (8–13). Therefore, optimal BP management is essential to improve graft outcomes and mortality rates.

Recently, the target of BP management was lowered to <120 mmHg in patients with chronic kidney disease based on the Systolic BP Intervention Trial (SPRINT), in which the intensive lowering of clinic systolic BP (SBP) reduced the risk for cardiovascular disease and all-cause mortality (14). On the other hand, the 2021 Kidney Disease: Improving Global Outcomes (KDIGO) practice guidelines for BP management in adult KTR still recommends a target of <130/80 mmHg using standardized office BP measurement, consistent with the previous 2009 KDIGO BP guidelines for KTR (15, 16). Nevertheless, previous studies did not give a confirmative result to an increased risk of graft failure when the target kidney transplant recipient BP was ≥130/80 mmHg because they adopted an old definition of hypertension (8–11, 13, 17). Therefore, in this large nationwide population-based study, we investigated the association between hypertension based on the definition of 2021 KDIGO guidelines for KTR, subdivided BP components, and the risk of graft failure among patients with kidney transplants.

Materials and methods

Korean national health insurance service (KNHIS) data

In this study, we used a national health insurance claims database established by the KNHIS, which includes all claims data provided by the KNHIS and Medical Aid programs. Data extracted from the KNHIS database were considered representative of the entire South Korean population, and the details of this database have been previously described (18). Depending on their occupations, all insured Koreans undergo an annual or biennial health examination that is supported by the KNHIS. Anonymized data are publicly available from the National Health Insurance Sharing Service and can be accessed at https://nhiss.nhis.or.kr/bd/ab/bdaba000eng.do. The study protocol was approved by the Institutional Review Board of Chonnam National University Hospital (CNUH-EXP-2022-274) and has therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. The requirement for written informed consent was waived by the review board because anonymous and de-identified information was used for analysis.

Main study population and follow-up

Initially, 38, 227 patients who underwent kidney transplantation from 2002 to 2016 were identified. Of these, we included patients who had undergone health checkups from 2009 to 2017 because the questionnaire form changed in 2009. The index date was the date of the first health check-up after 2009. We excluded those aged <20 years, and those with graft failure or death before the index date and within 1-year of follow-up. We also excluded subjects with missing health examination data. Finally, 14, 249 KTR were included in the study and were followed-up from the index date to the date of graft failure during the follow-up period, death, loss of health insurance qualification, or the end of the study period (December 31, 2019). A detailed enrollment flowchart is shown in **Figure 1**.

Definitions

BP was measured by trained clinicians at least twice, using a mercury or automatic sphygmomanometer with the participants in a sitting position following a minimum of 5 min of rest in the index date. Hypertension was defined as SBP ≥ 130 mmHg or diastolic BP (DBP) ≥ 80 mmHg in the health examination database or a history of using antihypertensive medications according to the 2021 KDIGO BP guidelines and 2017 American College of Cardiology/American Heart Association guidelines (15, 19). Moreover, participants were classified into five hypertension groups as follows: (1) normal BP (<120/80 mmHg, patients with no prior diagnosis of hypertension); (2) elevated BP (120–129/ < 80 mmHg, but those with no prior diagnosis of hypertension); (3) incident hypertension without medication (≥130/80 mmHg, but not taking antihypertensive medications; (4) controlled hypertension (<130/80 mmHg, patients diagnosed with and taking medication for hypertension); and (5) uncontrolled hypertension (≥130/80 mmHg, patients diagnosed with and taking medication for hypertension). Participants were also classified into five groups based on their measured SBP: (1) <100 mmHg; (2) 100–119 mmHg; (3) 120–129 mmHg; (4) 130–139 mmHg; (5) ≥140 mmHg for SBP; DBP (1) <70 mmHg; (2) 70–79 mmHg; (3) 80–89 mmHg; (4) 90–99 mmHg; (5) ≥100 mmHg, as well as pulse pressure (PP) defined by SBP minus DBP (1) <40 mmHg; (2) 40–49 mmHg; (3) 50–59 mmHg; (4) 60–69 mmHg; (5) ≥70 mmHg. For each participant, the body mass index was calculated by dividing the body weight (kg) by the height squared (m^2). We defined obesity as a body mass index ≥ 25 kg/m^2 according to the WHO recommendations for Asian populations (20). The estimated glomerular filtration rate (eGFR) was calculated using the Modification of Diet in Renal Disease formula. Data on age, sex, health behaviour-related factors, and other definitions of smoking status, alcohol consumption, regular exercise, and diagnosis for diabetes, cardiovascular disease and dyslipidemia are described in **Supplementary Table S1**.

Study outcomes

The study outcome was incident death-censored graft failure, defined as the presence of hemodialysis, peritoneal dialysis, or kidney re-transplantation. Patients with death-censored graft

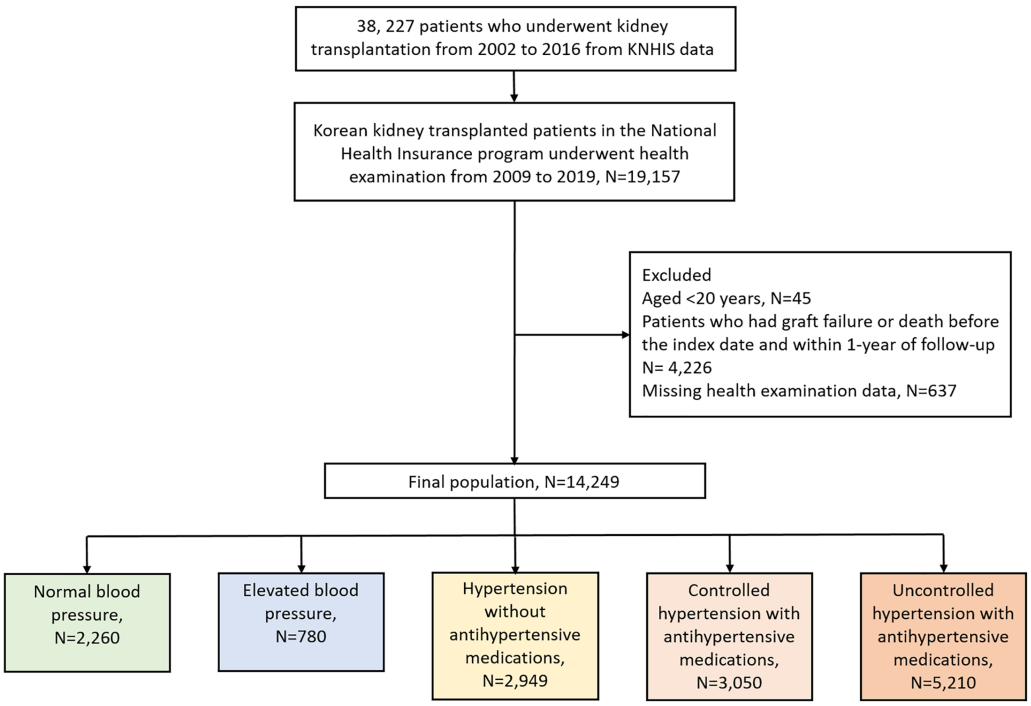

FIGURE 1
Flowchart of participant enrollment.

failure were identified using a combination of International Classification of Diseases Tenth Revision, Clinical Modification (ICD-10-CM) codes (N18–19, Z49, Z94.0, and Z99.2) and a special code (V001, procedure-related outpatient care or inpatient treatment on the day of hemodialysis; V003, peritoneal dialysis) at least three times during 3 months, and kidney transplantation code (V005). We excluded patients with a dialysis code on the same date as an acute kidney failure code (N17.9). In the event of death with a functioning graft, the follow-up period was censored at the date of death.

Statistical analyses

Continuous variables are described as the mean ± standard deviation and categorical variables are presented as numbers with proportions. Intergroup differences were tested using the chi-squared test or Student's *t*-test, as appropriate. The incidence rates of graft failure are presented as the number of cases calculated per 1,000 person-years. The cumulative incidence probability of graft failure was estimated using the Kaplan–Meier method, and between-group comparisons of the resulting curves were subjected to univariate analysis via the log-rank test. Multivariable analyses were performed using Cox proportional hazard regression models, and calculated hazard ratios (HRs) with 95% confidence intervals (CIs). The proportional hazards assumption was tested visually with the Schoenfeld residual plots. Model 1 was adjusted for age and sex. Model 2 was adjusted for age, sex, income level, smoking status, alcohol consumption status, physical activity, eGFR, obesity, diabetes mellitus, cardiovascular disease and dyslipidemia. Model 3 included all covariates in Model 2, along with the use of antihypertensive medications (diuretics, calcium channel blockers, β-blockers, α-blocker, angiotensin converting enzyme inhibitors, and/or angiotensin receptor blockers). Smooth cubic spline HR curves for the graft failure were plotted after adjusting for all covariates (Model 3). Subgroup analyses were conducted according to age, sex, smoking status, and diabetes as well as the duration from kidney transplantation to BP measurement. Interaction terms were added to test for effect modification across the subgroups. All statistical analyses were performed using the Statistical Analysis System (SAS) software (version 9.4; SAS Institute, Cary, NC, USA). All significance tests were 2-tailed and *P*-values < 0.05 were considered statistically significant.

Results

Baseline characteristics

The mean baseline age of the participants was 50.9 years, and 58.2% were men. The baseline characteristics of the study population according to hypertension are presented in **Table 1**. Of the total population, 11,209 (78.7%) KTR were diagnosed with hypertension. Among those with hypertension, 2949 (26.3%), 3050 (27.2%), and 5210 (46.5%) participants had incident hypertension, controlled, and uncontrolled hypertension, respectively. Participants with hypertension were more likely than

TABLE 1 Baseline characteristics of the study population.

Characteristics	Total	No hypertension	Hypertension	*P* value
Number of patients (%)	14,249 (100)	3,040 (21.3)	11,209 (78.7)	
Age, mean ± SD, years	50.9 ± 10.9	49.0 ± 11.0	51.4 ± 10.9	<0.001
20–39	1,956 (13.7)	507 (16.7)	1,449 (12.9)	<0.001
40–64	10,885 (76.4)	2,323 (76.4)	8,562 (76.4)	
≥65	1,408 (9.9)	210 (6.9)	1,198 (10.7)	
Sex, male (%)	8,299 (58.2)	1,302 (42.8)	6,997 (62.4)	<0.001
Smoking (%)				
Never	8,997 (63.1)	2,153 (70.8)	6,844 (61.1)	
Former	3,851 (27.0)	614 (20.2)	3,237 (28.9)	<0.001
Current	1,401 (9.8)	273 (9.0)	1,128 (10.1)	
Five hypertension groups (%)				
Normal BP	2,260 (15.9)	2,260 (74.3)		
Elevated BP	780 (5.5)	780 (25.7)		
Incident hypertension without medication	2,949 (20.7)		2,949 (26.3)	
Controlled hypertension	3,050 (21.4)		3,050 (27.2)	
Uncontrolled hypertension	5,210 (36.6)		5,210 (46.5)	
Alcohol consumption (%)	2,905 (20.4)	621 (20.4)	2,284 (20.4)	0.951
Regular physical activity (%)	3,181 (22.3)	629 (20.7)	2,552 (22.8)	0.015
Low income (%)	3,911 (27.5)	835 (27.5)	3,076 (27.4)	0.978
Diabetes mellitus (%)	4,259 (29.9)	617 (20.3)	3,642 (32.5)	<0.001
CVD (%)	613 (4.3)	79 (2.6)	534 (4.8)	<0.001
Dyslipidemia (%)	7,380 (51.8)	1,128 (37.1)	6,252 (55.8)	<0.001
WC, mean ± SD, cm	80.3 ± 9.5	76.9 ± 9.0	81.2 ± 9.4	<0.001
Height, mean ± SD, cm	164.0 ± 8.7	162.4 ± 8.5	164.4 ± 8.7	<0.001
Weight, mean ± SD, cm	62.2 ± 11.2	58.5 ± 10.2	63.2 ± 11.3	<0.001
BMI, mean ± SD, kg/m^2	23.1 ± 3.3	22.1 ± 3.0	23.3 ± 3.3	<0.001
Obesity (BMI ≥ 25 kg/m^2)	3,661 (25.7)	514 (16.9)	3,147 (28.2)	<0.001
Fasting glucose, mean ± SD, mg/dl	105.2 ± 33.3	100.6 ± 28.9	106.4 ± 34.3	<0.001
Total cholesterol, mean ± SD, mg/dl	184.2 ± 37.3	182.6 ± 35.7	184.7 ± 37.7	0.007
Antihypertensive medications[a]				
Diuretics (%)	2,057 (14.4)		2,057 (14.4)	
Calcium channel blockers (%)	5,795 (40.7)		5,795 (40.7)	
β-blockers (%)	1,702 (11.9)		1,702 (11.9)	
Angiotensin converting enzyme inhibitors (%)	683 (4.8)		683 (4.8)	
Angiotensin receptor blockers (%)	3,849 (27.0)		3,849 (27.0)	
Follow-up duration, mean ± SD, years	6.0 ± 2.9	6.3 ± 2.7	5.9 ± 2.9	<0.001

BP, blood pressure; HTN, hypertension; BMI, body mass index; CVD, cardiovascular disease; WC, waist circumference; SD, standard deviation.
[a]Claim within 1 year from index date.

those without hypertension to be male, older, smokers, take regular exercise, obese, and with a higher prevalence of diabetes, cardiovascular disease and dyslipidemia than those without hypertension.

Hypertension and risk of graft failure

During a mean follow-up period of 6.0 ± 2.9 years, 1934 (13.6%) participants developed graft failure. The incidence rates of graft failure were 12.2 and 25.3 (per 1,000 person-years) in patients without and with hypertension, respectively. The incidence rates of graft failure according to hypertension groups were 11.7, 13.8, 18.9, 22.8, and 31.3 for normal BP, elevated BP, incident hypertension, and controlled and uncontrolled hypertension with antihypertensive medications, respectively (Table 2). After adjusting for confounding factors (Cox Model 2), hypertensive patients had a significantly higher risk of graft failure than those without hypertension (adjusted HR, 1.703; 95% CI, 1.482–1.957). In the five hypertension groups, adjusted HRs for each group were 1 (reference), 1.198, 1.461, 1.590, and 2.127, respectively. Uncontrolled hypertension in the antihypertensive group had the highest risk for graft failure (adjusted HR, 2.127; 95% CI, 1.799–2.515). Kaplan-Meier curves for the incidence probability of graft failure according to hypertension and the five groups are shown in Figure 2, and similar results were obtained.

Participants were also classified based on SBP, DBP, and PP levels. The incidence rates and adjusted HRs (Cox Model 3) of graft failure were remarkably increased with an increase in the SBP, DBP, and PP in each group compared with the reference group (Table 3). These associations were confirmed by smooth HR curve analyses even after multivariable adjustments (Figure 3).

TABLE 2 Incidence rates and HRs of death-censored graft failure according to hypertension categories.

Group	Number of participants	Graft failure	Follow-up Duration, Person-years	Incidence Rate, Per 1,000 person-years	Unadjusted, HR (95% CI)	Model 1, HR (95% CI)[a]	Model 2, HR (95% CI)[b]
Hypertension							
No	3,040	235	19,257	12.2	1 (reference)	1 (reference)	1 (reference)
Yes	11,209	1,699	66,545	25.5	2.099 (1.831–2.406)	2.085 (1.816–2.393)	1.702 (1.481–1.956)
Hypertension categories							
Normal BP	2,260	170	14,537	11.7	1 (reference)	1 (reference)	1 (reference)
Elevated BP	780	65	4,720	13.8	1.180 (0.886–1.570)	1.190 (0.894–1.584)	1.199 (0.900–1.596)
Incident HTN without medications	2,949	349	18,431	18.9	1.622 (1.351–1.949)	1.625 (1.351–1.953)	1.464 (1.217–1.760)
Controlled HTN	3,050	418	18,300	22.8	1.960 (1.640–2.342)	1.969 (1.645–2.358)	1.589 (1.326–1.905)
Uncontrolled HTN	5,210	932	29,815	31.3	2.687 (2.282–3.165)	2.708 (2.293–3.197)	2.125 (1.797–2.513)

BP, blood pressure; HR, hazard ratio; CI, confidential interval; SBP, systolic blood pressure; DBP, diastolic blood pressure; HTN, hypertension.
[a]Model 1 was adjusted for age and sex.
[b]Model 2 was adjusted for age, sex, low income, smoking, alcohol consumption, regular exercise, obesity, estimated glomerular filtration rate, and history of diabetes, cardiovascular disease and dyslipidemia.

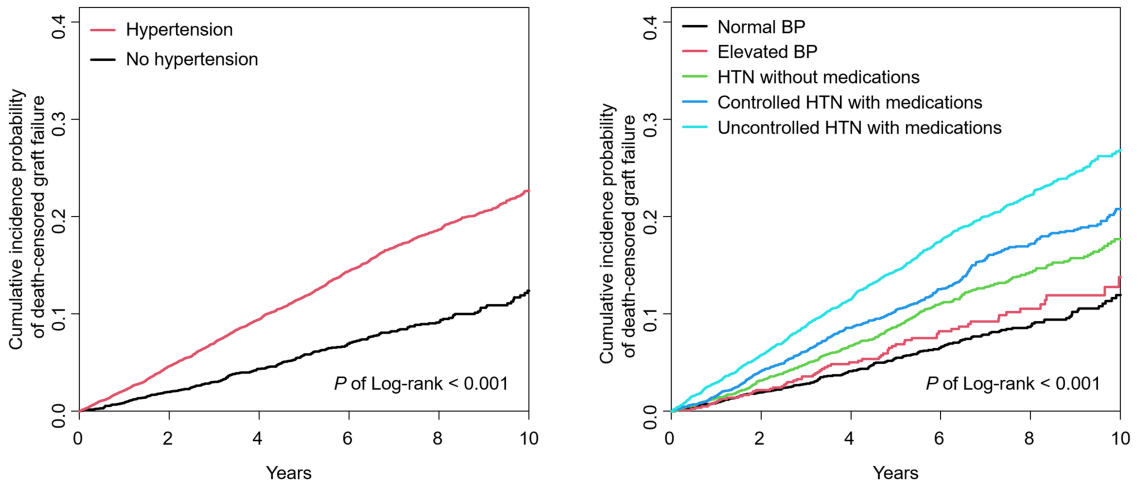

FIGURE 2
Kaplan–Meier curve for the incidence probability of death-censored graft failure with or without hypertension, and five hypertension groups. BP, blood pressure; HTN, hypertension.

Subgroup analyses

For subgroup analyses according to age, the participants were classified into <40, 40–65, and ≥65 years. In all subgroup analyses according to age, sex, smoking, and diabetes mellitus, hypertension was consistently associated with the risk of graft failure, and there was no significant difference between the subgroups (Figure 4).

We also analyzed the association between the five hypertension groups, the SBP and DBP groups, and PP groups with graft failure among subgroups (Supplementary Tables S2–S5). The adjusted HRs indicated no significant differences between participants regardless of age group or sex. However, the increased risk of graft failure according to advanced hypertension groups and high SBP and DBP was significantly higher in participants without diabetes than in those with diabetes.

To determine the association between the duration from kidney transplantation to BP measurement and graft failure, participants were classified into two groups; <5 years and ≥5 years based on this duration. The results were found to be consistent in both subgroups of participants (Supplementary Table S6).

Discussion

The present study demonstrated that (1) the presence of hypertension (≥130/80 mmHg) as based on the 2021 KDIGO

TABLE 3 Incidence rates and HRs of death-censored graft failure according to blood pressure.

Group	Number of participants	Graft failure	Follow-up Duration, Person-years	Incidence Rate, Per 1,000 person-years	Unadjusted, HR (95% CI)	Model 1, HR (95% CI)[a]	Model 2, HR (95% CI)[b]	Model 3, HR (95% CI)[c]
SBP, mmHg								
<100	394	32	2,432	13.2	0.795 (0.556–1.138)	0.813 (0.568–1.164)	0.763 (0.533–1.093)	0.790 (0.552–1.131)
100–119	4,401	456	27,587	16.5	1 (reference)	1 (reference)	1 (reference)	1 (reference)
120–129	3,705	454	22,495	20.2	1.222 (1.073–1.392)	1.219 (1.070–1.388)	1.173 (1.030–1.336)	1.151 (1.010–1.311)
130–139	3,592	561	21,442	26.2	1.586 (1.402–1.795)	1.587 (1.401–1.797)	1.448 (1.278–1.640)	1.400 (1.235–1.586)
≥140	2,157	431	11,847	36.4	2.212 (1.939–2.524)	2.242 (1.962–2.562)	1.894 (1.657–2.164)	1.796 (1.571–2.055)
DBP, mmHg								
<70	2,391	261	14,370	18.2	0.931 (0.805–1.077)	0.946 (0.817–1.094)	0.935 (0.808–1.082)	0.947 (0.818–1.096)
70–79	4,948	590	30,234	19.5	1 (reference)	1 (reference)	1 (reference)	1 (reference)
80–89	5,120	764	30,893	24.7	1.269 (1.139–1.412)	1.259 (1.130–1.402)	1.207 (1.084–1.345)	1.194 (1.072–1.330)
90–99	1,348	220	7,921	27.8	1.424 (1.220–1.663)	1.417 (1.214–1.655)	1.274 (1.090–1.489)	1.230 (1.052–1.437)
≥100	442	99	2,385	41.5	2.137 (1.727–2.644)	2.103 (1.699–2.602)	1.859 (1.501–2.302)	1.807 (1.459–2.238)
Pulse pressure, mmHg								
<40	2,392	227	14,713	15.4	0.792 (0.681–0.920)	0.795 (0.684–0.924)	0.779 (0.671–0.906)	0.790 (0.680–0.918)
40–49	5,709	691	35,461	19.5	1 (reference)	1 (reference)	1 (reference)	1 (reference)
50–59	4,220	661	24,916	26.5	1.364 (1.226–1.518)	1.380 (1.240–1.537)	1.235 (1.110–1.376)	1.205 (1.082–1.342)
60–69	1,433	235	8,140	28.9	1.487 (1.282–1.724)	1.539 (1.325–1.787)	1.289 (1.109–1.498)	1.241 (1.067–1.442)
≥70	495	120	2,573	46.6	2.411 (1.986–2.926)	2.572 (2.112–3.133)	1.976 (1.620–2.409)	1.890 (1.550–2.306)

BP, blood pressure; HTN, hypertension; HR, hazard ratio; CI, confidential interval; SBP, systolic blood pressure; DBP, diastolic blood pressure.

[a]Model 1 was adjusted for age and sex.

[b]Model 2 was adjusted for age, sex, low income, smoking, alcohol consumption, regular exercise, obesity, estimated glomerular filtration rate, and history of diabetes, cardiovascular disease and dyslipidemia.

[c]Model 3 was adjusted for age, sex, low income, smoking, alcohol consumption, regular exercise, obesity, estimated glomerular filtration rate, and history of diabetes, cardiovascular disease and dyslipidemia, use of antihypertensive medications.

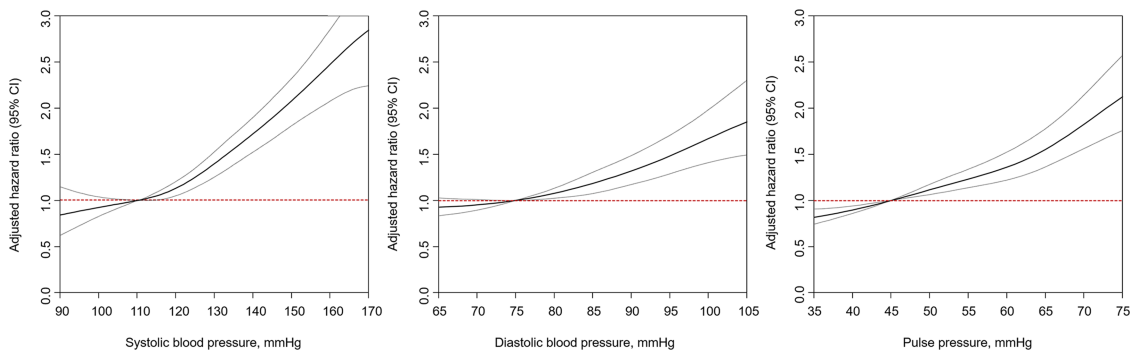

FIGURE 3
Smoothed hazard ratios curves of the associations of SBP, DBP, and PP with death-censored graft failure in kidney transplant recipients in adjusted Cox-model 3. CI, confidence interval.

BP guidelines for KTR increased the risk of graft failure; (2) uncontrolled hypertension (≥130/80 mmHg) albeit taking antihypertensive medications had the highest risk (2.1-fold) of graft failure compared with normal BP; (3) the risk of graft failure increased gradually as the SBP, DBP, and PP increased; (4) this association was present in the ≥120 mmHg SBP, ≥80 mmHg DBP, and ≥50 mmHg of PP groups.

Hypertension after kidney transplantation is common, although the prevalence ranges from 50% to 90% and varies depending on the definition, population, and use of antihypertensive medications (8, 21–24). Sustained hypertension is an established risk factor for worsening kidney function, cardiovascular morbidity, and mortality (25). Therefore, it is important to establish optimal BP control in relation to graft survival in KTR. A previous study of 392 allograft recipients from living donors showed that SBP and DBP levels during the first year after transplantation were associated with renal allograft failure, which was independent of renal function (9). Similarly, in a study of KTR from deceased donors at the same center, a 10 mmHg increment in BP in the first year post-transplantation strongly predicted allograft failure (26). In a large retrospective study using the Collaborative Transplant Study data, 24,404 KTR

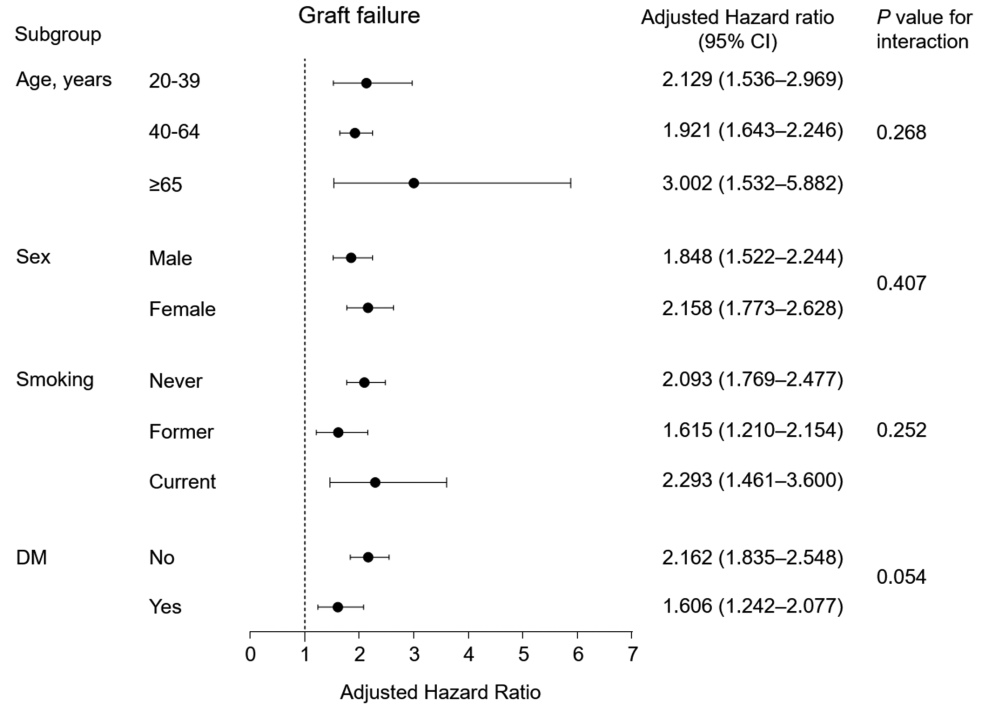

FIGURE 4
Subgroup analysis of the association between hypertension and death-censored graft failure in adjusted Cox-model 3. Points and bars represent hazard ratio estimates and their associated 95% CIs, respectively. CI, confidential interval; DM, diabetes mellitus.

with an SBP >140 mmHg at 1-year post-transplantation but controlled to ≤140 mmHg at 3 years had improved long-term renal allograft survival compared with those with a persistent SBP of >140 mmHg to 3 years (10). However, these results did not provide a definite cutoff for BP target regarding the risk of graft survival.

Our results are consistent with a previous hypothesis that a higher BP is associated with an increased risk of graft failure. Especially, hypertension of ≥130/80 mmHg, as per the 2021 KDIGO BP guidelines, in KTR increased the risk of death-censored graft failure by 1.7-fold compared with non-hypertension. Furthermore, an elevated SBP or DBP of ≥120 mmHg/80 mmHg had a significant association with graft failure, suggesting that a modestly increased BP in KTR could worsen kidney function. Although a retrospective study of 815 KTR who achieved a mean SBP <130 mmHg showed a lower mortality rate, these results were not maintained in graft survival (12). In addition, a secondary analysis of the Folic Acid for Vascular Outcome Reduction in Transplantation trial of 3,598 KTR, found no associations of SBP or DBP with composite outcomes defined as a decline in ≥50% of eGFR or dialysis (17). Although our findings are not consistent with previous studies, this might be related to the relatively small sample size and different primary endpoints of previous studies (12, 17).

Our results also demonstrated that the risk of graft failure was associated with a linear relationship with SBP, DBP, or PP. Moreover, the HRs of uncontrolled hypertension, even while taking antihypertensive medication, increased the risk 2.1-fold than that of normal BP. Considering the results of our study and previous studies (9, 26), achieving an intensive BP target of <130/80 mmHg might be important for decreasing the risk of graft failure in KTR.

Another important finding of this study was that increased PP had a linear association with the risk of graft failure. It is generally accepted that PP, which reflects arterial stiffness, is linked to the progression of CKD and cardiovascular mortality (27), suggesting it might be a good surrogate marker for predicting graft failure in KTR.

The strength of this study was the enrollment of a large population of approximately 14,000 KTR from a nationwide health checkup database over a relatively long follow-up duration. Because of the large population, we classified the patients into several hypertensive groups and subdivided BP groups to determine the association between a lower hypertension definition and various BP levels and the development of graft failure. This study had several limitations. First, we used a single BP measurement taken in the office to determine hypertension. However, BP variability is common in patients with kidney disease, and office BP measurements do not reflect nocturnal hypertension, masked hypertension, and white coat hypertension (28, 29). Second, we did not capture data on allograft rejection and use of immunosuppressive agents for KTR that could affect allograft failure due to the nature of this retrospective study. Third, there was a possibility of coding inaccuracies due to limitations by an administrative database. Fourth, our findings cannot be generalized to other ethnic groups, because this study was limited to the Korean population. Finally, this was a retrospective study design;

therefore, randomized controlled trials to examine optimal BP levels in KTR to prolong graft survival are needed in the future.

In conclusion, this Korean nationwide population-based cohort study found that hypertension ≥130/80 mmHg based on the 2021 KDIGO BP guidelines in KTR, as well as elevated SBP, DBP, and PP were associated with the risk of developing graft failure in patients with kidney transplantation after adjusting for various covariates. Whether intensive treatment of BP can reduce the risk of graft failure needs further large randomized controlled trials.

Data availability statement

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

Ethics statement

The study protocol was approved by the Institutional Review Board of Chonnam National University Hospital (CNUH-EXP-2022-274). Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

CK, KH, and SK: contributed to the study concept and design and revised the draft. CK, JJ, and BK: contributed the acquistion of data, and statistical analyses. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2023.1185001/full#supplementary-material

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A risk model for the early diagnosis of acute myocardial infarction in patients with chronic kidney disease

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Introduction: Acute myocardial infarction (AMI) remains a critical disease, characterized by a high fatality rate in several countries. In clinical practice, the incidence of AMI is increased in patients with chronic kidney disease (CKD). However, the early diagnosis of AMI in the above group of patients is still poor.
Methods: In the present study, a total of 829 patients with CKD, defined by an estimated glomerular filtration rate (eGFR) of <60 ml/min/1.73 m^2 or 60–90 ml/min/1.73 m^2 for patients with mildly reduced kidney function, who attended the Sichuan Provincial People's Hospital (SPPH) between January 2018 and November 2022 were enrolled. All patients underwent coronary angiography due to the presence of typical or atypical symptoms of AMI. Patients were divided into the following two groups: The training cohort, including 255 participants with AMI and 242 without AMI; and the testing cohort, including 165 and 167 subjects with and without AMI, respectively. Furthermore, a forward stepwise regression model and a multivariable logistic regression model, named SPPH-AMI-model, were constructed to select significant predictors and assist the diagnosis of AMI in patients with CKD, respectively.
Results: The following factors were evaluated in the model: Smoking status, high sensitivity cardiac troponin I, serum creatinine and uric acid levels, history of percutaneous coronary intervention and electrocardiogram. Additionally, the area under the curve (AUC) of the receiver operating characteristic curve were determined in the risk model in the training set [AUC, 0.78; 95% confidence interval (CI), 0.74–0.82] vs. the testing set (AUC, 0.74; 95% CI, 0.69–0.79) vs. the combined set (AUC, 0.76; 95% CI, 0.73–0.80). Finally, the sensitivity and specificity rates were 71.12 and 71.21%, respectively, the percentage of cases correctly classified was 71.14%, while positive and negative predictive values of 71.63 and 70.70%, respectively, were also recorded.
Discussion: The results of the current study suggested that the SPPH-AMI-model could be currently considered as the only risk scoring system for the early diagnosis of AMI in patients with CKD. This method could help clinicians and emergency physicians to quickly and accurately diagnose AMI in patients with CKD to promote the immediate and effective treatment of these patients.

KEYWORDS

acute myocardial infarction, chronic kidney disease, early diagnose, SPPH-AMI-model, test accuracy

Abbreviations

AMI, acute myocardial infarction; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; SPPH, sichuan provincial people's hospital; hs-cTn I, high sensitivity cardiac troponin I; Scr, serum creatinine; UA, uric acid; PCI, percutaneous coronary intervention; ECG, electrocardiogram; CAD, coronary artery disease; DM, diabetes mellitus; PVD, peripheral vascular disease; SD, standard deviation; IQR, interquartile range; AUC, area under the receiver operating characteristic curve; ROC, receiver operating characteristic curve; 95% CI, 95% confidence interval; NO, nitric oxide.

1. Introduction

Acute myocardial infarction (AMI) is characterized by myocardial cell death caused by prolonged myocardial ischemia and hypoxia. AMI is considered as a sever disease since it is characterized by a high fatality rate. Delayed diagnosis of AMI could prevent the immediate treatment of patients with effective therapies (1). Therefore, the early diagnosis of AMI is crucial for its treatment. The diagnosis of AMI in patients with chronic kidney disease (CKD) needs more attention. This finding could be due to the fact that several patients with CKD do not experience the classic clinical symptoms of AMI (2, 3). Secondly, several electrocardiography (ECG) changes, such as ST deviations and T-wave inversion, could occur due to left ventricular hypertrophy. The above changes could mimic or obscure AMI (4). Thirdly, cardiac troponin (cTn) levels and more particularly those of high-sensitivity cTn (hs-cTn) are often elevated in patients with CKD, thus reducing their diagnostic effectiveness. Several previous studies also suggested that the assessment of hs-cTn levels could display a lower clinical specificity for AMI in the setting of CKD (5–9). Additionally, it has been reported that patients with CKD are more likely to experience adverse events associated with coronary intervention (10). Therefore, the early diagnosis of AMI in patients with CKD remains a challenge for clinicians. According to the 2021 ACC/AHA guidelines, clinicians should be aware that in elderly patients with renal disease the assessment of changes in serial measurements is very significant for improving diagnostic specificity (11). However, currently, no studies have been conducted on the development of a risk scoring system for predicting AMI in patients with CKD via analyzing several risk factors, such as arterial hypertension, dyslipidaemia and diabetes mellitus (DM) (12, 13). Therefore, the current study aimed to evaluate all associated risk factors and indicators to establish a scoring model for the early diagnosis of AMI in patients with CKD.

2. Methods

2.1. Patient selection

In the present study, patients who experienced the typical or atypical symptoms of myocardial ischemia, including chest pain, chest distress, dyspnea, palpitations or fatigue, and diagnosed with CKD [estimated glomerular filtration rate (eGFR), < 60 ml/min/1.73 m^2], mildly reduced kidney function (eGFR, 60–90 mL/min/1.73 m^2) or other CKD-related diseases, such as chronic glomerulonephritis (13) or albuminuria (2) were enrolled. AMI was diagnosed, according to the universal definition of AMI (14), based on the patient's medical history, laboratory tests, including hs-cTnI levels, electrocardiography, echocardiography and coronary angiographic morphology assessment. Therefore, a total of 1,504 patients with CKD who underwent coronary angiography, due to the onset of typical or atypical symptoms of AMI, at the Sichuan Provincial People's Hospital (SPPH) between January 2018 and November 2022 were included in the study. Additionally, both 12-lead ECG and laboratory tests, such as hs-cTnI, were performed within 24 h after the onset of the symptoms. Patients ($n = 569$) with mildly reduced kidney function (eGFR, 60–90 ml/min/1.73 m^2), but without CKD, were excluded from the study. In addition, patients with missing data ($n = 106$) were also excluded. Finally, the data of a total of 829 participants, including 420 patients with AMI and 409 without AMI, were analyzed.

2.2. Data acquisition

Several risk factors have been identified in previous studies to be associated with AMI. Therefore, in the present study all these factors, including age, sex, smoking status, obesity, family history of coronary artery disease (CAD), arterial hypertension and DM, atrial fibrillation, peripheral vascular disease, history of valvular heart diseases ($n = 68$) or cardiomyopathies, such as dilated cardiomyopathy ($n = 7$) and hypertrophic cardiomyopathy ($n = 3$), history of cerebral infarction and history of percutaneous coronary intervention (PCI), were evaluated. Relevant laboratory tests, such as the assessment of blood lipid, myocardial enzyme, eGFR, serum creatinine (Scr) and uric acid (UA) levels, and ECG were also performed. ECG results were evaluated independently by a diagnostician blinded to the other data. Changes in the ECG results were considered positive when ST deviations of ±1 mm in two contiguous leads (II, III and avF or I, avL, V5, V6 or V1–V4), ST deviations of ±1 mm in avR or V1 lead and hyperacute T wave or T-wave inversion as coronal T-wave were recorded. All the other ECG findings were considered negative. All the aforementioned factors are listed in **Table 1**.

2.3. Statistical analysis

All baseline characteristics were described and compared between the AMI and non-AMI groups in the training, testing and combined set. The normally distributed variables are expressed as the mean ± standard deviation (SD). The differences between two groups were compared using t test. Additionally, the non-normally distributed variables are expressed as the median and interquartile range (IQR). The above date was compared using Kruskal–Wallis rank-sum test. The binomial variables are expressed as frequency and proportion, and were compared by Chi-square test or Fisher's exact test. In the training set, a forward stepwise regression model was constructed to select significant predictors and a multivariable logistic regression model was then established. All p-values were two-sided and the 95% confidence interval (95% CI) were also presented. All analyses were performed using R software (R Foundation for Statistical Computing, Vienna, Austria).

3. Results

3.1. Study population

All the 1,504 patients with CKD underwent coronary angiography after the onset of the typical or atypical symptoms

TABLE 1 The comparison of factors between AMI group and non-AMI group in the training,testing and combined set.

Variables	–	Training set				Testing set				Combined set			
		Non-AMI (*N* = 242)	AMI (*N* = 255)	Statistic	*P*	Non-AMI (*N* = 167)	AMI (*N* = 165)	Statistic	*P*	Non-AMI (*N* = 409)	AMI (*N* = 420)	Statistic	*P*
Sex	Female	81 (33.47)	64 (25.1)	$\chi^2 = 3.82$	0.051	52 (31.14)	47 (28.48)	$\chi^2 = 0.17$	0.683	133 (32.52)	111 (26.43)	$\chi^2 = 3.41$	0.065
	Male	161 (66.53)	191 (74.9)			115 (68.86)	118 (71.52)			276 (67.48)	309 (73.57)		
Age	Median (Q1,Q3)	68.50 (62.00, 75.00)	70.00 (60.50, 75.00)	$H = 0.06$	0.803	67.00 (59.50, 75.50)	69.00 (63.00, 75.00)	$H = 3.43$	0.064	68.00 (61.00, 75.00)	69.00 (61.00, 75.00)	$H = 1.88$	0.170
Obesity	0	230 (95.04)	241 (94.51)	$\chi^2 < 0.01$	0.949	156 (93.41)	150 (90.91)	$\chi^2 = 0.42$	0.519	386 (94.38)	391 (93.1)	$\chi^2 = 0.38$	0.537
	1	12 (4.96)	14 (5.49)			11 (6.59)	15 (9.09)			23 (5.62)	29 (6.9)		
Diabetes mellitus	0	155 (64.05)	136 (53.33)	$\chi^2 = 5.44$	0.020	115 (68.86)	79 (47.88)	$\chi^2 = 14.75$	<0.01	270 (66.01)	215 (51.19)	$\chi^2 = 18.54$	<0.001
	1	87 (35.95)	119 (46.67)			52 (31.14)	86 (52.12)			139 (33.98)	205 (48.81)		
Hypertension	0	62 (25.62)	53 (20.78)	$\chi^2 = 1.37$	0.241	43 (25.75)	33 (20)	$\chi^2 = 1.25$	0.264	105 (25.67)	86 (20.48)	$\chi^2 = 2.87$	0.090
	1	180 (74.38)	202 (79.22)			124 (74.25)	132 (80)			304 (74.33)	334 (79.52)		
Drinking	0	184 (76.03)	189 (74.12)	$\chi^2 = 0.15$	0.697	128 (76.65)	113 (68.48)	$\chi^2 = 2.38$	0.123	312 (76.28)	302 (71.90)	$\chi^2 = 1.85$	0.174
	1	58 (23.97)	66 (25.88)			39 (23.35)	52 (31.52)			97 (23.72)	118 (28.10)		
Smoking	0	161 (66.53)	143 (56.08)	$\chi^2 = 5.28$	0.022	98 (58.68)	92 (55.76)	$\chi^2 = 0.18$	0.669	259 (63.33)	235 (55.95)	$\chi^2 = 4.38$	0.036
	1	81 (33.47)	112 (43.92)			69 (41.32)	73 (44.24)			150 (36.67)	185 (44.05)		
Family history	0	238 (98.35)	241 (94.51)	$\chi^2 = 4.20$	0.041	164 (98.2)	161 (97.58)	*Fisher*	0.722	402 (98.29)	402 (95.71)	$\chi^2 = 3.86$	0.050
	1	4 (1.65)	14 (5.49)			3 (1.8)	4 (2.42)			7 (1.71)	18 (4.29)		
History of cerebral infarction	0	213 (88.02)	213 (83.53)	$\chi^2 = 1.69$	0.193	140 (83.83)	144 (87.27)	$\chi^2 = 0.54$	0.462	353 (86.31)	357 (85.00)	$\chi^2 = 0.19$	0.661
	1	29 (11.98)	42 (16.47)			27 (16.17)	21 (12.73)			56 (13.69)	63 (15.00)		
Atrial fibrillation	0	208 (85.95)	216 (84.71)	$\chi^2 = 0.07$	0.791	127 (76.05)	139 (84.24)	$\chi^2 = 3.00$	0.083	335 (81.91)	355 (84.52)	$\chi^2 = 0.84$	0.360
	1	34 (14.05)	39 (15.29)			40 (23.95)	26 (15.76)			74 (18.09)	65 (15.48)		
PDA	0	88 (36.36)	92 (36.08)	$\chi^2 < 0.01$	>0.999	61 (36.53)	58 (35.15)	$\chi^2 = 0.02$	0.883	149 (36.43)	150 (35.71)	$\chi^2 = 0.02$	0.887
	1	154 (63.64)	163 (63.92)			106 (63.47)	107 (64.85)			260 (63.57)	270 (64.29)		
Cholesterol	Median (Q1, Q3)	3.84 (3.21, 4.75)	3.81 (3.22, 4.64)	$H = 0.38$	0.540	3.92 (3.28, 4.61)	4.03 (3.17, 4.61)	$H = 0.05$	0.823	3.89 (3.22, 4.72)	3.86 (3.20, 4.63)	$H = 0.36$	0.550
TG	Median (Q1, Q3)	1.46 (1.07, 2.1)	1.53 (1.18, 2.2)	$H = 1.38$	0.240	1.51 (1.06, 2.25)	1.54 (1.11, 2.2)	$H = 0.49$	0.485	1.50 (1.07, 2.13)	1.54 (1.15, 2.20)	$H = 1.75$	0.185
LDL	Median (Q1, Q3)	1.92 (1.44, 2.53)	2.04 (1.52, 2.7)	$H = 1.13$	0.288	2.00 (1.57, 2.65)	2.18 (1.54, 2.72)	$H = 0.52$	0.471	1.95 (1.47, 2.57)	2.10 (1.53, 2.72)	$H = 1.51$	0.219
HDL	Median (Q1, Q3)	1.12 (0.9, 1.38)	1.04 (0.88, 1.31)	$H = 3.82$	0.051	1.11 (0.94, 1.38)	1.05 (0.87, 1.23)	$H = 5.63$	0.018	1.12 (0.92, 1.38)	1.04 (0.87, 1.27)	$H = 9.16$	0.002
BNP	Median (Q1, Q3)	120 (62, 255)	141 (64, 390.5)	$H = 2.03$	0.154	130.00 (66.50, 347.00)	168.00 (66.00, 456.00)	$H = 1.33$	0.249	124.00 (65.00, 285.00)	153.00 (64.00, 427.50)	$H = 3.33$	0.068
Lipoprotein A	Median (Q1, Q3)	20.5 (16.22, 26.67)	20.8 (15.9, 26.7)	$H = 0.13$	0.718	20.50 (16.10, 27.05)	20.50 (15.20, 25.00)	$H = 1.14$	0.285	20.50 (16.20, 26.80)	20.60 (15.80, 25.92)	$H = 0.16$	0.689
CK-MB	Median (Q1, Q3)	1.20 (0.80, 2.10)	1.80 (1.00, 5.10)	$H = 26.46$	<0.001	1.10 (0.80, 1.90)	2.00 (1.10, 5.70)	$H = 31.62$	<0.001	1.20 (0.80, 2.00)	1.90 (1.00, 5.40)	$H = 56.61$	<0.001
Myohemoglobin	Median (Q1, Q3)	88.8 (58.95, 186.12)	150.2 (79.25, 368.2)	$H = 35.27$	<0.001	95.70 (63.40, 154.90)	135.10 (71.30, 322.50)	$H = 12.64$	<0.001	93.2 (60.80, 178.00)	146.70 (75.90, 350.95)	$H = 47.34$	<0.001
hs-cTn I	Median (Q1, Q3)	18.60 (6.55, 46.77)	120.20 (18.65, 3,198.20)	$H = 76.11$	<0.001	16.40 (5.45, 43.40)	181.30 (19.00, 1,868.70)	$H = 58.18$	<0.001	17.70 (6.20, 44.90)	142.26 (18.92, 2,988.20)	$H = 134.05$	<0.001
eGFR	Median (Q1, Q3)	37.02 (18.7, 46.73)	27.51 (9.57, 41.27)	$H = 15.28$	<0.001	36.53 (20.14, 47.06)	34.43 (14.09, 45.61)	$H = 0.19$	0.662	36.97 (19.07, 47.00)	30.41 (11.15, 43.61)	$H = 11.07$	<0.001
Scr	Median (Q1, Q3)	152.70 (125.95, 250.07)	192.30 (140.70, 501.02)	$H = 17.28$	<0.001	151.40 (125.70, 259.65)	158.10 (123.70, 341.80)	$H = 0.02$	0.885	151.4 (125.80, 254.30)	180.00 (132.30, 390.30)	$H = 11.02$	<0.001
UC	Median (Q1, Q3)			$H = 2.14$	0.143			$H = 0.01$	0.909	433.00 (357, 528)		$H = 1.01$	0.315

(*Continued*)

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TABLE 1 Continued

Variables	–	Training set				Testing set				Combined set			
		Non-AMI (*N* = 242)	AMI (*N* = 255)	Statistic	*P*	Non-AMI (*N* = 167)	AMI (*N* = 165)	Statistic	*P*	Non-AMI (*N* = 409)	AMI (*N* = 420)	Statistic	*P*
		427.00 (345.00, 519.00)	448.00 (356.00, 550.00)			442.00 (375.50, 544.00)	455.00 (373.00, 544.00)				450.50 (357.75, 547.25)		
Valvulopathy or cardiomyopathy	0	215 (88.84)	234 (91.76)	$\chi^2 = 0.90$	0.342	146 (87.43)	156 (94.55)	$\chi^2 = 4.29$	0.038	361 (88.26)	390 (92.86)	$\chi^2 = 4.60$	0.032
	1	27 (11.16)	21 (8.24)			21 (12.57)	9 (5.45)			48 (11.74)	30 (7.14)		
History of PCI	0	173 (71.49)	157 (61.57)	$\chi^2 = 5.04$	0.025	115 (68.86)	99 (60)	$\chi^2 = 2.47$	0.116	288 (70.42)	256 (60.95)	$\chi^2 = 7.81$	0.005
	1	69 (28.51)	98 (38.43)			52 (31.14)	66 (40)			121 (29.58)	164 (39.05)		
ECG	0	124 (51.24)	50 (19.61)	$\chi^2 = 53.22$	<0.001	105 (62.87)	40 (24.24)	$\chi^2 = 48.79$	<0.001	229 (55.99)	90 (21.43)	$\chi^2 = 103.10$	<0.001
	1	118 (48.76)	205 (80.39)			62 (37.13)	125 (75.76)			180 (44.01)	330 (78.57)		

of AMI, including acute chest pain, palpitation, dyspnea or syncope. In the present study, not only patients with CKD and eGFR valus of <60 ml/min/1.73 m^2 were included, but also patients with mild CKD-related diseases (eGFR, 60–90 ml/min/1.73 m^2), such as nephrotic syndrome (1), chronic glomerulonephritis (13) and secondary albuminuria (17). However, 569 patients with mildly reduced kidney function (eGFR, 60–90 ml/min/1.73 m^2), but without CKD, and 106 patients with missing data were excluded. The remaining 829 patients were randomly divided into the following two groups: The 60% of patients as training cohort, including 255 patients with AMI and 242 without AMI, and the 40% of patients as testing cohort, including 165 and 167 patients with and without AMI, respectively.

3.2. Study factors

In the current study, a total of 13 AMI-related clinical risk factors were evaluated, including 12 laboratory testing factors and ECG data. The comparisons of all factors are shown in **Table 1**. The analysis revealed that the most common cardiovascular risk factors were sex (male in AMI vs. non-AMI, 73.57 vs. 67.48%), smoking status (AMI vs. non-AMI, 44.05 vs. 36.67%), obesity (AMI vs. non-AMI, 6.9 vs. 5.62%), hypertension (AMI vs. non-AMI, 79.52% vs. 74.33%), DM (AMI vs. non-AMI, 48.81 vs. 33.98%), atrial fibrillation (AMI vs. non-AMI, 15.48 vs. 18.09%) and history of PCI (AMI vs. non-AMI, 39.05 vs. 29.58%). The laboratory testing factors included the levels of cholesterol (AMI vs. non-AMI, 3.86 vs. 3.89), triglyceride (AMI vs. non-AMI, 1.54 vs. 1.50), low-density lipoprotein (AMI vs. non-AMI, 2.10 vs. 1.95), creatine kinase MB (AMI vs. non-AMI, 1.9 vs. 1.2), myoglobin (AMI vs. non-AMI, 146.7 vs. 93.2), hs-cTn (AMI vs. non-AMI, 142.26 vs. 17.7), eGFR (AMI vs. non-AMI, 30.41 vs. 36.97), serum creatinine (AMI vs. non-AMI, 180 vs. 151.4) and UA (AMI vs. non-AMI, 450.5 vs. 433). In addition, the ECG positive sign rate in the AMI group was 78.57% compared with 44.01% in the non-AMI group.

Subsequently, a forward stepwise regression model was established to select significant predictors (**Table 1**) and a multivariable logistic regression model was then developed (**Table 2**). In the model, the following factors were included:

TABLE 2 The result of univariate logistic regression analysis and the SPPH-AMI-model.

Variables	B	*OR*	95% CI		*z*	*P*
Smoking (1 vs. 0)	0.597	1.817	1.202	2.758	2.82	0.005
Hs-cTn I per 100	0.041	1.042	1.024	1.065	4.18	2.86×10^{-5}
Scr per 100	0.116	1.122	1.046	1.208	3.15	0.002
UC per 100	0.139	1.149	0.997	1.329	1.91	0.057
History of PCI (1 vs. 0)	0.394	1.483	0.964	2.282	1.80	0.073
ECG (1 vs. 0)	1.079	2.94	1.908	4.579	4.84	1.31×10^{-6}
Constant term	−2.350					

The SPPH-AMI-model: $\pi(Y = 1) = \frac{1}{1+\exp(-Score)}$.
Score = −2.350 + 0.597 × (smoking = 1) + 0.041 × hs-cTn I per 100 + 0.116 × Scr. Per 100 + 0.139 × UA per 100 + 0.394 × (history of PCI = 1) + 1.079 × (ECG = 1).

Smoking status, hs-cTnI, Scr, UA, history of PCI and ECG. The risk score of each factor was calculated when the corresponding value of each variable was entered into the following formula: $\pi = (Y = 1) = 1/1 + \exp(\text{-score})$, where $\text{score} = -2.350 + 0.597 \times (\text{smoking} = 1) + 0.041 \times \text{hs-cTnI per } 100 + 0.116 \times \text{Scr per } 100 + 0.139 \times \text{UA per } 100 + 0.394 \times (\text{history of PCI} = 1) + 1.079 \times (\text{ECG} = 1)$. Subsequently, each score was inserted into the logistic regression model to determine the probability of AMI. The use of the above risk model (SPPH-AMI-model) could promote the early diagnosis of AMI in patients with CKD. Therefore, these patients could be timely treated with the appropriate treatment approach, thus avoiding the delay in patient therapy due to misdiagnosis.

In the combined set, the threshold (0.46) of the predicted probability of each case was determined once the balance of sensitivity and specificity was achieved. As shown in **Figure 1**, the corresponding score was −0.1418. The above finding indicated that when a risk score of >−0.1418 was obtained, patients with CKD could experience AMI.

The accuracy of the discrimination of the model was evaluated using receiver operating characteristic (ROC) curve and area under the ROC curve (AUC). As shown in **Figure 2**, the AUC values of the risk model in the training vs. testing vs. combined sets were 0.78 vs. 0.74 vs. 0.76, respectively. In addition, the model was calibrated using a calibration curve and the observed vs. expected ratio (**Figure 3**). Furthermore, all parameters in the model were reserved, and the model was independently evaluated in the testing set. In the combined set, the threshold (0.46) of the predicted probability of each case was calculated when the balance of sensitivity and specificity was achieved. As shown in **Table 3**, the sensitivity and specificity rates were 71.12 and 71.21%, respectively. Additionally, the rate of cases correctly classified was 71.14%, while the positive and negative predictive rates were 71.63 and 70.70%, respectively (**Table 3**).

The association between eGFR and hs-cTnI levels is shown in **Table 4**. The results demonstrated that the median levels of hs-cTnI increased with the deterioration of renal function in the non-AMI and combined groups.

4. Discussion

Currently, the incidence of AMI- or CAD-related deaths is increasing each year (15). The Fourth Universal Definition of Myocardial Infarction Consensus Document in 2018 provided by the Joint ESC/ACC/AHA/WHF Task Force (14), suggested that the early diagnosis of AMI could depend on the symptoms of myocardial ischemia, the ischemic ECG changes and elevated cTn levels. In fact, diagnosing AMI in patients with CKD could be very difficult. However, previous studies indicated that serial changes on cTn levels could be equally effective in diagnosing AMI in patients with CKD and in those with normal

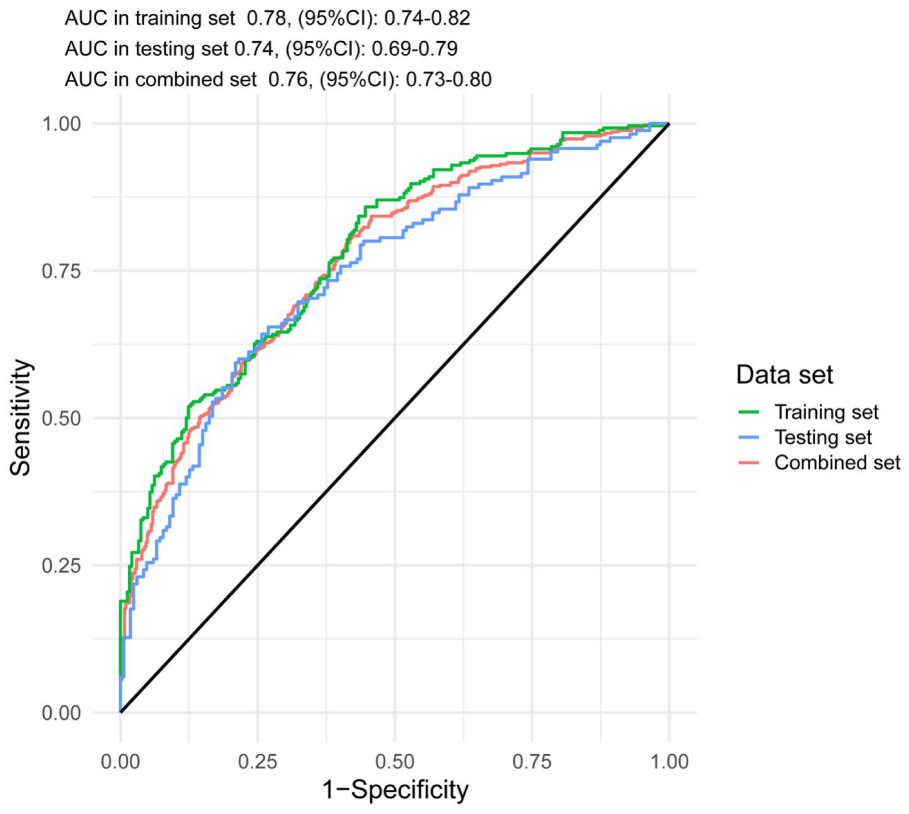

FIGURE 1
The ROC and AUC of SPHH-AMI-model in training set, testing set and combined set.

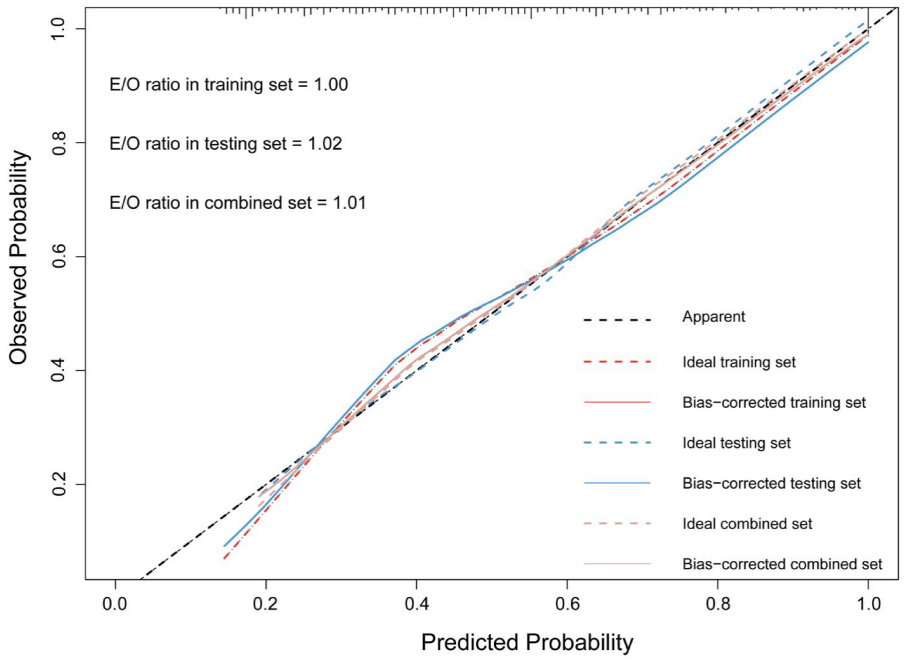

FIGURE 2
The calibration curve and E:O ratio of SPHH-AMI-model in training set, testing set and combined set.

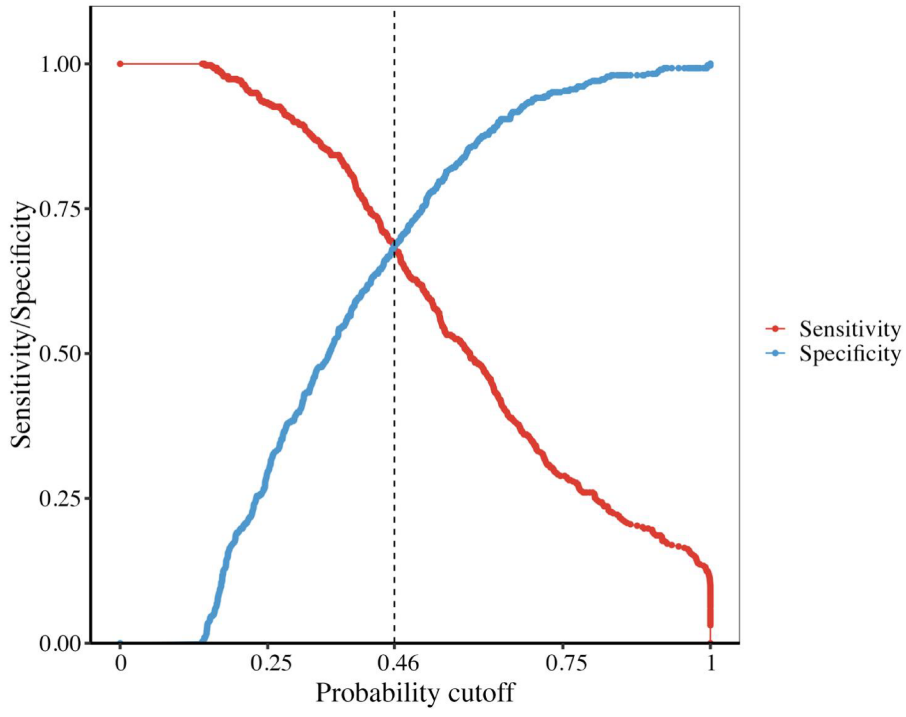

FIGURE 3
The sensitivity and specificity of our model intersected at the point 0.46 and the corresponding score is −0.1428.

renal function (16, 17). However, the dynamic changes in the levels of cTn could delay the treatment of these patients. The present study aimed to establish a practical and convenient model to promote the early diagnosis of AMI in patients with CKD via comprehensively analyzing relevant clinical risk factors and laboratory test indexes.

Herein, a new scoring system, namely SPPH-AMI-model, which included six novel risk factors, such as smoking status, hs-

TABLE 3 The predictive effectiveness of the model.

Prediction result	True result		合计
	Positive	Negative	
Positive	298	118	416
Negative	121	292	413
合计	419	410	829

Sensitivity: 71.12%.
Specificity: 71.21%.
Positive predictive value (PPV): 71.63%.
Negative predictive value (NPV): 70.70%.
Correction rate: 71.14%.

cTn, Scr and UA levels, history of PCI and ECG, was established. Emerging evidence has suggested that smoking is a major risk factor for CVD (18, 19). This observation is not only due to the fact that smoking has direct toxic effect on myocytes, such as in smoking cardiomyopathy, but also since smoking can cause several comorbidities, such as hypertension and atherosclerotic syndromes, which can also remodel and damage the heart (20). In addition, smoking can also result in vascular stiffness, injury and inflammation, possibly due to the increased levels of several biomarkers (21). It has been reported that impaired kidney function is an independent risk factor for adverse cardiovascular disease outcomes, including AMI, stroke and heart failure (22–25). Other studies also revealed that that higher Scr levels were associated with CVD mortality (26, 27). It has been also previously reported that UA is a significant risk factor for CVD (28). Another study demonstrated that UA could reduce the bioavailability of nitric oxide (NO) via promoting L-arginine degradation, blocking the uptake of L-arginine or scavenging NO from UA-generated oxidants or by UA itself (29). Additionally, UA could induce inflammatory responses (30), which in turn could promote vascular smooth muscle cell proliferation (31). Overall, UA could serve as an intrinsic risk factor in CVD. Interestingly, in the current model, the history of PCI was also a significant risk factor. A previous report on myocardial infarction in Norway showed that a high proportion of patients with AMI had a history of myocardial infarction (32).

Consistent with previous studies (33, 34), the results of the present study also verified that the levels of hs-cTnI were enhanced in several patients with CKD. Several pathological conditions could be involved in the above finding, including anemia, hypotension, small-vessel coronary obstruction, increased ventricular pressure and the direct toxic effects observed in uremic myocardiopathy (35). Overall, the above findings indicated that the increased levels of hs-cTnI could be strongly associated with the diagnosis of AMI in patients with CKD. Therefore, the higher the hs-cTn levels, the stronger the likelihood of developing AMI. Additionally, a previous study suggested that although hs-cTn could exhibit a high diagnostic accuracy in patients with AMI and CKD, the assay-specific optimal cut-off levels of hs-cTn in patients with CKD should be considered higher to ensure the best possible clinical use (4). Therefore, the SPPH-AMI model could more effectively quantify the association between hs-cTnI levels and AMI. In addition, changes in ECG can be also associated with the onset of AMI in clinical practice. Although the challenges in diagnosing AMI in patients with CKD using ECG are great, several patients with AMI and CKD may lack persistent ST-segment elevation. Additionally, it has been reported that ST-segment depression and T-wave inversion are very common in patients with CKD, even in the absence of AMI (36–38). Therefore, the results of the current study suggested that the ECG changes in AMI in patients with CKD, such as ST-segment depression or T-wave inversion, should be considered.

Previous studies also showed that in patients with CKD, regardless the presence of symptoms and clinical risk factors for AMI, ECG and the levels of hs-cTnI exhibited lower-than-expected diagnostic accuracy for AMI (5, 15, 39). Herein, all relevant clinical risk factors and laboratory test indexes, including several new biomarkers, such as B-type natriuretic peptide, were evaluated to establish the SPPH-AMI risk model for the early diagnosis of AMI in patients with CKD. Currently, no similar models have been developed. To the best of our knowledge, the SPPH-AMI-model is currently the only available risk scoring system, which can be used to help clinicians and emergency physicians to directly diagnose AMI in patients with CKD, thus preventing delayed treatment. Furthermore, herein, unlike other studies, patients with CKD-related mild renal insufficiency (eGFR, 60–90 ml/min/1.73 m^2) were also investigated.

However, the present study has some limitations. Firstly, the current study was a retrospective one. Therefore, further larger multicenter prospective studies are needed to verify the diagnostic value of the SPPH-AMI-model. As shown in **Table 3**, the correction rate of the model was unsatisfactory. This finding could be due to several reasons. Firstly, this was a retrospective study. Secondly, AMI in patients with CKD could be more insidious and the individual differentiation could be therefore greater. Furthermore, the association of AMI with other significant novel biomarkers, such as procalcitonin and Soluble ST2 (sST2), were not evaluated. Overall, further large multicenter prospective studies are required to identify novel biomarkers or risk factors for establishing a more accurate risk prediction model.

TABLE 4 The comparison of hs-cTn I in different eGFR groups in training set, testing set and combined set.

Group	eGFR [Median (Q1,Q3)]				*P*
	<15	15–30	30–60	60–90	
Combined group	0.72 (0.27, 7.16)	0.43 (0.15, 12.74)	0.19 (0.06, 1.11)	0.07 (0.03, 1.68)	<0.001
Non-AMI group	0.36 (0.17, 0.71)	0.20 (0.11, 0.42)	0.12 (0.05, 0.38)	0.04 (0.02, 0.15)	<0.001
AMI group	2.23 (0.42, 34.7)	6.28 (0.31, 84.24)	0.47 (0.10, 11.82)	0.43 (0.04, 21.76)	<0.001

Data availability statement

The data analyzed in this study is subject to the following licenses/restrictions: The original dataset contains some personal information. Requests to access these datasets should be directed to s18583798060@163.com.

Ethics statement

The study was approved by the ethical review board of the Sichuan Provincial People's Hospital [approval no. Lun Shen (Research) 2023 No. 201].

Author contributions

XS: Writing – original draft, Conceptualization, Data curation, Methodology. XC: Data curation, Methodology, Writing – original draft. TZ: Methodology, Visualization, Writing – review & editing. JS: Data curation, Investigation, Visualization, Writing – review & editing. XL: Data curation, Investigation, Writing – review & editing. XX: Methodology, Software, Writing – review & editing. NF: Conceptualization, Supervision, Writing – review & editing.

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Conflict of interest

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Impact of components of metabolic syndrome on the risk of adverse renal outcomes in patients with atrial fibrillation: a nationwide cohort study

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Background: The renal effect of metabolic syndrome components is unclear in patients with atrial fibrillation. This study aimed to investigate the association between metabolic syndrome components and incident end-stage renal disease among patients with atrial fibrillation.

Methods: A total of 202,434 atrial fibrillation patients without prevalent end-stage renal disease were identified from the National Health Insurance Service database between 2009 and 2016. We defined the metabolic score range from 0 to 5 points such that a patient received every 1 point if the patient met each component listed in the diagnostic criteria of metabolic syndrome. The population was divided into 6 groups: MS_0–MS_5 for a metabolic score of 0–5, respectively. Multivariate Cox regression analysis was used to estimate the risks of end-stage renal disease.

Results: There were 12,747, 31,059, 40,361, 48,068, 46,630, and 23,569 patients for MS_0–MS_5, respectively. Compared with MS_0, MS_5 had a higher CHA_2DS_2-VASc score (3.8 vs. 1.0) ($P < .001$). During a median follow-up of 3.5 years, compared with MS_0, MS_1–MS_5 were associated with a gradually increasing incidence of end-stage renal disease, in relation to an increase in the metabolic score, (log-rank $P < .001$). After multivariate adjustment, a higher metabolic score was associated with a greater risk of incident end-stage renal disease: adjusted hazard ratio [95% confidence interval] = 1.60 [0.78–3.48], 2.08 [1.01–4.31], 2.94 [1.43–6.06], 3.71 [1.80–7.66], and 4.82 [2.29–10.15], for MS_1–MS_5, respectively.

Conclusions: Metabolic syndrome components additively impacts the risk of incident end-stage renal disease among patients with atrial fibrillation.

KEYWORDS

atrial fibrillation, end-stage renal disease, epidemiology, metabolic syndrome, risk factor

1. Introduction

Atrial fibrillation (AF) and chronic kidney disease (CKD) have common risk factors, and they impact the progression of each other (1). AF is associated with an increased risk of CKD (2), while AF concurrent with CKD accelerates renal function decline, which may lead to renal failure (3). Renal failure has a crucial impact on AF management by limiting the choice of antiarrhythmic agents and oral anticoagulants that are used for stroke prevention (4). Relative to normal renal function, end-stage renal disease (ESRD) increases the risk of stroke or hemorrhage in patients with AF by 1.8-fold (5). Therefore, predicting a high-risk population for incident ESRD is important for managing AF.

Metabolic disorders are the leading cause of ESRD (6). In particular, hypertension and diabetes mellitus are common comorbidities in patients with AF, with prevalence rates as high as 68% and 23%, respectively (7). Furthermore, metabolic syndrome is prevalent in up to 22.7% of the AF population (8). However, the evidence for an association between metabolic syndrome and incident ESRD in patients with AF is scarce. Metabolic syndrome is a comprehensive disorder that includes obesity, lipid imbalance, hypertension, and impaired glycemic control (9). Although some studies have reported that hypertension or diabetes mellitus increases the risk of incident ESRD (10), there remains a lack of evidence on whether different types of metabolic disorders contribute additively to an increased risk of ESRD in patients with AF.

Considering that most patients with AF have multiple comorbidities, incident ESRD may be predicted better by stratifying patients according to the severity of metabolic disorders. The definition of metabolic syndrome includes five components: increased waist circumference, elevated triglycerides, low high-density lipoprotein cholesterol, increased blood pressure, and impaired fasting blood glucose (9). In this context, the status of metabolic syndrome may be considered severer when more criteria are met. Investigating the impact of each criterion on incident ESRD may help identify patients with AF who are at a high risk of ESRD.

This study aimed to investigate the impact of metabolic syndrome components on the risk of incident ESRD in patients with AF using a nationwide cohort study.

2. Materials and methods

This retrospective cohort study used the health checkup data from 2009 to 2016 available at the National Health Insurance Service (NHIS) of the Republic of Korea. Korean adults aged ≥40 years are subject to routine health checkups biannually. These health checkups are supported by the NHIS, which is the single public health insurer in Korea. The health check-up database comprises demographic information, history of claimed diagnostic codes, results of simple blood tests, and surveys on health habits. The use of the NHIS database for cardiovascular research has been described elsewhere previously (11). This study conformed to the Declaration of Helsinki revised in 2013, and was approved by the Institutional Review Board of the Seoul National University Hospital (No. 2301–030–1392). The requirement for informed consent was waived because of the nature of the study (anonymized data used retrospectively).

2.1. Study population

The flowchart of the study population is shown in **Figure 1**. From the database, we extracted the data of patients diagnosed with AF during 2009 to 2016. We excluded the following populations: (1) patients with prevalent ESRD ($n = 2091$); (2) patients with mitral stenosis or prosthetic heart valves ($n = 15{,}207$); (3) patients who had no available health checkups within 2 years from the diagnosis of AF ($n = 366{,}197$); (4) patients aged <20 years ($n = 29$); (5) patients with missing values for study covariates ($n = 1189$); and (6) patients with a follow-up period <1 year ($n = 4137$). Consequently, 202,434 patients with AF without prior ESRD were investigated.

2.2. Definitions of metabolic syndrome and the metabolic score

We defined the metabolic score range from 0 to 5 points, such that a patient received 1 point if he/she met each diagnostic criteria for metabolic syndrome. The diagnostic criteria of metabolic syndrome were defined based on an international guideline (9), with the adoption of the criteria for increased waist circumference according to the Korean Society for the Study of Obesity (12). The five diagnostic criteria are summarized in **Table 1**. The study population was then categorized into six groups (MS_0 to MS_5) according to their metabolic scores (0–5).

2.3. Study covariates

The study covariates were measured using data from the NHIS database. Individual covariates were obtained at the index health checkup, and **Supplementary Table S1** summarizes their detailed definitions. General information regarding the population's characteristics, including age, sex, height, body weight, CHA_2DS_2-VASc scores, alcohol consumption (yes/no), smoking (yes/no), regular exercise (yes/no), and low-income status (yes/no) was collected. Comorbidities were investigated using established diagnostic codes, including diabetes mellitus, ischemic heart disease, heart failure, ischemic stroke, peripheral artery disease, dyslipidemia, diabetes mellitus, chronic obstructive pulmonary disease, CKD, and any malignancy. Diagnostic codes were encoded according to the International Classification of Diseases, Tenth Revision, Clinical Modification. Data about concomitant medication, including oral anticoagulants (warfarin or direct oral anticoagulants), antiplatelet agents

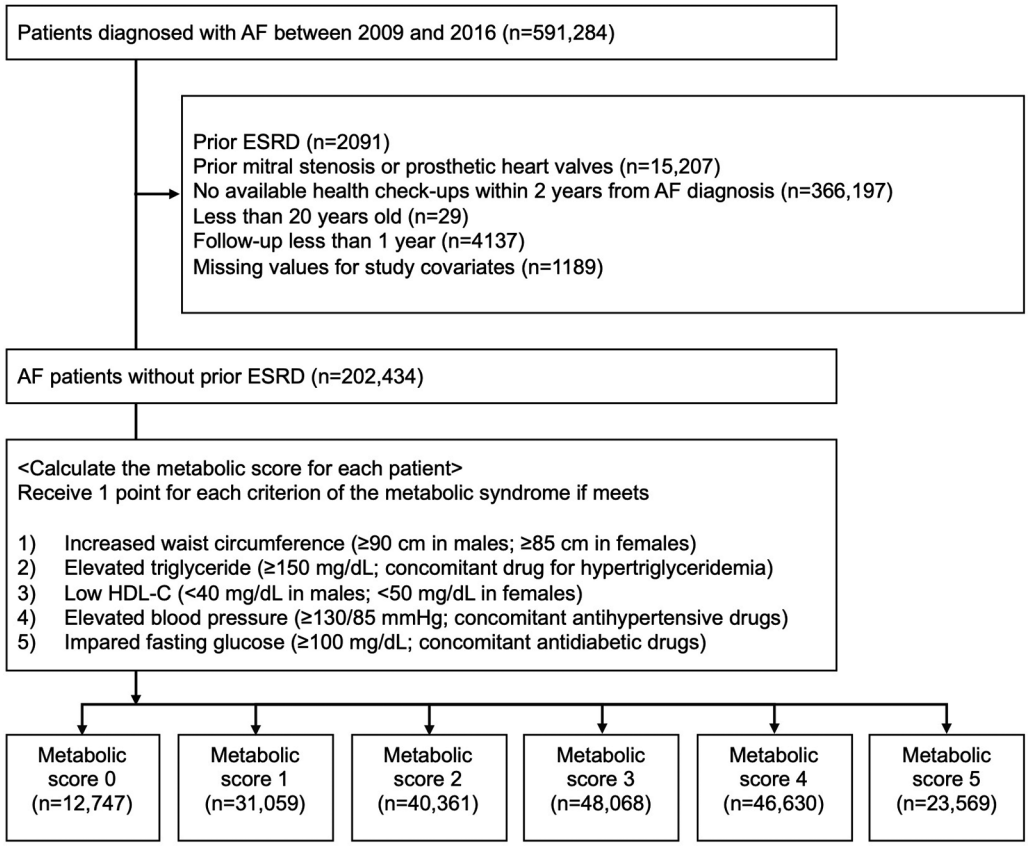

FIGURE 1
The flowchart of the study population. The study population was divided into 6 groups (MS0–MS5) according to each metabolic score (0–5). AF, atrial fibrillation; ESRD, end-stage renal disease; HDL-C, high-density lipoprotein cholesterol.

(aspirin or P_2Y_{12} inhibitors), antidiabetic drugs (sulfonylurea, meglitinide, metformin, thiazolidinedione, alpha-glucosidase inhibitors, dipeptidyl peptidase–4 inhibitors, and insulin), antihypertensive drugs (angiotensin receptor blockers, angiotensin-converting enzyme inhibitors, beta-blockers, calcium channel blockers, and diuretics), and statins were obtained from the claims database. Data for blood pressure, fasting blood glucose, total cholesterol, high- and low-density lipoprotein cholesterol (HDL-C, LDL-C), triglyceride, serum creatinine, and estimated glomerular filtration rate (eGFR) were obtained from the health checkup database.

TABLE 1 The definition of diagnostic criteria for metabolic syndrome (9).

Measure	Categorical cut points
Increased waist circumference	≥90 cm in males; ≥85% cm in females (12)
Elevated triglycerides	≥150 mg/dl (1.7 mmol/L); concomitant use of drugs for hypertriglyceridemia
Low HDL cholesterol	<40 mg/dl (1.0 mmol/L) in males; <50 mg/dl (1.3 mmol/L) in females
Elevated blood pressure	Systolic ≥130 mmHg and/or diastolic ≥85 mmHg; concomitant use of antihypertensive drugs
Impaired fasting blood glucose	Fasting plasma glucose ≥100 mg/dl (5.6 mmol/L); concomitant use of antidiabetic drugs

HDL, high-density lipoprotein.

2.4. Study outcomes and the follow-up

The primary outcome was incident ESRD, which was defined as having a diagnostic code (N18.5 or Z49) with hemodialysis or peritoneal dialysis ≥2 times during the follow-up period. Individuals were right-censored when the primary outcome occurred and were followed up from the index health checkup to December 31st, 2018.

2.5. Statistical analyses

Baseline characteristics were compared across the six groups (MS_0–MS_5) using a one-way analysis of variance or Kruskal–Wallis *H* test according to the type of covariate. Survival analysis was performed using the Kaplan–Meier method, and a log-rank test was used to compare survival across the six groups. Crude incidence rates (IRs) of ESRD were calculated in 1000 person-years. The risk of incident ESRD was estimated by multivariate Cox regression analyses and reported as adjusted hazard ratios (HRs) with 95% confidence intervals (CIs). The final model used covariates, including age, sex, body mass index, low-income status, health habits (including alcohol consumption, smoking, and regular exercise), comorbidities (including ischemic heart

disease, heart failure, stroke, peripheral artery disease, chronic obstructive pulmonary disease, and any malignancy), concomitant drug use (including oral anticoagulants and antiplatelet agents), the five metrics used in the definition of metabolic syndrome (including waist circumference, fasting blood glucose, blood pressure, triglyceride, and HDL-C), and renal function (eGFR). Subgroup analyses were performed for sex, strata of CHA_2DS_2-VASc scores (0–1 vs. ≥2), and strata of eGFR (≥60 vs. <60 ml/kg/1.73 m^2) and concurrent use of oral anticoagulant (OAC) (any vs. none). All statistical analyses were performed using SAS version 9.3 (SAS Institute, Cary, NC, USA). Two-sided $P < .05$ were used to reject the null hypothesis.

2.6. Additional analyses

To investigate the impact of each diagnostic criterion of metabolic syndrome on incident ESRD, the study population was divided according to the presence or absence of each diagnostic criterion of metabolic syndrome. The risk of incident ESRD was compared across the five groups based on patients meeting each diagnostic criterion. The impact of systolic blood pressure and fasting blood glucose levels on the incident ESRD risk was visualized using cubic spline curves.

We also calculated the area under the receiver operating characteristics curves (AUROCs) of metabolic scores and five components of metabolic syndrome (waist circumference, fasting blood glucose, systolic blood pressure, HDL-C, and triglyceride) to predict incident ESRD at 1-year.

2.7. Sensitivity analyses

A total of 11 statistical models were created using different sets of covariates for model adjustment, and their results were compared with those of the final model. A complete list of the statistical models is presented in **Supplementary Table S2**. We also compared the results of the final model with those of the other three models each with different covariates for renal function: eGFR, presence of CKD diagnosis (N18), and presence of decreased eGFR (<60 ml/kg/1.73 m^2) for Model 8, 9, and 10, respectively.

3. Results

3.1. Baseline characteristics

In total, 202,434 patients with AF without prior ESRD were included in the analysis. The study population was divided into six groups (MS_0–MS_5) according to their metabolic scores (0–5), with $n = 12{,}747$ (6.3%), 31,059 (15.3%), 40,361 (19.9%), 48,068 (23.7%), 46,630 (23.0%), and 23,569 (11.6%) in each subgroup, respectively. The population's mean age, male proportion, and CHA_2DS_2-VASc score were 63.5 ± 12.1 years, 49.5%, and 2.8 ± 1.6, respectively.

As the metabolic score increased, the population's age, body mass index, and comorbidities (except malignancy) also increased (**Table 2**); mean ages increased from 52.5 years (MS_0) to 66.3 years (MS_5); body mass index from 22.0 kg/m^2 (MS_0) to 27.7 kg/m^2 (MS_5); all $P < .001$. Furthermore, the concomitant medication (oral anticoagulants, antiplatelet agents, antidiabetic drugs, antihypertensive drugs, and statins) also increased in relation to metabolic score (from MS_0 to MS_5, **Table 2**); all $P < .001$. Among the laboratory test results, blood pressure, fasting blood glucose, triglyceride, and serum creatinine increased as the metabolic score increased, while total cholesterol, HDL-C, LDL-C, and eGFR decreased (**Table 2**); all $P < .001$.

3.2. Impact of the metabolic score on the risk of incident ESRD among AF patients

During a median follow-up of 3.5 (interquartile ranges, 1.7–5.6) years, the crude incidence rate of ESRD among AF patients gradually increased for higher metabolic scores; 0.16, 0.45, 0.70, 1.13, 1.87, and 2.48 per 1000 person-years for MS_0–MS_5, respectively. There was a significant difference in ESRD-free survival across the five groups (log-rank $P < .001$), although there was a comparable result between MS_0, MS_1, and MS_2 (pairwise log-rank $P \geq 0.05$) (**Figure 2**).

Metabolic syndrome was associated with a 2.9-fold increase in the risk of ESRD [adjusted HR 2.94 (95% CI, 1.43–6.06)]. After multivariate adjustment, the final model showed a trend for higher risk of incident ESRD in relation to higher metabolic scores (P-for-trend <.001) (**Figure 3**). Compared to MS_0, all others (except MS_1) were associated with significantly increased risks of incident ESRD (adjusted HR, 1.60 [95% CI 0.78–3.48], 2.08 [1.01–4.31], 2.94 [1.43–6.06], 3.71 [1.80–7.66], and 4.82 [2.29–10.15] for MS_1–MS_5, respectively (**Figure 3**).

3.3. Impact of metabolic syndrome component on incident ESRD

Among the five metabolic syndrome components, the increased risk of ESRD due to metabolic syndrome was primarily driven by elevated blood pressure; adjusted HRs (95% CI) in decreasing order, 2.20 (1.60–3.03), 1.66 (1.42–1.95), 1.61 (1.36–1.91), and 1.19 (1.02–1.40) for elevated blood pressure, impaired fasting blood glucose, low HDL-C, and elevated triglycerides, respectively (**Supplementary Figure S1**). In contrast, increased waist circumference did not significantly impact the risk of ESRD [adjusted HR 1.12 (95% CI, 0.90–1.38)]. The cubic spline curves showed that the systolic blood pressure and fasting blood glucose thresholds for increased ESRD risks were 125 mmHg and 113 mg/dl, respectively (**Figure 4**).

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TABLE 2 Baseline characteristics of the study population according to the metabolic score.

	MS_0 (n = 12,747)	MS_1 (n = 31,059)	MS_2 (n = 40,361)	MS_3 (n = 48,068)	MS_4 (n = 46,630)	MS_5 (n = 23,569)	P
Demographics							
Age, year	52.5 ± 14.8	60.7 ± 14.0	63.3 ± 12.7	64.7 ± 11.8	66.0 ± 10.9	66.3 ± 10.4	<.001
Men, %	6,808 (53.4)	19,301 (62.1)	25,103 (62.2)	28,403 (59.1)	27,150 (58.2)	13,168 (55.9)	<.001
Height, cm	163.8 ± 8.9	162.9 ± 9.4	162.5 ± 9.6	161.8 ± 9.7	161.6 ± 9.7	162.0 ± 9.8	<.001
Weight, kg	59.2 ± 9.5	60.8 ± 10.3	63.3 ± 11.4	64.5 ± 11.9	66.2 ± 11.9	72.9 ± 11.8	<.001
Body mass index, kg/m^2	22.0 ± 2.5	22.8 ± 2.7	23.9 ± 3.0	24.5 ± 3.2	25.3 ± 3.2	27.7 ± 3.1	<.001
CHA_2DS_2-VASc score							<.001
Mean	1.0 ± 1.0	2.1 ± 1.5	2.5 ± 1.7	3.0 ± 1.7	3.5 ± 1.7	3.8 ± 1.7	<.001
Median	1 (0–1)	2 (1–3)	2 (1–4)	3 (2–4)	3 (2–5)	4 (3–5)	<.001
Current smoker, %	2,026 (15.9)	4,797 (15.4)	5,974 (14.8)	6,645 (13.8)	6,296 (13.5)	2,953 (12.5)	<.001
Alcohol drinker, %	4,647 (36.5)	10,780 (34.7)	13,925 (34.5)	14,977 (31.2)	13,727 (29.4)	6,977 (29.6)	<.001
Regular exercise, %	2,807 (22.0)	6,763 (21.8)	8,468 (21.0)	9,862 (20.5)	9,519 (20.4)	4,521 (19.2)	<.001
Low-income status, %	2,482 (19.5)	6,300 (20.3)	8,336 (20.7)	9,932 (20.7)	9,736 (20.9)	5,128 (21.8)	<.001
Comorbidities, %							
Hypertension	0 (0)	16,981 (54.7)	26,904 (66.7)	38,031 (79.1)	42,184 (90.5)	22,656 (96.1)	<.001
Ischemic heart disease	187 (1.5)	689 (2.2)	1,081 (2.7)	2,254 (4.7)	3,101 (6.7)	1,569 (6.7)	<.001
Heart failure	1,031 (8.1)	5,501 (17.7)	8,339 (20.7)	11,281 (23.5)	12,325 (26.4)	6,589 (28.0)	<.001
Ischemic stroke	518 (4.1)	2,255 (7.3)	4,058 (10.1)	7,398 (15.4)	8,781 (18.8)	4,414 (18.7)	<.001
Peripheral artery disease	1,016 (8.0)	4,564 (14.7)	7,093 (17.6)	10,055 (20.9)	11,442 (24.5)	6,216 (26.4)	<.001
Dyslipidemia	871 (6.8)	2,214 (7.1)	6,858 (17.0)	24,260 (50.5)	35,137 (75.4)	20,623 (87.5)	<.001
Diabetes mellitus	0 (0)	1,163 (3.7)	5,799 (14.4)	8,508 (17.7)	17,448 (37.4)	13,424 (57.0)	<.001
COPD	1,568 (12.3)	5,268 (17.0)	7,151 (17.7)	8,572 (17.8)	8,848 (19.0)	4,552 (19.3)	<.001
Chronic kidney disease	600 (4.7)	3,042 (9.8)	5,310 (13.2)	7,850 (16.3)	9,545 (20.5)	5,557 (23.6)	<.001
Any malignancy	943 (7.4)	1,933 (6.2)	2,302 (5.7)	2,332 (4.9)	2,116 (4.5)	1,018 (4.3)	<.001
Concomitant drug, %							
Oral anticoagulant	1,530 (12.0)	6,341 (20.4)	9,412 (23.3)	13,563 (28.2)	14,870 (31.9)	8,117 (34.4)	<.001
Warfarin	1,313 (10.3)	5,140 (16.6)	7,397 (18.3)	10,399 (21.6)	10,962 (23.5)	5,727 (24.3)	<.001
DOAC	268 (2.1)	1,563 (5.0)	2,681 (6.6)	4,229 (8.8)	5,181 (11.1)	3,159 (13.4)	<.001
Antiplatelet agent	4,088 (32.1)	16,008 (51.5)	22,968 (56.9)	31,443 (65.4)	33,103 (71.0)	17,203 (73.0)	<.001
Aspirin	3,852 (30.2)	14,929 (48.1)	21,257 (52.7)	28,698 (59.7)	30,071 (64.5)	15,566 (66.0)	<.001
P_2Y_{12} inhibitors	895 (7.0)	3,893 (12.5)	6,247 (15.5)	12,051 (25.1)	14,742 (31.6)	7,830 (33.2)	<.001
Antidiabetic drugs	0 (0)	822 (2.7)	4,304 (10.7)	6,551 (13.6)	14,694 (31.5)	11,520 (48.9)	<.001
Antihypertensive drugs	0 (0)	15,657 (50.4)	24,951 (61.8)	36,020 (74.9)	40,670 (87.2)	22,178 (94.1)	<.001
Statin	0 (0)	0 (0)	3,540 (8.8)	21,341 (44.4)	33,558 (72.0)	20,259 (86.0)	<.001
Laboratory tests							
SBP, mmHg	112.3 ± 9.5	122.5 ± 14.7	125.6 ± 15.4	126.8 ± 15.6	128.6 ± 15.5	130.6 ± 15.7	<.001
DBP, mmHg	70.3 ± 7.4	75.8 ± 10.0	77.3 ± 10.3	77.8 ± 10.4	78.2 ± 10.5	78.9 ± 10.5	<.001
Fasting blood glucose, mg/dl	88.2 ± 7.3	93.1 ± 15.3	101.7 ± 23.6	102.8 ± 25.4	113.4 ± 32.7	124.1 ± 35.5	<.001
Total cholesterol, mg/dl	188.8 ± 32.9	188.3 ± 34.3	189.4 ± 39.3	182.1 ± 43.5	174.9 ± 44.4	171.1 ± 41.7	<.001
HDL-C, mg/dl	60.9 ± 16.2	57.4 ± 15.8	53.7 ± 17.3	50.7 ± 17.8	49.0 ± 17.2	48.1 ± 30.2	<.001
LDL-C, mg/dl	111.6 ± 34.6	112.5 ± 77.5	112.6 ± 42.6	103.9 ± 45.2	95.7 ± 44.2	91.0 ± 39.5	<.001
Triglyceride, mg/dl	82.9 ± 28.8	96.9 ± 50.6	120.2 ± 74.9	144.0 ± 98.5	158.8 ± 107.7	168.6 ± 112.1	<.001
Serum creatinine, mg/dl	0.91 ± 0.65	0.95 ± 0.63	0.98 ± 0.64	0.99 ± 0.80	1.01 ± 0.77	1.02 ± 0.53	<.001
Estimated GFR, ml/min/1.73m^2	89.6 ± 28.3	84.7 ± 29.8	82.1 ± 28.3	79.9 ± 31.2	77.3 ± 29.7	75.6 ± 27.4	<.001

COPD, chronic obstructive pulmonary disease; DBP, diastolic blood pressure; DOAC, direct oral anticoagulant; GFR, glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure.

MS_0–MS_5 denotes the populations with a metabolic score of 0–5, accordingly.

Data are presented as n (%), mean ± standard deviation, or median (interquartile range). P-values are for across six groups.

3.4. Subgroup analyses

There was no significant interaction for strata of CHA_2DS_2-VASc scores (0–1 vs. ≥2) and sex (P-for-interaction = .966 and.838, respectively) (**Supplementary Table S3**). Compared to the subgroup with preserved eGFR (≥60 ml/kg/1.73 m^2), the trend of increased risk for ESRD in relation to higher metabolic scores was accentuated in the subgroup with decreased eGFR (<60 ml/kg/1.73 m^2) (**Supplementary Table S3**). For the subgroup without OAC use, there was a trend of increasing risks of incident ESRD with higher metabolic scores (**Supplementary Table S3**). Conversely, for the subgroup with OAC use, no definitive trend was observed. However, there was no significant interaction (P-for-interaction = .115).

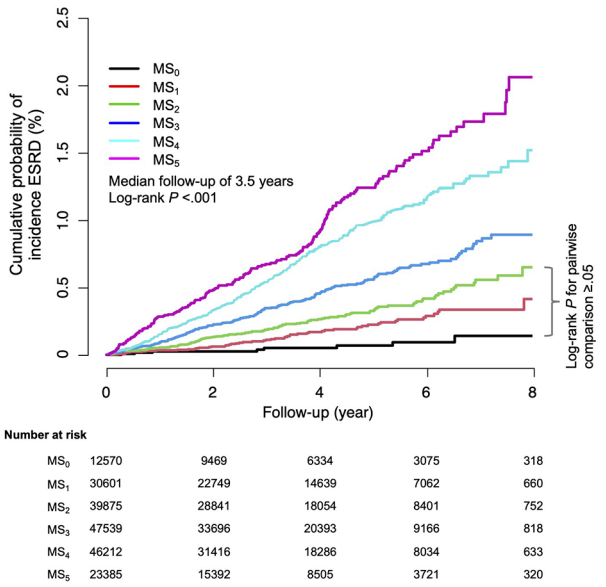

FIGURE 2
The cumulative incidence of ESRD among AF patients according to the metabolic score. The crude incidence rates of ESRD increased significantly as metabolic score increased (*P*-for-trend <.001). AF, atrial fibrillation; ESRD, end-stage renal disease; MS, metabolic score.

3.5. Sensitivity analyses

The main result was compared with different multivariate Cox regression analyses (Models 1–10). Regardless of the statistical models, there was a consistent trend of increasing risk of ESRD in relation to higher metabolic scores. However, the magnitudes of HRs decreased as more covariates were adjusted for (all *P*-for-trend < .001) (**Supplementary Table S4**). Consistent results were observed across the models regardless of the covariates representing renal function: eGFR, the presence of CKD diagnosis, or the presence of decreased eGFR (<60 ml/kg/1.73 m^2) for models 8, 9, and 10, respectively (**Supplementary Table S4**).

3.6. Performance of metabolic scores to predict incident ESRD at 1-year

The AUROCs of metabolic scores and the five components of metabolic syndrome are presented in **Table 3**. Compared to the metabolic components, except for systolic blood pressure, metabolic scores showed a significantly higher AUROC (0.68 with a 95% CI of 0.65–0.72). Compared to the AUROC of systolic blood pressure, that of metabolic scores showed a higher value with marginal significance (AUROC = 0.68 [95% CI 0.65–0.72] vs. 0.64 [95% CI 0.61–0.68], *P* = .096).

4. Discussion

This study investigated the impact of metabolic syndrome on the risk of incident ESRD in patients with AF using a nationwide cohort. Our principal findings were: (1) metabolic syndrome was associated with a 2.9-fold increase in the risk for ESRD; (2) there was a trend of increasing risks of incident ESRD as metabolic scores increased; and (3) the increased risk of ESRD due to metabolic syndrome was mainly driven by elevated blood pressure and impaired fasting blood glucose. To our knowledge, this is the first study to demonstrate an association between metabolic syndrome and incident ESRD in a nationwide AF population.

AF and renal function are closely interrelated (1, 2). Recent retrospective cohort studies showed a bidirectional association between AF and renal function (3, 13). While renal dysfunction was associated with an increased risk of AF, it may further aggravate the underlying renal dysfunction (3, 13), especially when blood pressure is poorly controlled (10). As a result, AF is vulnerable to renal failure.

Appropriate medical management becomes difficult if renal failure coexists with AF. First, the medical management of rhythm control is limited. Flecainide or sotalol are not recommended because of their dependency on renal excretion (14). Second, renal failure limits the optimal drug choice for stroke prevention and rhythm control in patients with AF. Although warfarin is

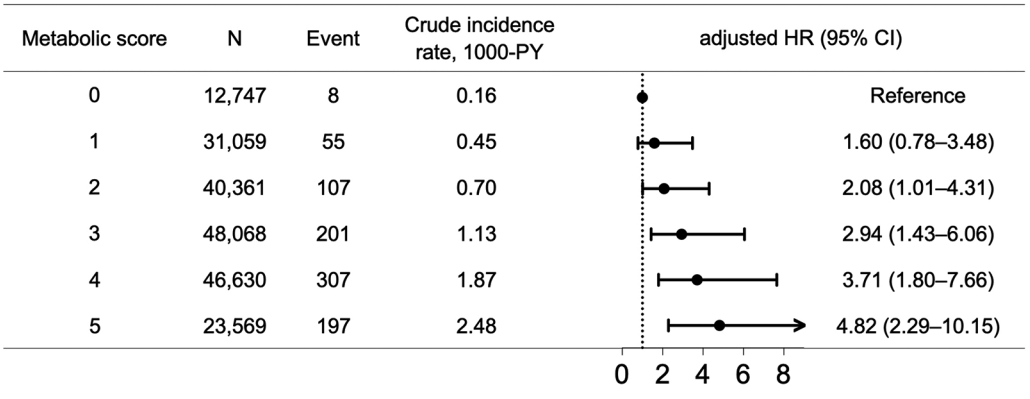

FIGURE 3
The risks of incident ESRD among AF patients across metabolic scores. There was a trend of increasing risks of incident ESRD for higher metabolic scores (*P*-for-trend <.001). AF, atrial fibrillation; CI, confidence interval; ESRD, end-stage renal disease; HR, hazard ratio; PY, person-year.

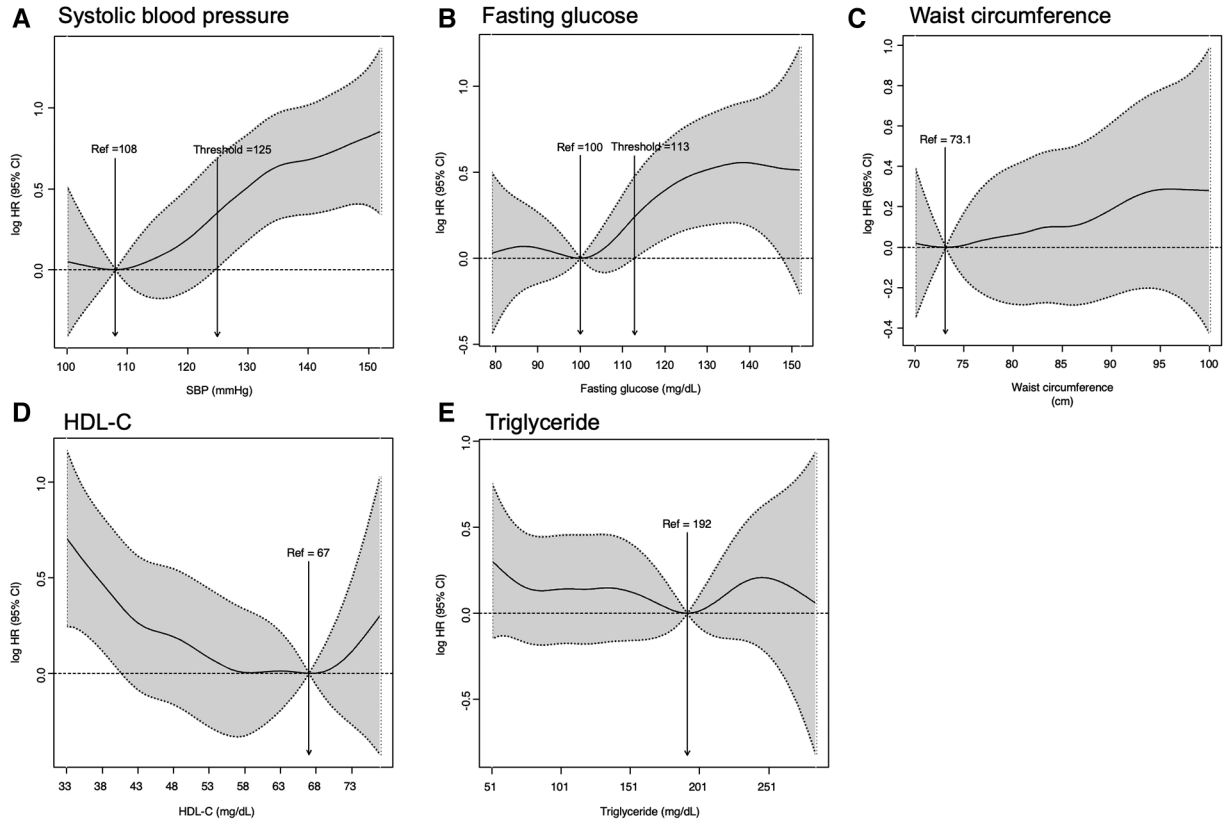

FIGURE 4
Impact of metabolic components on the risks of incident ESRD; (A) systolic blood pressure; (B) fasting blood glucose; (C) waist circumference; (D) HDL-C; (E) triglyceride. CI, confidence interval; ESRD, end stage renal disease; HDL-C, high-density lipoprotein cholesterol; HR, adjusted hazard ratio; Ref, reference; SBP, systolic blood pressure.

associated with a higher risk of bleeding compared to direct oral anticoagulants, it remains the mainstream treatment for stroke prevention in patients with AF and ESRD because direct oral anticoagulants are contraindicated due to their dependency on renal excretion (15). However, warfarin also accelerates calcific uremic arteriolopathy in ESRD, and increases mortality (16). While apixaban is approved by the Food and Drug Administration for stroke prevention among patients with AF requiring dialysis (17), the evidence is relatively weaker than its indicated general use among non-dialysis patients (18). Therefore, underlying renal failure complicates stroke prevention in patients with AF.

The medical management of AF with concurrent renal failure is a challenging task. Although there have been studies that reported the association between individual components of metabolic syndrome and ESRD, the impact of their interaction on ESRD is not well understood, especially in patients with AF. In the general population, some components of metabolic syndrome, such as hypertension and diabetes mellitus, are well-known risk factors for ESRD (19, 20). However, hypertension and diabetes often coexist with other metabolic disorders such as obesity and dyslipidemia. Therefore, a more comprehensive approach is necessary to improve the prediction of ESRD.

Metabolic syndrome, which is a broader concept (compared to hypertension or diabetes mellitus), has been reported to increase the risk of CKD by 34% in the Chinese population (21). In contrast, our study showed that metabolic syndrome increased the risk of ESRD by 2.9-fold. The higher impact of metabolic syndrome on ESRD could be due to an additive effect between metabolic syndrome and AF, since the latter also increases the risk of ESRD by 51% (22). AF itself may increase the risk of ESRD by multiple mechanisms, including renin-angiotensin-aldosterone system activation, volume retention, heart failure aggravation, renal artery thromboembolism, and decreased cardiac output and renal perfusion due to rapid/irregular ventricular rate (23). Furthermore, metabolic syndrome may further aggravate the risk of ESRD among patients with AF. Risk prediction for ESRD could be improved if it is individualized according to a patient's metabolic status.

TABLE 3 Comparison of AUROCs of metabolic scores and components of metabolic syndrome to predict incident ESRD at 1-year.

	AUROC (95% CI)	*P*
Metabolic scores	0.68 (0.65–0.72)	Reference
Systolic blood pressure	0.64 (0.61–0.68)	.096
HDL-C	0.62 (0.59–0.66)	.020
Fasting blood glucose	0.59 (0.54–0.64)	<.001
Waist circumference	0.57 (0.53–0.61)	<.001
Triglyceride	0.53 (0.49–0.57)	<.001

AUROC, the area under the receiver operating characteristics curve; CI, confidence interval; HDL-C, high-density lipoprotein cholesterol.

In this study, we compared the effect of each metabolic syndrome component. We found that the impact on the risk of incident ESRD varied across the five metabolic syndrome components (**Supplementary Figure S1**). The results suggest possible differences in the risk of ESRD among patients with AF and metabolic syndrome, depending on the diagnostic criteria they meet. Therefore, modifiable risk factors for ESRD should be identified and individualized management of AF is necessary to prevent ESRD.

4.1. Limitations

Some limitations of this study need to be addressed. First, because this study was retrospective, a nationwide cohort is needed to ascertain the causal relationship between metabolic syndrome and incident ESRD. Second, the five metrics used for defining metabolic syndrome, especially blood pressure, may vary from time to time among patients with AF. Therefore, the reliability of the results may be a concern. Third, our results may not be applicable to the Western population because the definition of increased waist circumference was based on the Korean guideline (12). Fourth, although we observed consistent results across different multivariate Cox regression analyses, hidden confounders might have significantly affected the results. Fifth, the etiology of incident ESRD among patients is unknown in our study. We presume that most causes were hypertension or diabetic nephropathy, as they are the two major risk factors for ESRD. Sixth, there could be the potential influence of warfarin use on our results, considering its known impact on vascular calcification and renal function decline. According to **Table 2**, the proportion of warfarin use increased from 10.3% in MS_0 to 24.3% in MS_5. If the increased use of warfarin had a significant biasing effect on our results, we would expect to observe divergent outcomes between Model 4 and Model 3, because Model 4 incorporated the covariates from Model 3, along with the inclusion of oral anticoagulants and antiplatelet agents. However, **Supplementary Table S4** demonstrates that both models yield comparable results. Based on these findings, we concluded that the potential bias arising from the increased use of warfarin might not be significant in our analysis. Seventh, this study could not analyze temporal trends in the associations between ESRD risks and metabolic scores. Metabolic scores could be dynamic and vary as patients age or receive medical management. However, this study utilized cross-sectional health check-up data, and therefore the dataset did not contain serial health check-up data for the study population. A further study is warranted to investigate the impact of temporal changes in metabolic status on the risk of ESRD. Eighth, the difference in the classes of antihypertensive and antidiabetic medications across groups could be potential bias in our study. To further investigate this issue, we analyzed the use of different drug classes among the groups, as presented in **Supplementary Table S5**. Our analysis revealed that the most used antihypertensive drug class was angiotensin receptor blockers, while the least used drug class was angiotensin-converting enzyme inhibitors, with similar patterns observed across the groups (excluding MS_0, where the use of antihypertensive drugs would not be expected). Furthermore, regardless of the metabolic score groups, the two most used antidiabetic drugs were metformin and sulfonylurea. Based on this analysis, it appears that the distribution of drug classes was similar among the different metabolic score groups. Ninth, although the use of OAC may prevent thromboembolic events, such as renal infarction, and potentially reduce the risk of incident ESRD, our study did not observe any significant interaction (**Supplementary Table S3**; *P*-for-interaction = .115). This lack of significant interaction could be attributed to the relatively low number of events among the subgroup with OAC use. Finally, this study has the potential for selection bias because it excluded patients who did not have health check-ups within two years of AF diagnosis. Furthermore, patients with longer AF durations may have results different from those of this study.

5. Conclusions

Metabolic syndrome is associated with an increased risk of incident ESRD in patients with AF. Metabolic syndrome components have an additive impact on the risk for incident ESRD. Among the five diagnostic criteria for metabolic syndrome, elevated blood pressure and impaired glycemic control were the most significant predictors, while increased waist circumference was not. Careful monitoring of declining renal function is advisable in patients with AF and severe metabolic syndrome.

Data availability statement

The raw data are available to researchers on relevant request and with approval by the Korean National Health Insurance Sharing Service.

Ethics statement

The studies involving humans were approved by Seoul National University Hospital Institutional Review Board. The studies were conducted in accordance with the local legislation and institutional requirements. The Ethics Committee/ institutional review board waived the requirement of written informed consent for participation from the participants or the participants' legal guardians/next of kin because The study used retrospective anonymized data.

Author contributions

Conceptualization: SK, SRL, EKC, SWL, JHJ, KDH, HJA, SO, and GYHL; Data curation: SK, SRL, EKC, SWL, JHJ, KDH, SO, and GYHL; Formal analysis: SK, SRL, EKC, SWL, JHJ, KDH, SO, and GYHL; Funding acquisition: EKC; Investigation: SK, SRL, EKC, SWL, JHJ, KDH, HJA; Methodology: SK, SRL,

EKC, SWL, JHJ, KDH; Project administration: EKC, and KDH; Resources: EKC, SWL, JHJ, and KDH; Software: SK, SRL, SWL, JHJ, and KDH; Supervision: SRL, EKC, KDH, SO, and GYHL; Validation: SK, SRL, EKC, SWL, JHJ, and KDH; Visualization: SK and SWL; Writing – original draft: SK and SRL; Figure and table generation: SK and SRL; Writing – review & editing: SK, SRL, EKC, KDH, SO, and GYHL. All authors contributed to the article and approved the submitted version.

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Conflict of interests

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Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2023.1208979/full#supplementary-material

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Diagnostic value of high sensitivity cardiac troponin T (hs-cTnT) in dialysis patients with myocardial infarction

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Background: As a sensitive diagnostic marker for myocardial infarction (MI) in people with normal renal function, elevated high sensitivity cardiac troponin T (hs-cTnT) was often found in chronic kidney disease (CKD) patients requiring dialysis. However, the accuracy of baseline hs-cTnT in the diagnosis of MI (including Type 1 MI (T1MI) and Type 2 MI (T2MI)) in dialysis patients is still controversial. The aim of this study was to retrospectively explore whether there were any clinical indices that could increase the predictive value of hs-cTnT on admission for MI occurrence in dialysis patients.

Methods: Here, 136 patients with uremia who underwent regular dialysis with coronary angiography in the First Affiliated Hospital of Nanjing Medical University from August 2017 to October 2021 were enrolled. According to the coronary angiography results and the presence of clinical symptoms, the patients were divided into: (1). AMI group ($n = 69$; angiography positive) and Control group ($n = 67$; angiography negative); (2). T1MI group ($n = 69$; angiography positive), T2MI group ($n = 7$; angiography negative & symptomatic), and Control group ($n = 60$; angiography negative & asymptomatic).

Results: Here, we found the mean hs-cTnT on admission in the Control group was much lower than that in the AMI group. Hs-cTnT alone had a mediocre predictive performance, with an AUROC of 0.7958 (95% CI: 0.7220, 0.8696). Moreover, the ROC curve of hs-cTnT combined with the Triglyceride (TG), Time of dialysis, and Albumin (Alb) showed a higher sensitivity area [0.9343 (95% CI: 0.8901, 0.9786)] than that of single hs-cTnT. Next, hs-cTnT combined with the TG, Time of dialysis, and Alb also presented a better performance in predicting T1MI [0.9150 (95% CI: 0.8678, 0.9621)] or T2MI (0.9167 [0.9167 (95% CI: 0.8427, 0.9906)] occurrences. Last, these combined variables could better distinguish patient between T1MI and T2MI group than hs-cTnT alone.

Abbreviations

AMI, acute myocardial infarction; hs-cTnT, cardiac troponin T; CKD, chronic kidney disease; Scr, serum creatinine; BUN, urea nitrogen; TC, total cholesterol; TG, triglyceride; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; ROC, receiving operational curve; AUC, the area under curve.

Conclusions: On admission, a combination of hs-cTnT, TG, Time of dialysis, and Alb presented a higher sensitivity than hs-cTnT alone in predicting MI occurrence in dialysis patients, suggesting a better diagnostic approach for future clinical applications.

KEYWORDS

chronic kidney disease, dialysis patients, MI occurrence, hs-cTnT, Albumin (Alb), triglyceride (TG)

Introduction

Chronic kidney disease (CKD), due to its incidence estimated to continuously grow, will bring a heavy global burden of disease (1, 2). Epidemiological study predicts that the number of dialysis patients in China will exceed 870,000 by 2025 (2). Cardiovascular disease (CVD), including acute myocardial infarction (AMI), is the most common cause of death for dialysis patients (3). Cardiac troponin T (hs-cTnT) can be used as a sensitive serological marker for the diagnosis of myocardial damage in people with normal renal function (4), but its levels vary across a considerable number of patients, who suffer end-stage renal disease (including dialysis patients), but show no clinical symptoms of MI (5, 6). At present, its prognostic significance in this patient population is still controversial.

In addition, serum hs-cTnT level increases nonlinearly with the deterioration of renal function, which makes it more difficult to predict the occurrence of MI in CKD patients (6). Also, a previous study has reported that hs-cTnT, just like tossing a coin, achieves a low accuracy in diagnosing MI in non-dialysis patients with renal insufficiency (7).

Here, we aimed to investigate the accuracy of baseline hs-cTnT in the diagnosis of MI in dialysis patients., and further explore whether any other clinical indices could increase the predictive value of hs-cTnT on admission.

Material and methods

Ethics statement and consent to participate

The clinic data of patients were collected according to the Declaration of Helsinki and the First Affiliated Hospital of Nanjing Medical University's ethics committee (No. 2023-SR-787). All the patients have been informed about this research, so that their written informed consent have be obtained in addition to other procedural safeguards.

Study design and population

A retrospective study was conducted on 136 patients with uremia who underwent regular dialysis with coronary angiography in the First Affiliated Hospital of Nanjing Medical University from August 2017 to October 2021. Patients' age, medical history, comorbidities, and risk factors for coronary heart disease (e.g., hypertension, diabetes, hyperlipidemia) were detailed. Among the 136 patients [93 males and 43 females, age 28–86 years (mean 64.14 ± 12.07 years)], 116 had hypertension and 77 had diabetes. 1. According to the coronary angiography results, the patients were divided into angiography positive group (AMI group, $n = 69$) and angiography negative group (Control group, $n = 67$). 2. According to the coronary angiography results and the presence of clinical symptoms, the patients were divided into Type 1 MI (T1MI) group ($n = 69$; angiography positive), Type 2 MI (T1MI) group ($n = 7$; angiography negative & symptomatic), and Control group ($n = 60$; angiography negative & asymptomatic).

Inclusion criteria

(1) Regular dialysis for uremia was performed in a period of over 6 months; (2) Blood hs-cTnT levels elevated; (3) The patient was accompanied with or without chest pain, chest tightness, dyspnea and other symptoms; (4) During dialysis, coronary angiography was performed to clarify coronary artery lesions.

All enrolled patients received coronary angiography for the following reasons: (1). Presented clinical signs of myocardial ischemia; (2). Abnormal cardiac markers; (3). Abnormal electrocardiogram results; (4). The required cardiovascular evaluation before surgery.

Exclusion criteria

The patient had other diseases that may cause hs-cTnT elevation, such as acute pericarditis, acute myocarditis, cardiomyopathy, tachycardia, myocardial contusion, subarachnoid hemorrhage, acute pulmonary embolism, sepsis, or post-AMI, etc.

Evaluation of coronary heart disease severity

Coronary angiography was performed by two experienced interventional cardiologists. Stenosis ≥50% was positive, and stenosis < 50% was negative. Since the well-known role of Gensini score in evaluating the severity of coronary atherosclerosis (8), Gensini score was calculated according to the location and degree of coronary stenosis in each patient. First, the basic score was determined according to the degree of

coronary artery stenosis: diameter stenosis <25% was given a score of 1 point, ≥25%–<50% of 2 points, ≥50%–<75% of 4 points, ≥75%–<90% of 8 points, ≥90%–<99% of l6 points, and 99%–100% of 32 points. Then, the basic scores in different coronary branches were multiplied by the following coefficients: left main artery (LM) disease ×5; left anterior descending branch (LAD) disease, proximal segment ×2.5, middle segment ×1.5, distal segment ×1, diagonal branch disease D1 × 1, D2 × 0.5; left circumvolute branch (LCX) disease, proximal segment ×2.5, blunt margin branch ×1, distal segment ×1, posterior descending branch ×1, posterior lateral branch ×0.5; right coronary artery (RCA) lesions, proximal, middle, distal and posterior descending branches ×1. The scores of all diseased vessels were summed to indicate the severity of coronary heart disease in one patient.

Physical and blood biochemical tests

Lung infection was evaluated based on the preoperative chest CT. After admission, the patient's resting blood pressure was measured by an electronic sphygmomanometer. Cubital venous blood was collected after 12 h of fasting before dialysis procedure. Measured were hs-cTnT, leukocyte, hemoglobin, serum creatinine (Scr), urea nitrogen (BUN), uric acid, serum Albumin (Alb), total cholesterol (TC), triglyceride (TG), high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C), electrolyte potassium, sodium, calcium, phosphorus and NT-proBNP levels. hs-cTnT was determined in serum using an Elecsys 2010 automated immunochemistry analyzer (Roche Diagnostics, Mannheim, Germany). LVEF level was evaluated by Simpson echocardiography. Serum levels of white blood cell, hemoglobin, Scr, BUN, uric acid, serum Alb, TC, TG, HDL-C, LDL-C, electrolyte potassium, sodium, calcium, phosphorus and NT-proBNP were measured. The level of LVEF was evaluated by Simpson method of cardiac echocardiography.

Random forest algorithm to assess predictive values

We performed receiving operational curve (ROC) analysis and calculated the area under curve (AUC) to assess the predictive performance of the model with the "pROC" R package. An optimal cut-off value was determined based on the ROC analysis, and the sensitivity and specificity were calculated according to the cut-off value.

Statistical analysis

Continuous variables were expressed by means ± standard deviations, and categorical variables by frequencies and percentages. The independent-samples t test was used to compare mean values in case and control groups. The chi-squared and Fisher exact test was used to describe qualitative data. hs-cTnT levels were log transformed, and partial correlation analysis was used to analyze the correlation coefficient between hs-cTnT level and influencing factors. The statistical significance level was set at $P < 0.05$. SPSS 20 statistical software was used to process the data.

Results

Patients' characteristics between AMI and control group

On admission, the epidemiological data, medical history, underlying comorbidities, and clinical symptoms of all the 136 dialysis patients were obtained with standardized forms. According to the results of coronary angiography, the dialysis patients were divided into the AMI group and the Control group. The AMI group ($n = 69$, 52 males, age 65.06 ± 10.82 years) was matched with the Control group ($n = 67$, 41 males, age 63.19 ± 13.25 years) in sex ($F = 0.097$, $P = 0.097$) and age ($F = 0.81$, $P = 0.371$). There were 49 patients (71%) with diabetes mellitus in the AMI group, which was significantly higher than that in the Control group ($P = 0.001$). The white blood cell count and uric acid level in the AMI group were significantly higher than those in the Control group ($P = 0.016$; $P = 0.036$), while the TG level, LVEF and dialysis time were significantly lower than those in the Control group (all $P < 0.05$; **Table 1**). Besides, the means of hs-cTnT were higher than the conventional reference in both groups. Nevertheless, the mean hs-cTnT in the Control group (100.35 ± 81.9) was much lower than that in the AMI group (1400.78 ± 2536.16) ($P = 0$).

The level of hs-cTnT was converted to log hs-cTnT, and the correlation between log hs-cTnT and Gensini score or physical and chemical indexes was analyzed by partial correlation analysis. The results showed that the level of log hs-cTnT was positively correlated with Gensini score, NT-proBNP and white blood cell count ($r = 0.364$, $r = 0.268$, $r = 0.326$, $P < 0.05$), and negatively correlated with TG, serum Alb and LVEF (%) ($r = -0.171$, $r = -0.171$, $P < 0.05$). $r = -0.313$, $r = -0.18$, both $P < 0.05$), but the correlation was weak (**Table 2**).

ROC curve of hs-cTnT for AMI diagnosis on admission

First, the value of hs-cTnT on admission in predicting the occurrence of AMI in the patients included in our study was assessed. As shown in **Figure 1**, hs-cTnT alone had a mediocre predictive performance, with an AUROC of 0.7958 (95%CI: 0.7220, 0.8696).

The areas under the ROC (AUCs) of hs-cTnT combined with diabetes, leukocyte count, uric acid, and LVEF (%) were 0.6907 (95% CI: 0.6009, 0.7804), 0.7994 (95% CI: 0.7263, 0.8725), 0.7923 (95% CI: 0.7173, 0.8674), and 0.9029 (95% CI: 0.8541, 0.9516), respectively (**Figure 2**). Interestingly, the AUC of a combination

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TABLE 1 Characteristics of the study subjects.

Characteristic	Control ($n = 67$)	Case ($n = 69$)	c^2 or F	P
Age (years)	63.19 ± 13.25	65.06 ± 10.82	0.81	0.371
Sex (male/female)	41/26	52/17	0.097	0.097
SBP (mmHg)	141.6 ± 23.37	144.1 ± 22.12	0.398	0.529
DBP (mmHg)	78.36 ± 12.61	78.93 ± 12.61	0.061	0.805
cTnT	100.35 ± 81.9	1400.78 ± 2536.16	17.59	0*
White blood cell ($\times 10^9$/L)	7.31 ± 3.13	8.86 ± 4.25	5.872	0.016*
Hemoglobin (g/L)	102.25 ± 21.26	98.10 ± 21.99	1.252	0.265
Scr (umol/L)	697.26 ± 226.98	625.6 ± 243.7	3.14	0.078
BUN (mmol/L)	20.5 ± 7.00	21.13 ± 7.30	0.275	0.601
Uric acid (umol/L)	330.84 ± 91.62	371.9 ± 130.46	4.479	0.036*
TG (mmol/L)	2.12 ± 1.88	1.50 ± 0.73	6.168	0.014*
TC (mmol/L)	3.94 ± 1.39	3.90 ± 1.39	0.051	0.822
HDL-C (mmol/L)	0.97 ± 0.27	0.93 ± 0.26	0.536	0.466
LDL-C (mmol/L)	2.38 ± 0.9	2.38 ± 0.98	0.009	0.924
Potassium (mmol/L)	4.34 ± 0.64	4.43 ± 0.63	0.598	0.441
Sodium (mmol/L)	138.64 ± 3.02	138.5 ± 4.06	0.043	0.836
Calcium (mmol/L)	2.24 ± 0.26	2.26 ± 0.24	0.075	0.785
Phosphorus (mmol/L)	1.74 ± 0.55	1.63 ± 0.42	1.858	0.177
NT-proBNP (pg/ml)	15973.41 ± 12316.96	19351 ± 12505	2.516	0.115
LVEF (%)	0.60 ± 0.07	0.53 ± 0.11	8.25	0.005*
Complication				
Hypertension (%)	54 (80.6%)	62 (89.9%)	0.151	0.151
Diabetes (%)	28 (41.8%)	49 (71%)	0.001	0.001*
Pulmonary infection (%)	26 (38.8%)	28 (40.6%)	0.862	0.862
Diabetic nephropathy (%)	17 (25.4%)	18 (26.1%)	1	1
Time of dialysis (years)	5.46 ± 5.12	3.45 ± 4.96	5.4	0.022*

*P-value < 0.05.

TABLE 2 Correlation analysis between cTNT level and influencing factors.

Demographics	log cTnT	
	Correlation coefficient	P value
Age (years)	0.122	0.163
Gensini score	0.364	0*
SBP (mmHg)	−0.085	0.33
DBP (mmHg)	−0.066	0.454
White blood cell ($\times 10^9$/L)	0.326	0*
Hemoglobin (g/L)	−0.089	0.31
Scr (umol/L)	−0.144	0.099
BUN (mmol/L)	0.154	0.076
Uric acid (umol/L)	0.081	0.357
TG (mmol/L)	−0.171	0.049*
TC (mmol/L)	0.049	0.576
HDL-C (mmol/L)	−0.041	0.639
LDL-C (mmol/L)	0.058	0.507
serum albumin (g/L)	−0.313	0*
Potassium (mmol/L)	0.15	0.085
Sodium (mmol/L)	0.02	0.817
Calcium (mmol/L)	0.024	0.78
Phosphorus (mmol/L)	0.079	0.366
NT-proBNP (pg/ml)	0.268	0.002*
LVEF (%)	−0.18	0.039*
Time of dialysis (years)	−0.073	0.408

*P-value < 0.05.

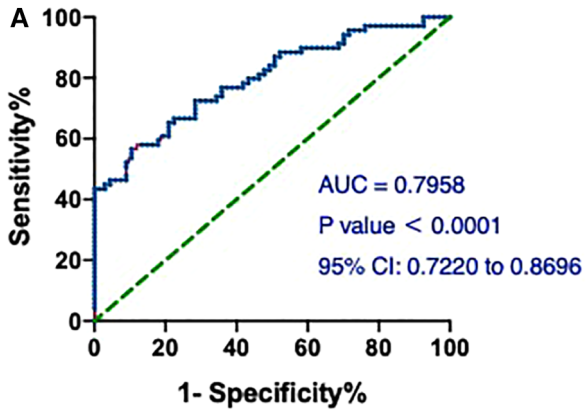

FIGURE 1
ROCs and AUC of hs-cTnT alone on admission in patients with AMI. A, hs-cTnT alone had a mediocre predictive performance, with an AUROC of 0.7958 (95% CI: 0.7220, 0.8696). The Random Forest algorithm was used to assess predictive values with the "pROC" R package.

of hs-cTnT, diabetes, leukocyte count, uric acid, and LVEF (%) was 0.9209 (95% CI: 0.8789, 0.9630).

Notably, the model showed a better predictive performance when including the combination of hs-cTnT and other clinical variables shown in Table 1 (AUROC: 0.9782, 95% CI: 0.9603, 0.9960) (Figure 3). We created a Random Forest model in R software to assess the effects of these variables on the predictive ability of hs-cTnT on admission. The results showed that TG, Time of dialysis, and Alb were the top three variables with the highest Mean Decrease Gini (Table 3). Next, on admission, the ROC curve of hs-cTnT combined with the TG, Time of dialysis, and Alb showed a higher sensitivity area [0.9343 (95% CI: 0.8901, 0.9786)] than that of single hs-cTnT (Figure 4), indicating the diagnostic value of these combined variables.

Patients' characteristics between T1MI, T2MI and control group

According to the newly released "Fourth Universal Definition of Myocardial Infarction", MI was classified into five types, the largest of which are T1MI and T2MI (9). Here, symptomatic patients with positive or negative angiographic results were enrolled in the T1MI o'r T2MI groups, respectively. The Control group ($n = 60$, 34 males, age 63.85 ± 13.49 years) was matched with the T1MI group ($n = 69$, 52 males, age 65.06 ± 10.82 years) and the T2MI group ($n = 7$, 7 males, age 57.57 ± 9.91 years) in age. However, there were significantly more males in T1MI and T2MI groups than in Control group ($P_{\text{Control vs. T1MI}} = 0.0388$; $P_{\text{Control vs. T2MI}} = 0.0375$). There were 49 and 6 patients with diabetes mellitus in

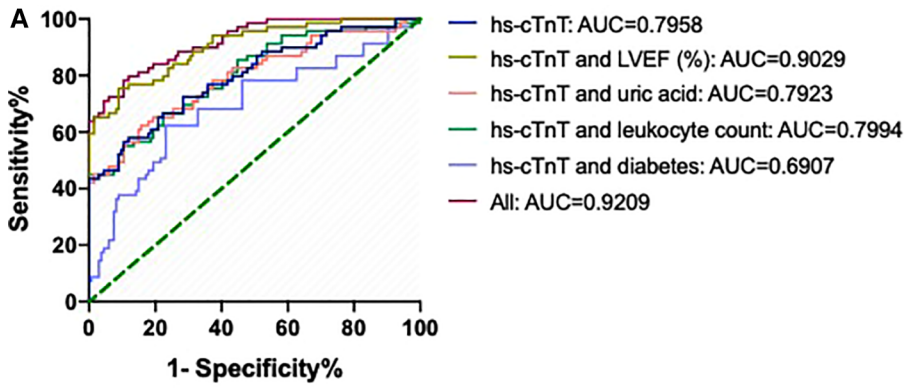

FIGURE 2
ROCs and AUCs of hs-cTnT combined with diabetes, leukocyte count, uric acid, and LVEF on admission in patients with AMI. Blue line: hs-cTnT alone; Light purple line: The combination of hs-cTnT and diabetes; Green line: The combination of hs-cTnT and leukocyte count; Pink line: The combination of hs-cTnT and uric acid; Golden line: The combination of hs-cTnT and LVEF (%); Diamond red line: The combination of hs-cTnT and diabetes, leukocyte count, uric acid, and LVEF. The Random Forest algorithm was used to assess predictive values with the "pROC" R package.

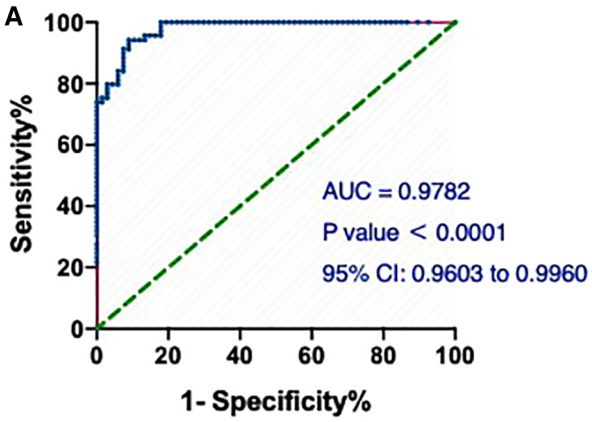

FIGURE 3
The ROC and AUC of hs-cTnT combined with other clinical variables on admission in patients with AMI. A, the model showed a better predictive performance when including the combination of hs-cTnT and other clinical variables shown in Table 1 (AUROC: 0.9782, 95% CI: 0.9603, 0.9960). The Random Forest algorithm was used to assess predictive values with the "pROC" R package.

the T1MI and T2MI group, respectively, which was significantly higher than that in the Control group ($P_{Control\ vs.\ T1MI} = 0.0001$; $P_{Control\ vs.\ T2MI} = 0.0183$). The White blood cell count and Uric acid level in the T1MI group were significantly higher than those in the Control group and T2MI group, while the TG level, Alb level, LVEF value and dialysis time were significantly lower than those in the Control group and T2MI (all $P < 0.05$; Table 4). Besides, the means of hs-cTnT were higher than the conventional reference in both groups. Nevertheless, the mean hs-cTnT in the T2MI group (1400.78 ± 2536.16) was much higher than that in the T2MI group (206.5 ± 77.56) and the Control group (87.97 ± 73.45) ($P = 0.0001$), while no significant difference of hs-cTnT was found between the T2MI and the Control group ($P = 0.9826$).

TABLE 3 Effects of clinical variables on the predictive ability of cTnT.

Demographics	Mean Decrease Gini
Serum albumin (g/L)	1.852768063
Time of dialysis (years)	1.013308308
Triacylglycerol (mmol/L)	1.001560376
LVEF (%)	0.911744318
Phosphorus (mmol/L)	0.814853869
Diabetes	0.751358035
White blood cell ($\times 10^9$/L)	0.667209224
LDL-C (mmol/L)	0.623972802
NT-proBNP	0.562943542
Hemoglobin (g/L)	0.542078011
Calcium (mmol/L)	0.533148112
Total cholesterol (mmol/L)	0.528054874
Age (years)	0.526987098
Uric acid (μmol/L)	0.519981876
Urea nitrogen (mmol/L)	0.516375421
Serum creatinine (μmol/L)	0.486196382
HDL-C (mmol/L)	0.459910766
Sodium (mmol/L)	0.450597923
Systolic pressure (mmHg)	0.408808899
Potassium (mmol/L)	0.399864695
Diastolic pressure (mmHg)	0.337324201
Hypertension (%)	0.205939855
Sex (male/female)	0.008855296

ROC curve of hs-cTnT for T1MI and T2MI diagnosis on admission

Then, we assessed the value of hs-cTnT on admission in predicting the occurrence of T1MI in the patients. As shown in Figure 5A, the AUCs of hs-cTnT alone were 0.8227 (95% CI: 0.7522, 0.8932). After combined with the top 3 variables (TG, Time of dialysis, and Alb) which generated from the Mean Decrease Gini data (Table 3), hs-cTnT showed a better predictive performance, with an AUROC of 0.9150 (95% CI: 0.8678, 0.9621) (Figure 5B).

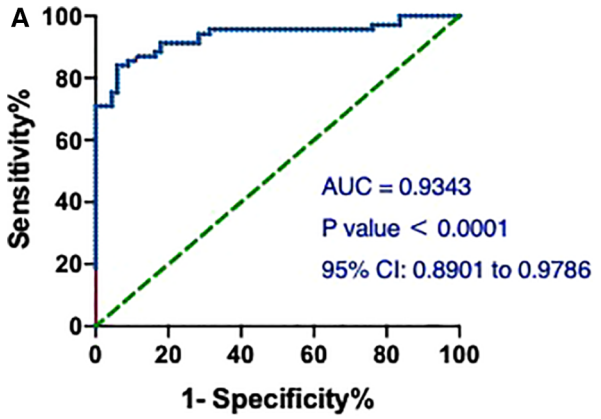

FIGURE 4
The ROC and AUC of hs-cTnT combined with the TG, time of dialysis (years) and Alb on admission in patients with AMI. A, the ROC curve of hs-cTnT combined with the TG, Time of dialysis, and Alb showed a higher sensitivity area [0.9343 (95% CI: 0.8901, 0.9786)] than that of single hs-cTnT. The Random Forest algorithm was used to assess predictive values with the "pROC" R package.

We next assessed the value of hs-cTnT on admission in predicting the occurrence of T2MI. The AUCs of hs-cTnT alone were 0.8976 (95% CI: 0.8076, 0.9877) (Figure 6A). Meanwhile, the ROC curve of hs-cTnT combined with the TG, Time of dialysis, and Alb showed a higher sensitivity area [0.9167 (95% CI: 0.8427, 0.9906)] than that of single hs-cTnT (Figure 6B).

Given the difference in mean hs-cTnT values between the T1MI and T2MI groups (Table 4), we performed ROC analysis and calculated the AUCs to assess the predictive performance of the model in distinguishing between patients in these 2 groups. The AUCs of hs-cTnT alone were 0.5652 ($P = 0.06537$) (Figure 7A). Notably, on admission, the ROC curve of hs-cTnT combined with the TG, Time of dialysis, and Alb showed a higher sensitivity area [0.7878 (95% CI: 0.5636, 1.000)] (Figure 7B).

Discussion

The large population of CKD in China, coupled with several "blocking points" in prevention and control, such as inadequate detection ability at the grassroots level, interaction with cardiovascular and metabolic diseases, and increasing number of end-stage patients requiring dialysis, will result in a greater public health burden in the future continuously, which requires urgent attention (1).

In this study, we for the first time found that hs-cTnT on admission, especially combined with some clinical variables, was sensitive to predict AMI in dialysis patients. In addition, it is often found that the CKD patients presenting with chest pain,

TABLE 4 Characteristics of the study subjects.

Characteristic	Control ($n = 60$)	T1MI ($n = 69$)	T2MI ($n = 7$)	P (Control vs. T1MI)	P (Control vs. T2MI)
Age (years)	63.85 ± 13.49	65.06 ± 10.82	57.57 ± 9.91	0.811	0.3443
Sex (male/female)	34/26	52/17	7/0	0.0388*	0.0375*
SBP (mmHg)	142.3 ± 23.82	144.1 ± 22.12	135.9 ± 19.57	0.8788	0.7259
DBP (mmHg)	78.45 ± 14.40	78.93 ± 12.61	77.57 ± 13.05	0.9739	0.9827
cTnT	87.97 ± 73.45	1400.78 ± 2536.16	206.5.78 ± 77.56	0.0001*	0.9826
White blood cell ($\times 10^9$/L)	7.20 ± 3.15	8.86 ± 4.25	8.21 ± 2.97	0.0261*	0.7448
Hemoglobin (g/L)	102.4 ± 21.16	98.10 ± 21.99	101.4 ± 23.80	0.4594	0.9926
Scr (umol/L)	701.9 ± 221.9	625.6 ± 243.7	657.0 ± 283.2	0.132	0.8626
BUN (mmol/L)	20.38 ± 7.09	21.13 ± 7.30	21.48 ± 6.74	0.7931	0.9087
Uric acid (umol/L)	325.6 ± 92.94	371.9 ± 130.46	375.9 ± 68.89	0.0425*	0.4553
TG (mmol/L)	2.20 ± 1.93	1.50 ± 0.73	1.39 ± 0.97	0.0109*	0.2752
TC (mmol/L)	4.09 ± 1.36	3.90 ± 1.39	2.89 ± 0.97	0.6751	0.0559
HDL-C (mmol/L)	0.96 ± 0.29	0.93 ± 0.26	0.83 ± 0.12	0.7271	0.4072
LDL-C (mmol/L)	2.47 ± 0.88	2.38 ± 0.98	1.64 ± 0.63	0.8053	0.0518
serum albumin (g/L)	37.61 ± 4.60	33.63 ± 4.73	33.46 ± 4.44	0.0001*	0.0528
Potassium (mmol/L)	4.30 ± 0.63	4.43 ± 0.63	4.61 ± 0.49	0.4574	0.3855
Sodium (mmol/L)	138.5 ± 3.00	138.5 ± 4.06	139.3 ± 3.15	0.9996	0.8207
Calcium (mmol/L)	2.29 ± 0.21	2.26 ± 0.24	2.21 ± 0.24	0.6373	0.5686
Phosphorus (mmol/L)	1.74 ± 0.53	1.63 ± 0.42	1.73 ± 0.65	0.3201	0.9982
NT-proBNP (pg/ml)	16515 ± 12361	19351 ± 12505	11330 ± 11755	0.35	0.4988
LVEF (%)	0.61 ± 0.07	0.53 ± 0.11	0.56 ± 0.10	0.0001*	0.4697
Complication					
Hypertension (%)	48 (80.0%)	62 (89.9%)	6 (85.7%)	0.1389	>0.9999
Diabetes (%)	22 (36.7%)	49 (71%)	6 (85.7%)	0.0001*	0.0183*
Pulmonary infection	24 (40.0%)	28 (40.6%)	2 (28.6%)	>0.9999	0.6972
Diabetic nephropathy (%)	14 (23.3%)	18 (26.1%)	3 (42.9%)	0.8386	0.358
Time of dialysis (years)	5.71 ± 4.88	3.45 ± 4.96	3.29 ± 6.97	0.0236*	0.4005

*P-value < 0.05.

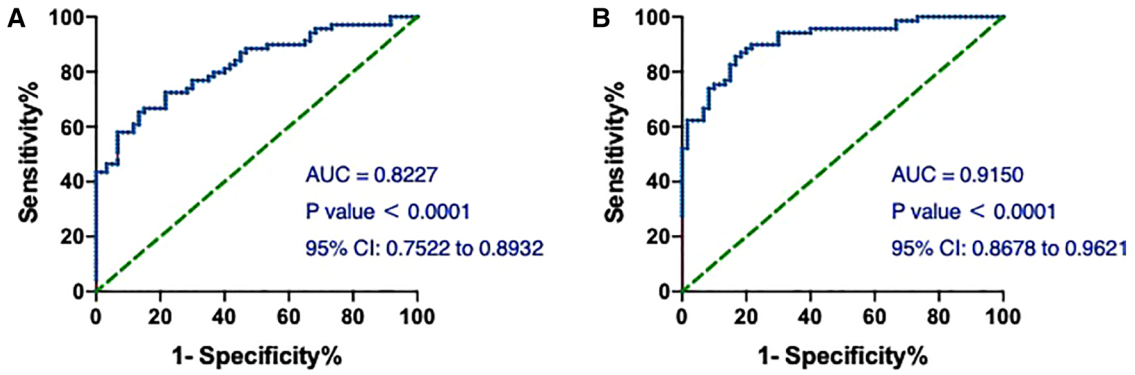

FIGURE 5
The ROC and AUC of hs-cTnT on admission in T1MI patients. (**A**) The ROC curve of hs-cTnT alone; (**B**) the ROC curve of hs-cTnT combined with the TG, Time of dialysis, and Alb. The Random Forest algorithm was used to assess predictive values with the "pROC" R package.

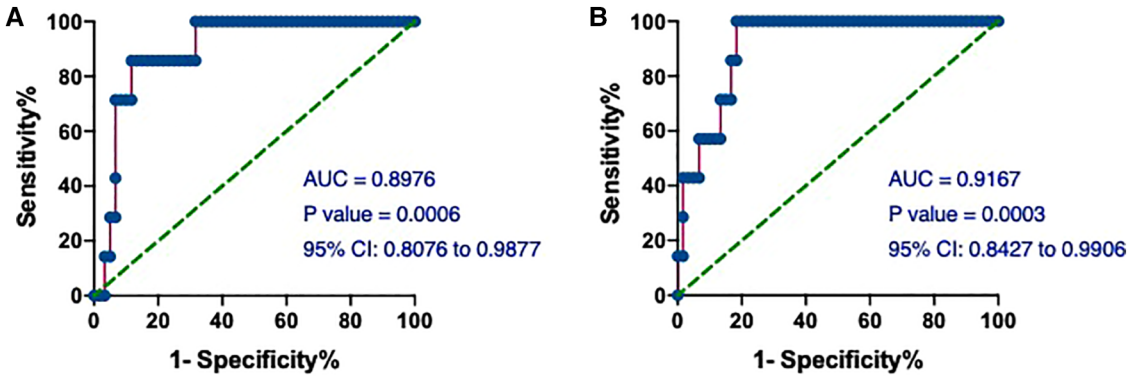

FIGURE 6
The ROC and AUC of hs-cTnT on admission in T2MI patients. (**A**) The ROC curve of hs-cTnT alone; (**B**) the ROC curve of hs-cTnT combined with the TG, Time of dialysis, and Alb. The Random Forest algorithm was used to assess predictive values with the "pROC" R package.

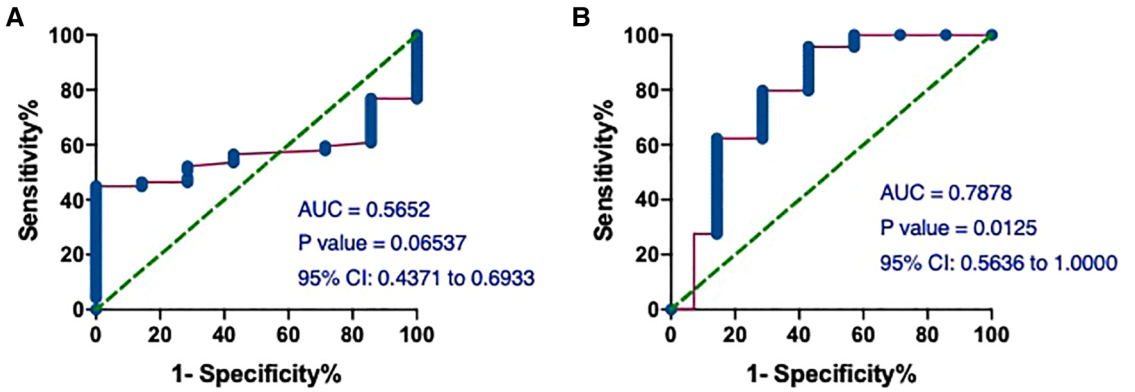

FIGURE 7
The ROC and AUC of hs-cTnT on admission between patients in T1MI and T2MI groups. (**A**) The AUCs of hs-cTnT alone were 0.5652 ($P = 0.06537$). (**B**) The ROC curve of hs-cTnT combined with the TG, Time of dialysis, and Alb showed a higher sensitivity area [0.7878 (95% CI: 0.5636, 1.000)]. The Random Forest algorithm was used to assess predictive values with the "pROC" R package.

though accompanied without AMI, have a permanently elevated high-sensitivity cardiac troponin (hs-cTn) (10, 11). Consistently, we found that the dialysis patients enrolled in our study, either with or without AMI, had hs-cTnT levels higher than the conventional reference.

As a protein mainly existing in the complex of hs-cTnT-cTnI-cTnC of cardiomyocyte filaments, hs-cTnT is commonly used as a biomarker for the diagnosis of acute coronary events (12). Specifically, when myocardial cells are damaged due to ischemia and hypoxia, hs-cTnT is unbound and released rapidly from the cells into the bloodstream, which may explain why hs-cTnT appears earlier in circulating blood and persists for a long period in diseases characterized by damage to cardiomyocytes, such as AMI (13, 14). It is reported that the sensitivity of hs-cTnT reaches more than 90% within 6 h after AMI onset and maintained for more than 5 days.

Although hs-cTnT is often used as a marker of AMI occurrence, its elevation is not specific. The fact that hs-cTnT is often higher than the conventional reference in other non-coronary diseases (including renal insufficiency) poses a great clinical challenge for physicians (5, 6). In our study, a large proportion of dialysis patients with elevated hs-cTnT levels did not have AMI. Several explanations have been proposed for the elevated hs-cTnT levels in patients with impaired renal function: (1) redistribution of hs-cTnT expression in striated muscle in patients with CKD; (2) antigen cross reaction; (3) myocardial microdamage by chronic renal insufficiency.

First, PCR can be used to detect the abnormal expression of hs-cTnT in patients with chronic renal insufficiency, which denies the first hypothesis (15). Then, the second generation hs-cTnT detection method can avoid antigen cross reaction (16, 17). Last, most scholars believe that the elevated serum hs-cTnT level in CKD patients is a sign of sustained damage or even apoptosis of cardiomyocytes caused by uremic toxin or complications (18). Advanced renal insufficiency, along with diabetes mellitus, is even regarded as an independent risk factor for ischemic heart diseases. Heart failure and ventricular remodeling, which are commonly complicated by CKD, may result in insufficient subendocardial perfusion and abnormal troponin release. Meanwhile, uremic toxin-induced uremic pericarditis, uremic myocarditis and uremic cardiomyopathy may be secondary to elevated serum troponin levels. In addition, population-based cohorts (19, 20) and pathological studies (21, 22) found that the estimated glomerular filtration rate (eGFR) was negatively correlated with the incidence of coronary atherosclerosis, and microvascular and macrovascular calcification. Asymptomatic myocardial ischemia or myocardial necrosis caused by these diseases may also cause the release of hs-cTnT from the myocardium into the bloodstream. Recent evidence suggests that the inflammatory response in patients with end-stage renal diseases may accelerate myocardial damage (23).

In addition to abnormal necrosis-unrelated release, impaired renal clearance provides a possibility to explain the elevated troponin in CKD patients. Free hs-cTnT, hs-cTnT-cTnI-cTnC complex and some hs-cTnT fragments are released into the bloodstream after myocardial damage. The relative molecular weight of hs-cTnT is 37 kDa, and that of hs-cTnT-cTnI-cTnC complex is 77 kDa. Healthy human kidneys can clear away cleaved hs-cTnT fragments (24). However, when renal function is impaired, decreased eGFR leads to the accumulation of hs-cTnT fragments in the body, which is manifested as an increase in serum hs-cTnT level (24). The rapid decline of serum hs-cTnT level after kidney transplantation can support this explanation (25).

Wayand et al. showed that the increase of serum hs-cTnT after hemodialysis was related to the concentration of blood after dialysis, but not with dialysis membrane and dialysis mode (26). Other scholars have suggested that hypotension and myocardial stunning during dialysis may also cause myocardial damage (27). Non-traditional risk factors, including uremic toxins, can also elevate infarct-unrelated troponin in uremic patients who need dialysis (28).

Therefore, hs-cTnT elevation is more accurate to predict acute or chronic myocardial injury, but does not necessarily indicate the occurrence of AMI. Nevertheless, an elevated hs-cTnT is strongly associated with poorer clinical outcomes and a higher mortality in CKD patients, no matter whether they are receiving dialysis or not (29). The US Food and Drug Administration has also endorsed the use of hs-hs-cTnT measurement for risk stratification in dialysis patients (30). Higher level of hs-cTnT was also linked to greater risk of long-term major adverse cardiovascular events (MACEs) (31). Indeed, a great difference in the AMI and the Control group for the values of hs-cTnT was observed. Besides, the predictive performance of hs-cTnT alone on admission for AMI was 0.7958 (95% CI: 0.7220, 0.8696) in our study, which is not too low. In addition, even in asymptomatic dialysis patients with or without known coronary diseases, temporal changes in hs-cTnT has been shown to be beneficial in predicting all-cause mortality, cardiovascular death, and sudden cardiac death independently (32, 33). Taking into consideration the fact that the huge differences of individual baseline hs-cTnT levels among dialysis patients (34), it is becoming increasingly important to better understand and quantify the expected temporal change of hs-cTNT over time, especially for patients with increased risks of CVDs. Though some authors preferred to increase the troponin threshold that signal MI (34), it would be better to check hs-cTnT level regularly in stable asymptomatic dialysis patients every 1–3 months or in cardiac symptomatic dialysis patients every 1–3 h to more rapidly rule-in and rule-out cases of MI. However, due to patients' compliance and economic conditions, we were not able to perform long-term follow-up of cTnT before and after PCI surgery or even after discharge for every enrolled patient, which remains to be further explored in our future investigation. Nevertheless, we explored other clinical indicators that could increase the sensitivity of hs-cTnT to predict the occurrence of AMI. Here, we ound that hs-cTnT combined with TG, Time of Dialysis (years), and Alb on admission showed a higher sensitivity than single hs-cTnT.

The low serum Alb level with high diagnostic sensitivity and specificity for ACS has attracted considerable attention (35). As a powerful predictor of all-cause mortality in patients with ACS (36), serum Alb level is initially proposed as an independent

predictor of MACEs (37). Recent studies also reported that the CRP-Alb ratio or ischemia-modified Alb (IMA) is associated with high thrombus burden in patients with MI (38, 39). In addition, the serum Alb level was correlated significantly with cTnT levels in patients with acute ischemic stroke (AIS) (40). The combination of hs-cTnT, serum Alb, and other clinical variables allowed a risk distinction for morbidity in heart failure with preserved ejection fraction (HFpEF) patients (41).

Previous studies also revealed that serum TG was independently associated with the occurrence of ACS and the risk of coronary heart disease (CHD) recurrence, which may be important for risk stratification and management of patients before and after ACS occurrence (42, 43). Besides, in patients with renal dysfunction, TG correlated with cTnT may be a renal risk parameter (44). In addition, the TG-glucose index (TyG index) was regarded as a non-linear and reliable predictor of MACE in patients with ACS (45).

Recently, novel hs-cTnT assays, which permit the detection of low levels of cTnT, indeed improved diagnostic sensitivity of patients with suspected AMI in the hospital setting. However, when applied to individuals with factors associated with higher levels of cTnT, including CKD, the test results may be less specific. Moreover, the false-positive diagnosis of AMI would lead to more unnecessary intensive treatment like percutaneous intervention (PCI) surgery, which brings heavy economic burden to the family and society, and causes great waste of medical resources. Thus, novel approach integrating more clinic indexes with hs-cTnT to improve the diagnostic accuracy of MI (including T1MI and T2MI) is needed. In the present study, an encouraging result we found is that cTnT combined with TG, Time of Dialysis (years), and Alb on admission had a higher predictive value, which may help in the early prevention and cure of the sudden cardiac death or other adverse cardiovascular outcomes for patients with MI, and further provide theoretical basis for our subsequent clinical cohort study.

Last, as a subset of ACS, MI is classified into five types according to the established "Fourth Universal Definition of Myocardial Infarction" which released by the Joint European Society of Cardiology (ESC)/American College of Cardiology (ACC)/American Heart Association (AHA)/World Heart Federation (WHF) Task Force (9), which subsequently increases the awareness and knowledge about a surge of suspicious MI cases. The pathogenetic mechanisms underlying five types of MI differs widely. T1MI, the most common type of MI, is defined as ischemic necrosis of cardiomyocytes secondary to coronary thrombosis. T2MI occurs due to the imbalanced oxygen supply and/or demand induced by pathological conditions other than acute plaque change in the coronary vasculature (46). The last 3 types of MI are reportedly less than 5% of the total MI cases, including cardiac death (9). The distinct demographics between T1MI and T2MI are obviously different (47). Notably, T2MI occurs frequently among the elderly with multiple comorbidities and high-risk cardiovascular profiles, and therefore has a poorer prognosis than T1MI (47). Till now, since no significant differences of clinical signs and symptoms between T1MI and T2MI, effective and timely diagnosis of T2MI remains challenging, which entails accurate prevalently angiography (48). However, compared to the invasive and expensive angiography, additional evidence-based patient-tailored therapeutic means of T2MI were warranted. Like the previous study (49), our analysis found that the value of hs-cTnT in T1MI was significantly higher than that in T2MI. Notably, compared with cTnT alone, cTnT combined with TG, Time of Dialysis (years), and Alb could not only better predict the occurrence of T1MI and T2MI, but also better distinguish T1MI and T2MI in our study. However, further cohort studies should be well-designed to evaluate whether diagnostic algorithms based on clinical symptoms and hs-cTnT values could improve the differential diagnosis among coronary events from non-coronary sources of MI, as well as between T1MI and T2MI.

Limitations

The number of enrolled patients' needs to be further increased. At the same time, data from more centers could have been included in this study, which would strongly support our results. In addition, the enrolled patients need to be followed up for a longer period of time to clarify the effect of hs-cTnT on the long-term outcome of hemodialysis patients.

Conclusions

A higher serum hs-cTnT level may be more predictive of AMI occurrence. On admission, a combination of hs-cTnT, TG, Time of Dialysis (years), and Alb presents a higher sensitivity than single hs-cTnT. The diagnostic value of these combined variables should be further evaluated before clinical application.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding authors.

Ethics statement

The clinic data of patients were collected according to the Declaration of Helsinki and the First Affiliated Hospital of Nanjing Medical University's ethics committee (No. 2021-SR-501). All the patients have been informed about this research, so that their written informed consent have be obtained in addition to other procedural safeguards. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

KZ: Funding acquisition, Writing – original draft, Writing – review & editing. BS: Investigation, Methodology, Writing – original draft. HW: Methodology, Project administration, Software, Supervision, Writing – original draft. RL: Formal Analysis, Project administration, Validation, Writing – original draft. YL: Data curation, Methodology, Project administration, Writing – original draft. CX: Data curation, Project administration, Validation, Writing – original draft. HC: Writing – review & editing. YH: Writing – review & editing. PL: Writing – review & editing. XY: Resources, Validation, Visualization, Writing – original draft. YL: Funding acquisition, Writing – review & editing, Writing – original draft.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Standardized risk-stratified cardiac assessment and early posttransplant cardiovascular complications in kidney transplant recipients

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Introduction: Cardiovascular disease (CVD) is the leading cause of morbidity and mortality in kidney transplant recipient (KTR). There is a dearth of standardized guidelines on optimal cardiovascular evaluation of transplant candidates.
Methods: This single-center cohort study aims to determine the effectiveness of our standardized risk-stratified pretransplant cardiovascular screening protocol, which includes coronary angiography (CAG), in identifying advanced CVD, the proper pretransplant management of which could lead to a reduction in the incidence of major cardiac events (MACE) in the early posttransplant period.
Results: Out of the total 776 KTR transplanted between 2017 and 2019, CAG was performed on 541 patients (69.7%), of whom 22.4% were found to have obstructive coronary artery disease (CAD). Asymptomatic obstructive CAD was observed in 70.2% of cases. In 73.6% of cases, CAG findings resulted in myocardial revascularization. MACE occurred in 5.6% ($N = 44$) of the 23 KTR with pretransplant CVD and 21 without pretransplant CVD. KTR with posttransplant MACE occurrence had significantly worse kidney graft function at the first year posttransplant ($p = 0.00048$) and worse patient survival rates ($p = 0.0063$) during the 3-year follow-up period compared with KTR without MACE. After adjustment, the independent significant factors for MACE were arrhythmia (HR 2.511, $p = 0.02$, 95% CI 1.158–5.444), pretransplant history of acute myocardial infarction (HR 0.201, $p = 0.046$, 95% CI 0.042–0.970), and pretransplant myocardial revascularization (HR 0.225, $p = 0.045$, 95% CI 0.052–0.939).
Conclusion: Asymptomatic CVD is largely prevalent in KTR. Posttransplant MACE has a negative effect on grafts and patient outcomes. Further research is needed to assess the benefits of pretransplant myocardial revascularization in asymptomatic kidney transplant candidates.

KEYWORDS

kidney, transplantation, cardiovascular disease, cardiovascular evaluation, cardiovascular complications, major adverse cardiac event, end-stage renal disease

1 Introduction

Cardiovascular disease (CVD) is the leading cause of morbidity and mortality in both patients with advanced chronic kidney disease (CKD) and kidney transplant recipients (KTR). The prevalence in these patient populations is approximately 30 times higher compared with age-adjusted non-CKD populations (1, 2). Furthermore, an increased

incidence of infections during the first year after transplantation contributes to a higher morbidity and mortality rate of KTR. The persistent inflammatory state associated with kidney transplantation may be aggravated by both endogenous and exogenous stimuli, leading to further activation of immune system which is a prerequisite for developing CVD (3). Prior to transplantation, the patients are already exposed to a uremia-associated chronic proinflammatory environment, which is characterized by elevated levels of proinflammatory cytokines (interleukin-6, IL-6, fibroblast growth factor-23, FGF-23), C-reactive protein (CRP), oxidative stress, endothelial dysfunction, and a calcium–phosphate metabolism disorder (4). This preexisting inflammatory state may be enhanced by posttransplant factors such as an inflammatory cytokine storm induced by donor brain death, ischemia-reperfusion injury, donor-specific antibodies associated with allograft rejection, cytomegalovirus infection stimulating innate immunity via interferon-stimulated genes, and calcineurin inhibitors (CNI) commonly used as concomitant immunosuppressive agents that promote endothelial activation, dysregulation of lipid and glucose metabolism, and hypertension (3, 5, 6). These pre- and posttransplant factors contribute to the acceleration of atherosclerosis and to an increased risk of cardiovascular events in KTR.

Recently, due to a marked improvement in patient survival, the criteria for accepting transplant candidates have been expanded, and the number of high-risk patients with CVD referred for transplantation has thus increased. Therefore, a complex pretransplant examination, especially of the cardiovascular system, has become ever more crucial for the proper assessment of the transplant candidates' suitability for transplantation and for the minimization of the incidence of posttransplant cardiovascular events that could negatively impact transplant outcomes. The data concerning pretransplant myocardial revascularization remain ambiguous due to a lack of clear evidence as to its beneficial impact on the posttransplant course of patients, particularly asymptomatic patients, as even controlled randomized studies in non-CKD populations did not provide any such evidence (7–9). Current guidelines recommend the performance of resting electrocardiography (ECG) and echocardiography (ECHO) in all renal transplant candidates. However, there were no definite guidelines on how to approach asymptomatic candidates or candidates with known CVD. For this reason, the scope of the cardiological examination was based on the risk stratification defined in the 2012 scientific statement by the American Heart Association/American College of Cardiology Foundation (AHA/ACC) that was written specifically for patients with ESRD being evaluated for kidney transplantation (10). These recommendations were based on published studies, surveys, and registry data and took into account the medical history, physical examination, cardiac conditions, and presence of risk factors. Risk factors such as age over 60 years, hypertension, dyslipidemia, smoking, diabetes mellitus, history of CVD, left ventricular hypertrophy, and dialysis therapy of more than a year are already present in most patients who are referred for kidney transplantation, and thus they can be stratified as "high-risk" patients (11). The recently published AHA scientific statement from 2022 provides clinicians additional precise guidance by specifically addressing the concerns of kidney transplant candidates (12).

In ESRD patients, clinically silent CVD is very common, and normal findings on the ECG and ECHO do not exclude serious coronary involvement. The majority of published studies recommend extended cardiovascular screening, including non-invasive cardiac stress tests (dobutamine stress echocardiography, myocardial perfusion scan) and coronary angiography (CAG), only in patients with multiple risk factors (13, 14). The situation in CKD patients is further complicated by the fact that there are significant differences in the sensitivity and specificity of cardiac stress tests ranging from 38% to 95% accuracy, despite the strong positive predictive value of up to 96% when detecting obstructive coronary artery disease (CAD) (15, 16). Besides ECG and ECHO, the gold standard for assessing the condition of the cardiovascular system is CAG, which represents the only method that allows for an objective assessment of the condition of patients' coronary arteries regardless of distinct symptoms that are often absent in the majority of end-stage renal disease (ESRD) patients. An alternate modality to CAG that can be used for imaging of the coronary arteries is CT angiography (coronary computed tomography angiography, CCTA), especially in the patients in whom non-significant finding is expected (17).

In this study, we aim to evaluate whether our standardized risk-stratified pretransplant cardiovascular protocol that includes CAG screening in addition to ECG and ECHO may be useful in the detection of advanced cardiovascular disease, the proper pretransplant management of which could lead to a reduction in the incidence of major cardiac events (MACE) in the early posttransplant period.

2 Materials and methods

2.1 Study design

This single-center, observational retrospective cohort study was conducted in adult patients who underwent kidney transplantation at our center between January 2017 and December 2019. Prior to transplantation, all individuals were evaluated using our standardized pretransplant risk-stratified cardiovascular protocol consisting of resting 12-lead electrocardiography (ECG), resting thoracic echocardiography, and coronary angiography. ECG and ECHO were performed in all kidney transplant candidates, while CAG was performed only in high-risk patients. A high-risk patient was defined as a patient with a presence of several risk factors: age over 40 years and/or with a history of diabetes, CVD or cardiovascular symptoms, and/or pathological findings on ECG and ECHO. A low-risk patient was defined as a patient aged 40 years and younger, with the absence of diabetes, with the absence of CVD or its symptoms, and with normal findings on resting ECG and ECHO (Figure 1). The pretransplant cardiovascular disease was recorded in patients with a history of myocardial infarction, heart failure or cardiac revascularization,

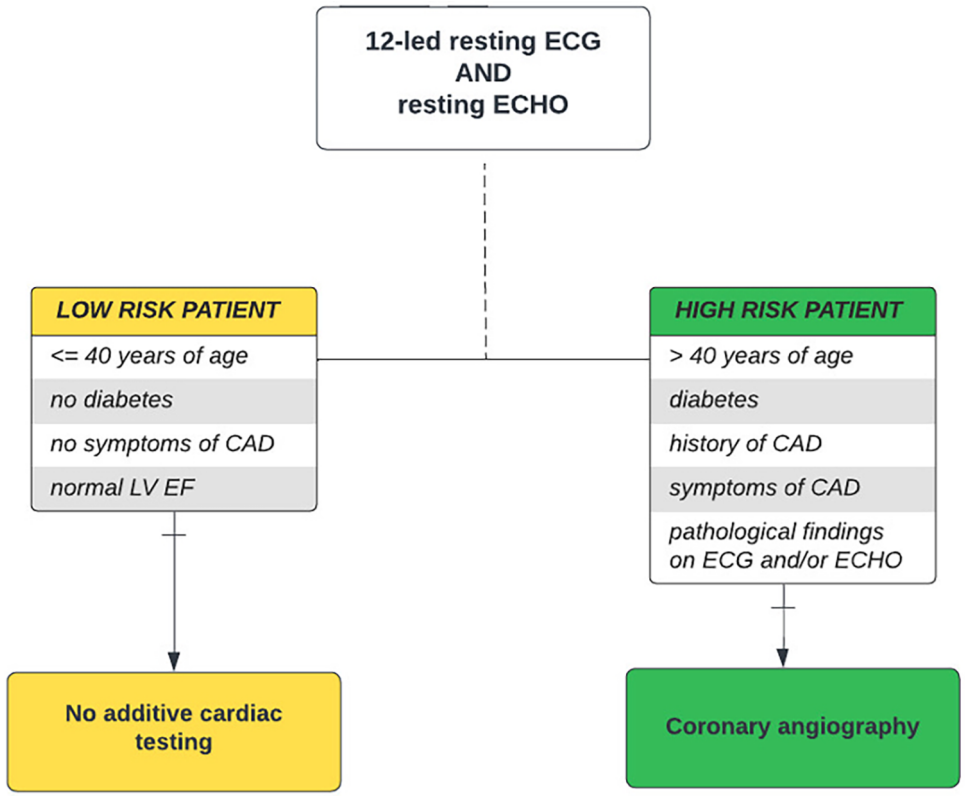

FIGURE 1
Pretransplant cardiovascular disease screening algorithm. Risk-stratified cardiovascular disease screening algorithm used in kidney transplant candidates at our center. It takes into account age, presence of diabetes, history and symptoms of cardiovascular disease, and pathological ECG and/or ECHO findings as risk factors, thereby distinguishing "low-risk" and "high-risk" kidney transplant candidates. CAD, coronary artery disease; DSE, dobutamine stress echocardiography; ECG, electrocardiography; ECHO, echocardiography; EF, ejection fraction; LV, left ventricle; MPS, myocardial perfusion scan.

percutaneous coronary intervention (PCI), and/or coronary artery bypass graft (CABG). A significant obstructive coronary artery disease was defined as stenosis of 50% or more of the left coronary artery (LCA) or 70% or more in at least one epicardial coronary artery or branch vessel detected using CAG (18, 19). Based on the findings, the patients were further indicated to stay on conservative therapy or to undergo myocardial revascularization, CABG, or PCI with (95.8% of patients) or without (4.2% of patients) last-generation drug-eluting stents (DES), according to the cardiological standard of care.

The primary endpoint was to determine the effect of our cardiovascular disease screening algorithm on the detection rate of obstructive CAD and on assessing the need for myocardial revascularization prior to transplantation. The secondary endpoint was to evaluate the impact of pretransplant CVD detection and management on the incidence of MACE in the early posttransplant period and to specify the prognostic indicators of MACE. MACE was defined as the need for a revascularization procedure (PCI, CABG), symptomatic arrhythmia (atrial fibrillation/flutter) with the need for intervention (electrocardioversion, radiofrequency ablation), myocardial infarction, heart failure, and sudden death (20, 21).

2.2 Statistical analysis

Continuous variables are expressed as medians (min, max) and compared using the Wilcoxon test, and categorical variables are expressed as *N* and a percentage of the total and compared using Pearson's chi-squared test. Survival analysis was performed using the Kaplan–Meier method, and the differences between groups were compared using the log-rank test. Univariable and multivariable Cox regression models were used to identify the risk and prognostic factors associated with posttransplant MACE. A *p*-value of less than 0.05 was considered statistically significant. The statistical analysis was performed using IBM SPSS Statistics, version 24 (International Business Machines Corp.) and RStudio software, version 4.1.3 (2022-03-10), development for R (RStudio, Inc., Boston, MA).

3 Results

3.1 Study cohort

A total of 776 kidney transplant recipients (KTR) enrolled in this study were followed for outcome measures for an average of

3 years posttransplant. The patients were analyzed based on the presence of pretransplant cardiovascular disease and posttransplant outcome measures.

The majority (93.6%) of KTR was transplanted from deceased donors, and 95.1% of KTR were on dialysis therapy (80% on hemodialysis, 20% on peritoneal dialysis). In our cohort, 94.7% of KTR treated with hemodialysis prior to transplantation were dialyzed using AV fistula, and 5.3% used a central venous catheter. The average vintage of dialysis before kidney transplantation was 2.2 years (median 2 years). After kidney transplantation, all KTR received our standard triple immunosuppressive therapy consisting of calcineurin inhibitor (CNI), purine synthesis inhibitor (mycophenolate mofetil, MMF), and steroids.

According to our risk-stratified cardiovascular algorithm, CAG was performed on a total of 541 out of 776 patients (69.7%). The obstructive CAD was detected in 121 of 541 KTR (22.4%). In 85 of 121 KTR (70.2%), CAD was fully asymptomatic and detected using our pretransplant screening protocol. The most commonly affected arteries were the left coronary artery and interventricular branch (LCA/RIA) ($N = 78$, 65.3%), right coronary artery (RCA) ($N = 45$, 37.2%), diagonal branch ($N = 33$, 27.3%), and obtuse marginal (OM) ($N = 32$, 26.4%) branch. Out of the total number of patients, 26 (21.5%) had two-vessel disease (2-VD), and 15 (12.4%) had three-vessel disease (3-VD), resulting in a total of 41 (33.9%) patients with multivessel disease (Table 1).

Based on CAG findings, myocardial revascularization was performed in 90 out of 121 patients (74.3%). The majority underwent PCI ($N = 61$, 67.8%), CABG was performed in 18 patients (20%), and 11 patients (12%) had a history of both PCI and CABG. Conservative therapeutic approach was opted for in 31 cases (25.6%). Asymptomatic obstructive CAD was treated conservatively in 30 patients (35.3%), and 55 patients (64.7%) received treatment either with PCI ($N = 41$, 74.5%), CABG ($N = 10$, 18.2%), or with both PCI and CABG ($N = 4$, 7.3%). Only one patient (2.8%) with a known pretransplant CAD ($N = 36$) was treated conservatively, whereas 35 (97.2%) patients were treated either with PCI ($N = 20$, 57.1%), CABG ($N = 8$, 22.9%), or with both PCI and CABG ($N = 7$, 20%). Prior to transplantation, 52 patients (43%) were treated with dual antiplatelet therapy (DAPT) due to the performance of myocardial revascularization (Figure 2).

Out of the 776 KTR, MACE occurred in 44 (5.6%) patients only, 23 with pretransplant CVD and 21 without pretransplant CVD (Figure 3). Interestingly, KTR with pretransplant CVD and posttransplant MACE did not significantly differ in the extent of coronary artery involvement (2-VD and 3-VD) compared with KTR with pretransplant CVD but without posttransplant MACE. Comparing KTR with MACE occurrence, KTR with no pretransplant CVD were younger ($p = 0.008$), had preserved residual diuresis ($p = 0.04$), preserved left ventricular ejection fraction ($p = 0.048$), and a tendency towards more frequent history of arrhythmia ($p = 0.052$). The most fundamental difference was that KTR with posttransplant MACE occurrence had significantly worse survival rates (log-rank $p = 0.0063$) during the 3-year follow-up period compared with KTR without MACE occurrence (Figure 4A) and also had worse kidney graft function at the first year posttransplant ($p = 0.00048$, Figure 4B).

TABLE 1 Characteristics of 121 patients with pretransplant cardiovascular disease.

	Number of patients (*N*)	Percentage (%)	[min, max]
Male	99	81.8	
Age at transplantation median	68		48.76
Dialysis vintage	115	95	
Diuresis < 500 ml	65	53.7	
History of arrhythmia	13	10.7	
History of diabetes mellitus	54	44.6	
Asymptomatic CAD	85	70.2	
Myocardial infarction	26	21.5	
Myocardial revascularization (PCI/CABG)	11	9.1	
Conservative management of CAD	32	26.4	
Dual antiplatelet therapy prior transplantation	95	78.5	
LVEF < 60%	24	19.8	
Pulmonary hypertension	10	8.3	
Valvular disease	18	14.9	
Myocardial kinetics disorder	26	21.5	
2-VD (> 50% artery stenosis of two of LCA/RCx/RIA/RCA)	26	21.5	
3-VD (> 50% artery stenosis of three of LCA/RCx/RIA/RCA)	15	12.4	
Presence of 2-VD or 3-VD	41	33.9	
Posttransplant MACE	23	19	

CAD, coronary artery disease; LV EF, left ventricular ejection fraction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; 2-VD, 2-vessel disease; 3-VD, 3-vessel disease; RCx, ramus circumflexus; LCA, left coronary artery; RIA, ramus interventricularis anterior; RCA, right coronary artery; MACE, major adverse cardiac event.

3.2 Analysis of risk factors for MACE

The univariable Cox regression model identified the most significant variables positively affecting MACE, including pretransplant CVD (HR 0.070, $p < 0.001$, 95% CI 0.035–0.136), asymptomatic CVD detected by pretransplant evaluation (HR 0.343, $p = 0.001$, 95% CI 0.035–0.136), pretransplant myocardial revascularization using PCI/CABG (HR 0.251, $p < 0.001$, 95% CI 0.135–0.470) with dual antiplatelet therapy (HR 0.397, $p = 0.014$, 95% CI 0.190–0.828), and, surprisingly, the history of myocardial infarction (HR 0.181, $p = 0.018$, 95% CI 0.044–0.750). History of arrhythmia (HR 3.051, $p = 0.001$, 95% CI 1.613–5.770) and radiofrequency ablation (HR 6.449, $p < 0.001$, 95% CI 2.493–16.680) were found to negatively affect MACE occurrence. Pulmonary hypertension showed some tendency, but the findings did not reach statistical significance (HR 1.938, $p = 0.091$, 95% CI 0.900–4.172) (Table 2).

The multivariable Cox regression model was constructed based on the results from the univariable regression model. After adjustments for radiofrequency ablation, pulmonary hypertension, and pretransplant antiplatelet therapy, the

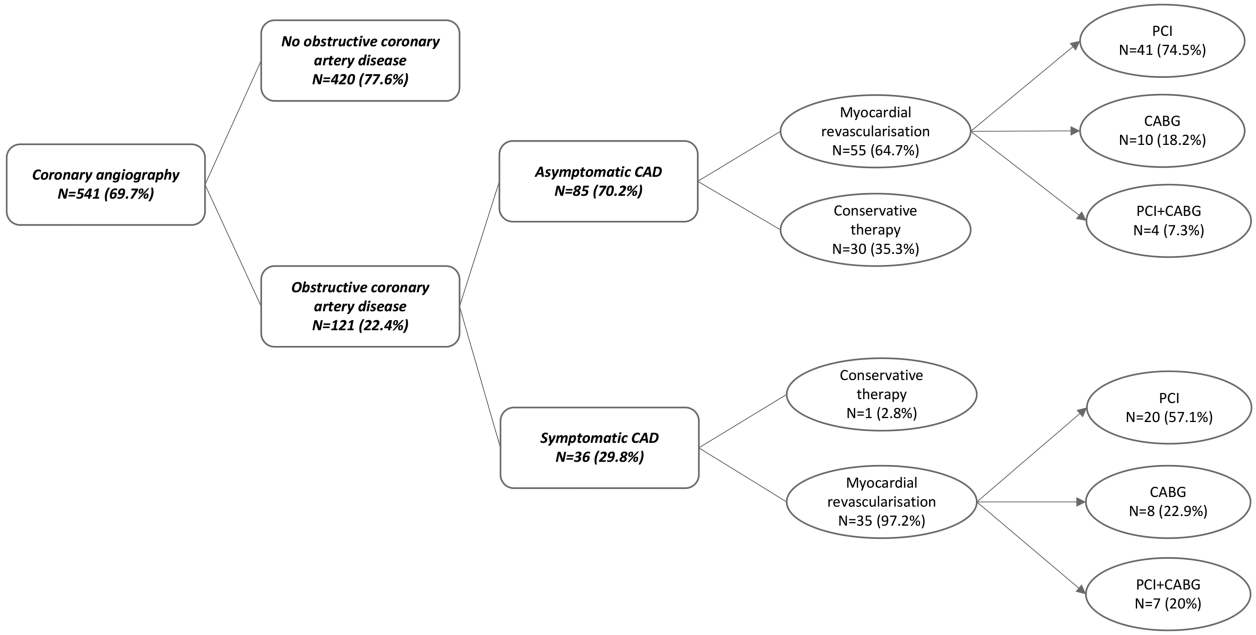

FIGURE 2
Pretransplant coronary angiography outcome in "high-risk" kidney transplant recipients. Obstructive coronary artery disease was detected in 22.4% of KTR who underwent coronary angiography according to the protocol. KTR with symptomatic CAD (29.8%) were in 97.2% managed with myocardial revascularization prior to transplantation. Asymptomatic CAD was detected in 70.2% of KTR, of which 64.7% were managed using myocardial revascularization as well. CAD, coronary artery disease; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft.

independent significant factors for MACE remained arrhythmia (HR 2.511, $p = 0.02$, 95% CI 1.158–5.444), pretransplant history of acute myocardial infarction (HR 0.201, $p = 0.046$, 95% CI 0.042–0.970), and pretransplant myocardial revascularization (HR 0.225, $p = 0.045$, 95% CI 0.052–0.939) (Table 3).

4 Discussion

The increasing numbers of high-risk cardiac patients are being considered as potential candidates for kidney transplantation. The main role of pretransplant evaluation is to determine whether the benefits of transplantation outweigh the risks of posttransplant cardiovascular complications in particular. Thus, screening for cardiovascular disease is essential for kidney transplantation acceptance. Pretransplant cardiovascular assessment approaches differ across transplantation centers due to the lack of standardized guidelines, which are currently based rather on recommendations that prioritize local practice (14, 22, 23).

Our study analyzed the effectiveness of our pretransplant risk-stratified protocol using screening coronary angiography in detecting significant cardiovascular disease in patients undergoing renal transplants and the impact of this approach on the incidence of posttransplant cardiac events. We believed that CAG is the most effective approach for CAD detection because in ESRD patients, the sensitivity and specificity of stress tests used for the detection of significant CAD are insufficient despite the high negative predictive value (15, 24, 25).

Based on our protocol, obstructive CAD was determined in 22.4% KTR who underwent CAG as "high-risk" patients, out of which 70.2% were clinically asymptomatic. The majority of patients with significant CAD (74.3%) were further treated with myocardial revascularization, PCI in 67.8%, CABG in 20%, and a combination of both PCI and CABG in 12%. Our findings are consistent with the knowledge of the high prevalence of CAD in patients with ESRD, particularly in those on dialysis (26, 27). Low occurrence of cardiac symptoms in dialyzed patients, including in those with advanced obstructive CAD, might be the cause for the underestimation of cardiovascular disease in this patient population. However, there still remains hesitation concerning the routine use of pretransplant coronary angiography for the detection of CAD in transplant candidates. This is because recent studies have not found conclusive evidence regarding the long-term impacts of prophylactic revascularization on patient morbidity and mortality (8, 18, 28). The prospective randomized ISCHEMIA-CKD trial including 777 patients with advanced chronic kidney disease (eGFR < 30 ml/min or dialysis dependence) did not conclude any cardioprotective benefits of myocardial revascularization in comparison with conservative strategies referencing the 3-year event rate of non-fatal myocardial infarction or death being 29% and 30%, respectively (29). However, several other studies detailed more frequent and more severe coronary adverse events and higher rates of death at 5 years posttransplant in patients in whom advanced CAD was being managed medically compared with those who had myocardial revascularization prior to transplantation (30–32).

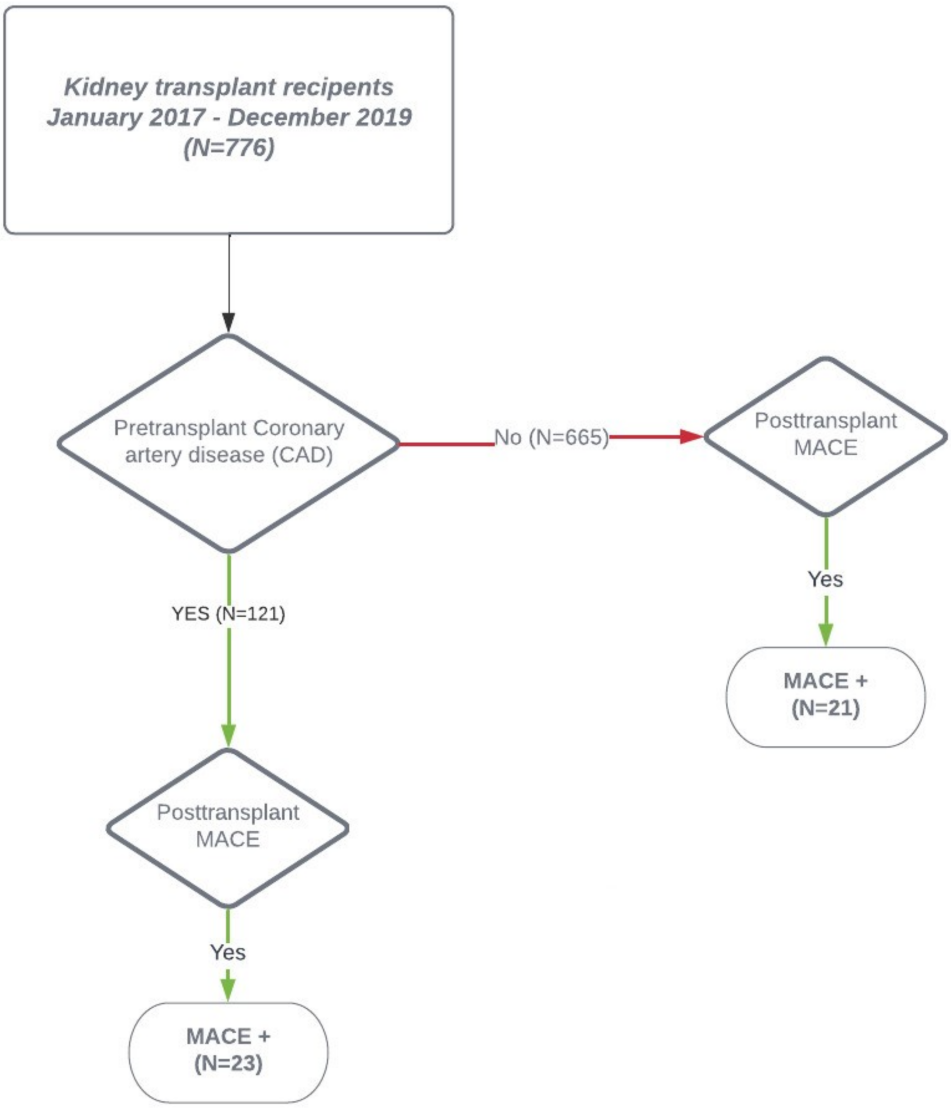

FIGURE 3
Post-transplant MACE manifestation. The 2-year posttransplant occurrence of MACE in the cohort of kidney transplant recipients. The overall MACE rate was low (5.7%) with a similar distribution between KTR with pretransplant obstructive coronary artery disease and KTR without pretransplant obstructive coronary artery disease. CAD, coronary artery disease; KTR, kidney transplant recipient; MACE, major adverse cardiac event.

On the other hand, there is some awareness regarding the association between CAG, myocardial revascularization, and a threefold increase in periprocedural morbidity and mortality in ESRD patients compared with non-CKD patients (33). In our cohort, we have not registered any major periprocedural complications, probably due to the elective nature of the conducted CAG. In general, the risk of experiencing major periprocedural complications appears to be low, varying between 0.1% and 0.25%, respectively, being 0.05% in diagnostically performed CAG (34). Similarly, another argument for not performing CAG routinely might be the risk of deterioration of residual renal function (RRF). RRF is an important predictor of survival in dialyzed patients; therefore, it is an effort to preserve RRF as long as possible. Recent studies analyzing the effect of contrast media on RRF have concluded that RRF is not significantly influenced by intravascular administered iso-osmolar contrast media with adequate prehydration in ESRD patients (35–38).

Nevertheless, a significant decrease in the risk of myocardial infarction and death in ESRD patients with multivessel CAD treated with CABG compared with PCI has been well determined. The use of multiple PCI procedures has shown similar benefits in patients with multivessel CAD (39, 40). Observational accounts also point to the long-term benefits of surgical revascularization in ESRD patients in cases of obstructive CAD compared with conservative management (31, 41, 42). Other concerns include longer waiting time of transplant candidates caused by the administration of dual antiplatelet therapy due to myocardial revascularization. However, we have observed that the pretransplant administration of dual

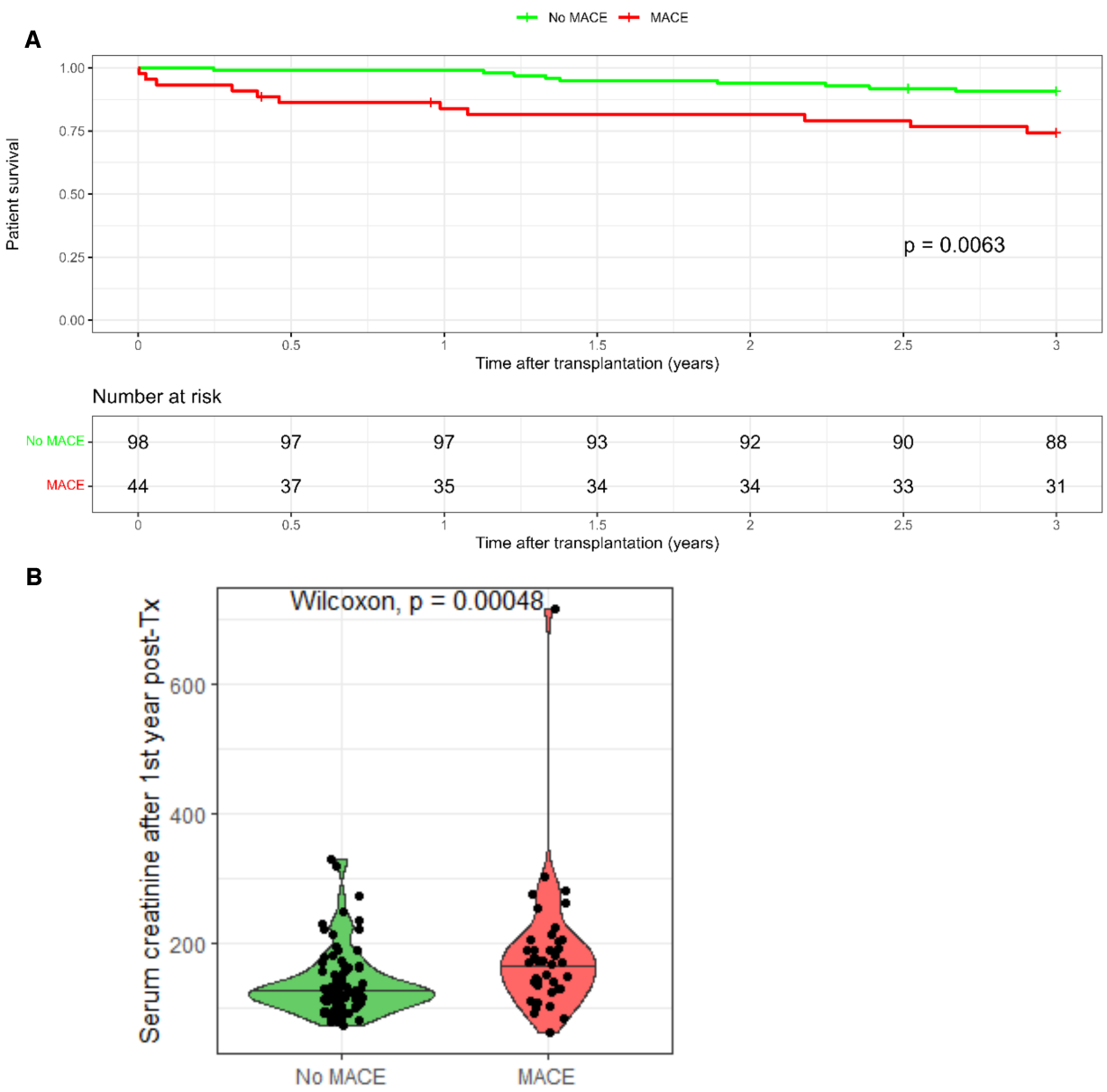

FIGURE 4
Outcomes of kidney transplant recipients with post-transplant MACE. (A) Kidney transplant recipients without MACE had significantly better survival compared to kidney transplant recipients experiencing MACE. (B) Kidney transplant recipients with MACE had significantly worse graft survival at 1st year post-transplant.

antiplatelet therapy has a significantly beneficial impact on posttransplant occurrence of cardiac events, similar to the impact of myocardial revascularization performed in cases of significant CAD (20, 43). Moreover, the use of last-generation drug-eluting stents reduced the need for DAPT therapy to only 3–6 months.

Major cardiac adverse events were observed in only 5.6% (44) of all KTR, out of which 23 had pretransplant CVD and 21 had no pretransplant CVD. The groups presented similar types of MACE and posttransplant survival rates (Table 4). This observation may be explained by preserved echocardiographic prognostic factors such as left ventricular geometry and ventricular kinetics (7, 44, 45). We believe that the low number of posttransplant MACE in our cohort is just due to the detection and adequate treatment of cardiovascular findings prior to transplantation.

Regarding the independent risk factors for posttransplant MACE occurrence in our cohort, we observed that arrhythmias and radiofrequency ablation performed prior to transplantation were found to significantly increase the risk of MACE (Table 2). Due to the high prevalence of ECG abnormalities in ESRD patients, we included only KTR with a documented history of persistent atrial fibrillation or pretransplant atrial fibrillation treated with radiofrequency ablation. This observation has an

TABLE 2 Univariable analysis of risk factors for MACE.

Variable	HR	95% CI	*p*-value
Age at transplantation, years	0.990	0.960–1.021	0.523
Donor age, years	0.998	0.979–1.018	0.872
Dialysis vintage, years	1.061	0.937–1.201	0.351
Pretransplant diabetes	0.961	0.911–1.014	0.145
Pretransplant diabetes on insulin therapy	0.426	0.168–1.089	0.075
Pretransplant CVD	0.070	0.035–0.136	<0.001
CVD detection within pretransplant evaluation	0.343	0.187–0.631	0.001
Pretransplant myocardial revascularization (PCI/CABG)	0.251	0.135–0.470	<0.001
Dual antiplatelet therapy prior to transplantation	0.397	0.190–0.828	0.014
Pretransplant arrhythmia	3.051	1.613–5.770	0.001
Pretransplant RF ablation	6.449	2.493–16.680	<0.001
History of myocardial infarction	0.181	0.044–0.750	0.018
Pulmonary hypertension	1.938	0.900–4.172	0.091
Myocardial kinetics disorder	0.753	0.336–1.689	0.491

CVD, cardiovascular disease; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; RF, radiofrequency; HR, hazard ratio; CI, confidence interval.

TABLE 3 Multivariable analysis of risk factors for MACE.

Variable	HR	95% CI	*p*-value
Pretransplant arrhythmia	2.511	1.158–5.444	0.020
Pretransplant radiofrequency ablation	1.565	0.446–5.498	0.485
History of myocardial infarction	0.201	0.042–0.970	0.046
Pretransplant myocardial revascularization (PCI/CABG)	0.225	0.052–0.939	0.045
Dual antiplatelet therapy prior to transplantation	0.358	0.104–1.233	0.103
Pulmonary hypertension	1.227	0.509–2.960	0.649

MACE, major adverse cardiac event; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; HR, hazard ratio; CI, confidence interval.

TABLE 4 Characteristics of 44 patients experiencing MACE.

	Pretransplant CVD (*N* = 23)	No pretransplant CVD (*N* = 21)	*p*-value
Male *N* (%)	18 (78.3)	13 (61.9)	0.325
Age at transplantation median [min, max]	67 [49,73]	65 [49,74]	0.008
Dialysis vintage < 1 year *N* (%)	2 (8.7)	1 (4.8)	1.000
Dialysis vintage 1–3 years *N* (%)	11 (47.8)	10 (47.6)	1.000
Dialysis vintage > 3 years *N* (%)	8 (34.8)	10 (47.6)	0.541
Diuresis < 500 ml *N* (%)	9 (39.1)	6 (28.6)	0.040
History of arrhythmia *N* (%)	4 (17.4)	10 (47.6)	0.052
History of diabetes	11 (47.8)	8 (38.1)	0.557
Pretransplant echocardiography			
LVEF ≥ 60% median [min, max]	18 (78.3)	20 (95.2)	0.048
Pulmonary hypertension *N* (%)	3 (13)	5 (23.8)	0.448
Significant valvular disease *N* (%)	6 (26.1)	4 (19)	0.724
Myocardial kinetics disorder *N* (%)	6 (26.1)	0 (0)	0.097
MACE			
Arrhythmia *N* (%)	11 (47.8)	13 (61.9)	0.382
Acute myocardial infarction *N* (%)	6 (26.1)	1 (4.8)	0.097
Heart failure *N* (%)	5 (21.7)	4 (19)	1.000
Cardiovascular death *N* (%)	1 (4.3)	2 (9.5)	0.599
Serum creatinine after MACE median [min, max]	174 [63,717]	169 [86,278]	0.583
Patients' outcome after total posttransplant follow-up			
Alive *N* (%)	21 (91.3)	19 (90.5)	0.169
Total death due to non-CVD cause *N* (%)	2 (8.7)	0 (0)	0.489
Total death due to CVD cause N (%)	6 (26.1)	4 (19)	0.724

MACE, major adverse cardiac event; CVD, cardiovascular disease; LV EF, left ventricular ejection fraction.

important clinical impact as the presence of atrial fibrillation at the time of transplantation not only increases the risk of cardiac complications, but also increases the risk of death at 5 years posttransplant (46, 47). Furthermore, the presence of cardiovascular disease and a history of myocardial infarction were identified as the strongest factors in preventing the occurrence of posttransplant MACE (Table 3). Based on our findings, it may be suggested that optimal myocardial revascularization and favorable echocardiographic findings made the acceptance of candidates for renal transplantation possible. For this reason, it is crucial to evaluate cardiological findings under conditions of effective dialysis and optimal hydration to avoid misinterpretation. There is evidence that dialysis efficiency, not dialysis modality (hemodialysis or peritoneal dialysis), is associated with the incidence of CVD (48, 49, 50). Heart failure is an important predictor of mortality in dialyzed and transplanted patients. Approximately 80% of patients with heart failure and systolic–diastolic dysfunction die within 3 years (51). Despite the clearly positive effect of a functional transplanted kidney on cardiac function, patients with a history of heart failure have a more than two times higher risk of heart failure or death, even 5 years after transplantation (52, 53). This risk increases as the ejection fraction decreases (54). Heart failure was observed as one of the most frequent MACE in our cohort. There was no significant difference observed between the groups in terms of the incidence of MACE or death caused by heart failure (50%), reaching approximately 20% of KTR experiencing these outcomes. Our findings appear to be in accordance with published data.

Pulmonary hypertension, with a prevalence rate ranging from 18%–56% in ESRD patients, is known to be a strong independent prognostic factor of morbidity and mortality in both patients with CKD and KTR, as well as of lower graft survival (55–57). In our cohort, pulmonary hypertension was found in 8.3% (10) of patients with CVD, out of which only three (13%)

patients developed MACE. Approximately 24% of patients without pretransplant CVD but with posttransplant MACE occurrence had pulmonary hypertension. The higher prevalence of pulmonary hypertension might be considered a prognostic factor for MACE in patients without pretransplant CVD, despite preserved myocardial kinetics (21, 58). However, the rate of pulmonary hypertension did not reach statistical significance, probably due to the small number of patients whose endpoint was MACE occurrence (Table 2). The similar percentage rate of patients who experienced the occurrence of MACE irrespective of CVD in our cohort supports the finding that atherosclerotic CAD represents only a portion of cardiovascular complications occurring in KTR. Dysrhythmias with high prevalence of systolic or diastolic dysfunction, left ventricular hypertrophy, and electrical instability are associated with approximately 50% of cardiovascular deaths in KTR (59). Siddiqui et al. (60) recently published a meta-analysis evaluating eight studies pertaining to the subject of strategy in kidney transplant candidates with established CAD. Independent of whether the management of CAD was invasive or conservative, they found no differences regarding all-cause mortality, cardiovascular mortality, and the occurrence of MACE, including myocardial infarction, heart failure, and arrhythmias. Based on this analysis, their recommendation is to perform revascularization procedures exclusively on patients with anatomically high-risk CAD in whom the intervention might be beneficial for the improvement of survival, but to not revascularize asymptomatic CAD patients routinely if the sole aim is to reduce the occurrence of perioperative cardiac events.

Among the factors that have an impact on posttransplant cardiovascular complications, the influence of concomitant immunosuppression cannot be neglected. Currently, KTR are standardly treated with a triple immunosuppressive regimen consisting of calcineurin inhibitor, purine synthesis inhibitor (MMF), and steroids. There are multiple studies suggesting the effects of CNI on human hearts, particularly on hypertrophy or increased left ventricle mass (61, 62). Recently published review dealing with cardiovascular effect of immunosuppressives reported that the increase of left ventricle mass may be primarily driven by CNI-induced fibrosis and collagen deposition rather than cardiomyocyte remodeling. On the other hand, there are no data suggesting the link between purine synthesis inhibitors and cardiac hypertrophy or fibrosis (63). This potential impact of CNI on the progression of CVD should be taken into account as a part of pretransplant decision-making process, particularly in marginal kidney transplant candidates.

In our study, we observed negative impacts of posttransplant cardiac events in all patients in whom MACE occurred, irrespective of the presence of CVD. Despite the similar characteristics of the patients with pretransplant CVD, those who experienced the occurrence of MACE had significantly worse renal graft function at 1 year and higher mortality rates. The patients without pretransplant CVD but with posttransplant MACE occurrence showed unfavorable outcomes comparable with those of the patients with pretransplant CVD and posttransplant MACE occurrence (Table 4). The patients with posttransplant MACE showed significantly worse renal graft function and patient survival rates in comparison with those without cardiac complications (Figure 4). Due to the lack of prospective randomized trials in renal transplant candidates, the optimal modality for the screening and management of ischemic heart disease in this patient population remains a matter of debate, and current practice guidelines suggest excluding asymptomatic CVD patients from routine invasive testing and proceeding them to transplantation (64). The 2022 AHA scientific statement recommends performing cardiac catheterization in asymptomatic kidney transplant candidates without a history of CVD individually based on the findings of the resting ECHO examination. Regarding the kidney transplant candidates with known CVD, it is recommended to have direct cardiac catheterization in patients with cardiac symptoms or in cases of pathological findings on a stress test in patients who have no cardiac symptoms. Currently, there is no established practice of routinely performing revascularization procedures on stable and asymptomatic kidney transplant candidates only for the purpose of reducing long-term cardiovascular mortality. However, pretransplant revascularization should be individualized depending on the risk associated with delayed transplantation and the benefits of reducing cardiovascular risk (12). Currently, there is a lack of guidelines or recommendations addressing the possible impact of pretransplant cardiovascular revascularization on short- or medium-term cardiovascular mortality.

We believe our observations might prove useful for optimizing the evaluation approaches used to assess pretransplant cardiovascular patients in kidney transplantation prior to listing candidates for transplantation, including candidates with asymptomatic advanced CVD.

5 Conclusion

Advanced cardiovascular disease is prevalent and largely asymptomatic in patients undergoing kidney transplantation. Posttransplant cardiovascular events are associated with decreased graft survival rates and adverse patient outcomes. Further studies are required to assess the benefits of pretransplant myocardial revascularization in asymptomatic kidney transplant candidates.

5.1 Strengths and limitations

This study aimed to describe our single-center experience with an algorithm that was developed as a part of a collaboration between transplant nephrologists and cardiologists to assess cardiovascular risk prior to kidney transplantation. The strengths of our study include the number of patients in whom CAG was performed in accordance with the pretransplant protocol and the availability of all data obtained from both ECHO and CAG procedures.

The presented study was conducted retrospectively at a single center. Another limitation of the study is its short-term design, allowing us to present only short-term patient outcomes. Thus,

we are not yet able to provide insights on the long-term impacts of our pretransplant cardiovascular screening algorithm on patient morbidity and mortality rates. We specifically focused our analysis on patients who underwent kidney transplantation, excluding those who were not accepted for the procedure.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving humans were approved by the Ethics Committee of the Institute for the Clinical and Experimental Medicine and the Thomayer University Hospital. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin due to the retrospective design of the study and the raw data of the enrolled patients were anonymously evaluated. Specific informed consent, ethical review, and approval were not required for this study on human participants in accordance with the local legislation and institutional requirements. The Ethics Committee of the Institute for the Clinical and Experimental Medicine and the Thomayer University Hospital had no objections to the publication of this article (Docket No. 16311/23).

Author contributions

SR: Conceptualization, Data curation, Investigation, Methodology, Visualization, Writing – original draft. BJ: Conceptualization, Investigation, Writing – original draft. KM: Conceptualization, Data curation, Investigation, Writing – original draft. PH: Conceptualization, Data curation, Formal Analysis, Methodology, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Pulmonary congestion and systemic congestion in hemodialysis: dynamics and correlations

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Introduction: Systemic congestion and pulmonary congestion (PC) are common in hemodialysis (HD) patients. However, the relationship between these two entities is not quite clear. We study this relationship and attempt to uncover the factors that may affect it considering different inter-dialytic intervals.

Methods: A prospective pilot observational and interventional study including 18 HD patients was conducted. The following were obtained: i) B-line score (BLS) by lung ultrasound (LUS) (reflecting significant pulmonary congestion if BLS > 5), ii) echocardiography, iii) bioelectrical impedance analysis (BIA) (reflecting global volume status), and iv) inferior vena cava (IVC) dynamics (reflecting systemic congestion) before and after the first two consecutive HD sessions of the week, with different inter-dialytic intervals (68 hours and 44 hours). Serum N-terminal pro-brain natriuretic peptide type B (NT-proBNP) levels were obtained before each session. Then, patients were randomized into two groups: the active group, where dry weight was reduced according to BLS + standard of care, and the control group, where dry weight was modified according to standard of care. All the measures were repeated on day 30.

Results: We found no correlation between pulmonary congestion represented by BLS and IVC dimensions and dynamics reflecting systemic congestion, independent of different inter-dialytic intervals. Pulmonary congestion was quite prevalent, as mean pre- and post-dialysis BLSs were quite elevated (16 $\pm$ 5.53 and 15.3 $\pm$ 6.63, respectively) in the first session compared with the second session (16.3 $\pm$ 5.26 and 13.6 $\pm$ 5.83, respectively). Systolic (left ventricular ejection fraction) and diastolic cardiac function (e/è ratio) parameters from one side and pulmonary congestion (BLS) from the other were not always correlated. BLS was correlated to e/è ratio before HD (session 1) (R^2 = 0.476, p = 0.002) and after HD (session 2) (R^2 = 0.193, p = 0.034). Pulmonary congestion reflected by BLS was correlated to the global volume state reflected by BIA only in the second HD session (HD2) (R^2 = 0.374, p = 0.007). NT-proBNP levels and BLS were correlated before both sessions (R^2 = 0.421, p = 0.004, and R^2 = 0.505, p = 0.001, respectively). Systemic congestion was quite prevalent, as mean pre- and post-dialysis IVC dimensions and dynamics were quite elevated in both sessions, with a higher level of systemic congestion in the first HD session (diameter and collapsibility of 2.1 cm and 23%, and 2.01 cm and 19%, respectively) compared with the second session (1.98 cm

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and 17.5%, and 1.9 cm and 22%, respectively) without reaching statistical significance. IVC dimensions and global volume status measured by BIA were correlated in the second dialysis session (R^2 = 0.260, p = 0.031). No correlation was found between IVC dimensions and diastolic cardiac function (e/è ratio) parameters or with NT-proBNP levels. On day 30, BLS was significantly reduced in the active group, whereas no difference was found in the control group. However, no real impact was observed on IVC dimensions and dynamics or in total volume status by BIA.

Conclusion: Pulmonary congestion is common in HD patients even after reaching their dry weight at the end of two consecutive sessions, and it is not correlated to systemic congestion, suggesting a complex multifactorial pathophysiology origin. Global volume status reflected by BIA and cardiac function are not always related to either systemic congestion represented by IVC dimensions or pulmonary congestion represented by BLS. Fluid redistribution anomalies may allow pulmonary congestion accumulation independently from systemic congestion and global volume status (non-cardiogenic pulmonary congestion). We recommend a personalised approach when managing HD patients by integrating systemic and pulmonary congestion parameters. Dry weight modification guided by repeat LUS may safely reduce pulmonary congestion. However, no impact was observed on systemic congestion or global volume status.

KEYWORDS

hemodialysis, pulmonary congestion, lung ultrasound, dry weight, systemic congestion

Introduction

End-stage kidney disease (ESKD) patients treated with hemodialysis (HD) have a complicated and dynamic volume status. As their urine output is low or even absent, they accumulate fluids between their dialysis sessions. Usually, they follow a thrice-weekly HD planning, with variable inter-dialytic intervals (68 hours *vs.* 44 hours), which makes their volume status more complicated to evaluate.

This variable accumulation of fluid produces systemic and pulmonary congestion. Clinical examination is important to evaluate the signs of congestion; however, it is not accurate enough to provide an objective dry weight (the best-estimated weight where the patient has no congestion) to guide the hemodialysis treatment prescription (1).

One additional tool to evaluate systemic congestion is to measure inferior vena cava (IVC) diameters and dynamics. Global volume status may be assessed by bioelectrical impedance analysis (BIA). Lung ultrasound (LUS) is a reliable tool to detect and quantify pulmonary congestion (2).

Adding these tools to the standard of care to better establish the dry weight may be advantageous. However, currently, there is no simple clear protocol for integrating them into the clinical practice.

In addition, the correlation between the objective measures by these tools reflecting different aspects of congestion is not completely clear.

It was shown that pulmonary congestion assessed by a validated B-line score (BLS) using LUS is common among asymptomatic HD and peritoneal dialysis patients (3). Furthermore, the presence of pulmonary congestion in patients on maintenance HD, regardless of volume overload, is associated with adverse outcomes (3, 4).

The challenge is thus to establish an early diagnosis of PC at the bedside before symptoms appear to maintain a good quality of life and potentially reduce the risk of morbidity and mortality, in addition to preventing full development of pulmonary oedema. Fluid redistribution cannot be assessed by classically determined dry weight (DW). Thus, DW is less reliable in reducing pulmonary congestion, giving a place for a multifactorial management strategy guided by LUS (2).

LUS consists of detecting discrete laser-like vertical hyperechoic reverberation artefacts arising from the pleural line, extending to the bottom of the screen, namely, the B-lines. B-line counts represent a simple and reliable method to assess PC and evaluate effective water retention in the lung. A meta-analysis comparing LUS with chest X-ray suggests that B-line count is more sensitive than radiography in detecting pulmonary oedema and that it should be included as an additional diagnostic modality in patients presenting with acute dyspnoea (4).

Estimating the ideal weight of hemodialysis patients is still challenging for nephrologists, as the available tools to obtain such estimations are not accurate in reflecting the global volume state of

the patient. Furthermore, there are limited approaches to evaluate congestion in different body compartments.

Understanding the relationship between different body compartment congestion using new tools may allow for better management of HD patients.

Our study aimed to examine the correlation between pulmonary congestion reflected by LUS, systemic congestion reflected by IVC, and global volume status reflected by BIA and investigate the impact of variable inter-dialytic intervals.

We examined the effect of simplified LUS-guided management on these parameters.

Methods

We conducted a prospective randomized pilot study in 18 HD patients, which was preceded by an observational phase on the same patient group. All participants were recruited from our HD unit at Brugmann University Hospital.

The study received approval from the Research Ethics Committee of our hospital and was performed according to institutional procedures and the Declaration of Helsinki. All participants provided signed written informed consent before inclusion.

Patient inclusion/exclusion criteria and clinical/biological data collection

Eighteen adult patients on maintenance HD for at least 3 months in our high-care unit were included. Patients diagnosed with interstitial lung disease or recent pneumonia, who had previous lung surgery, and or who had cancer were excluded.

Charts with the most current values available were reviewed to collect data, including demographics (age and sex), HD treatment parameters, cause of chronic kidney disease, laboratory parameters (serum urea, phosphate, albumin, and haemoglobin), body mass index (BMI), DW, weight before and after HD sessions, pre- and post-dialysis blood pressure, comorbidities such as diabetes and previous cardiovascular events, and antihypertensive therapy.

Design of the observational phase of the protocol

As schematically illustrated in Figure 1A, all patients underwent LUS and echocardiography in a supine or near-supine position before and after their regularly scheduled first and second HD sessions of the week. All measurements were performed by the same operator at the bedside using the same ultrasound machine (T-Lite system, Sonoscanner, Meditor, La Wantzenau, France).

To quantify pulmonary congestion, an individual BLS was obtained according to the eight-site method by LUS. The cutoff for the B-line score was fixed at 0.54 line per zone (5). Lung ultrasound is useful for assessing the presence and severity of pulmonary congestion, but the most extensively validated 28-zone study is time-consuming. Among HD patients, four-, six-, and eight-zone lung ultrasound protocols were comparable with 28-zone studies for PC assessment (5).

Echocardiography was performed pre- and post-HD sessions 1 and 2 together with LUS using a T-Lite system, applying a standardized protocol including parasternal long- and short-axis views and apical four-chamber views. Cardiac systolic function was evaluated by measuring left ventricular ejection fraction (LVEF). Pulsed-wave Doppler assessment of mitral valve inflow was used to calculate the E/A ratio. Tissue Doppler velocities were measured at the medial and lateral mitral valve annular tissues to determine the e/è ratio, reflecting cardiac diastolic function. The diameter and dynamics of the IVC were also examined. Echocardiographic parameters were compared with the results of patients' basic echocardiography, performed by a cardiologist within a year before the starting date of the study. LVEF and e/è were well correlated when basic echocardiography results were compared with the mean value of our six repeated measurements collected during the present study ($p = 0.006$, $R^2 = 0.352$, and $p = 0.006$, $R^2 = 0.386$, respectively) (As shown in Table 2).

In addition, BIA was performed before each HD session using a portable whole-body bioimpedance spectroscopy device (BCM, Fresenius Medical Care Deutschland GmbH, Biebesheim am Rhein, Germany). Serum N-terminal pro-brain natriuretic peptide type B (NT-proBNP) levels were obtained before each session.

Design of the interventional phase of the protocol

After completion of the observational phase, patients were randomized into two groups:

1. Interventional arm group ("active group"): Dry weight was modified according to individual BLS obtained after the second HD session, considered as day 1, in addition to standard of care. Practically, each patient's dry weight was reduced by 500 mg if the BLS was >0.54 line/zone. Another evaluation of the BLS was performed on day 15, where dry weight was also modified according to the same rule.
2. Control arm group ("control group"): Dry weight was modified according to the standard of care only.

The same measurements as those performed during the observational phase were repeated in the second HD session of the week on day 30 in both groups (Figure 1B).

Classical statistical methods (*t*-test and Q^2 test to test for differences, as appropriate) were applied using professional statistic software (Jamovi and SPSS).

Results

The patient's basic clinical and biological characteristics are summarised in Table 1.

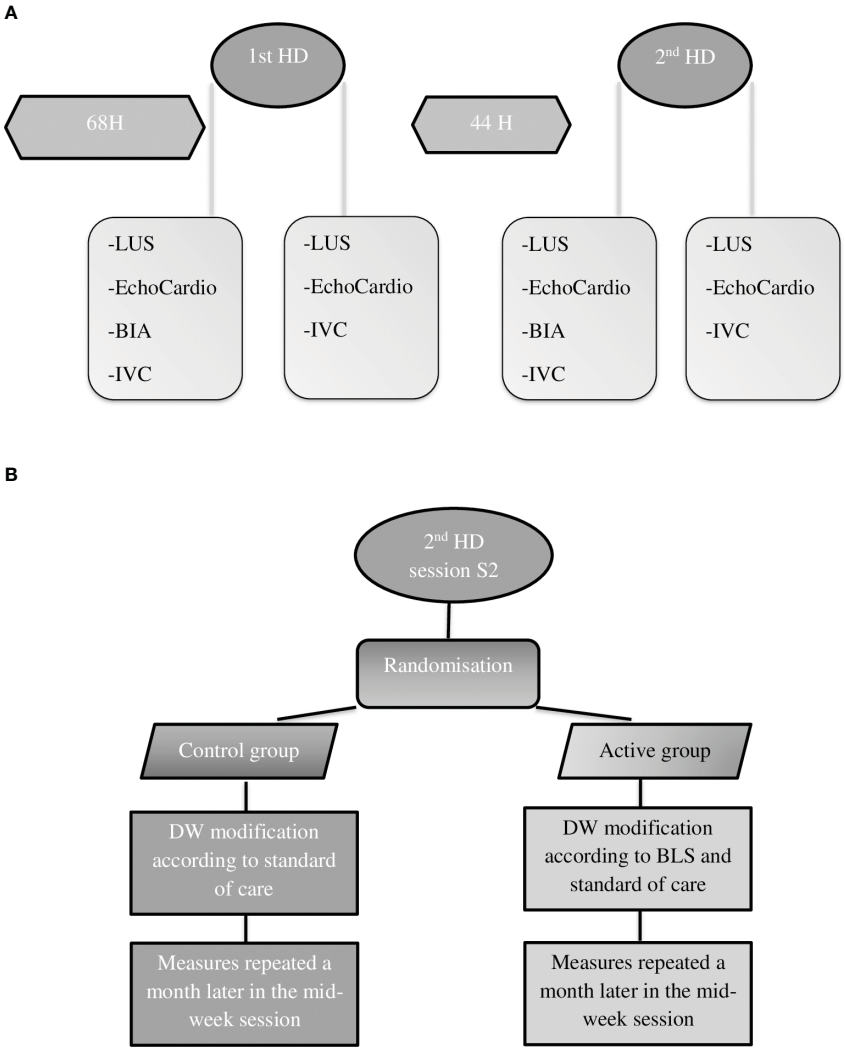

FIGURE 1
Study design of the observational phase **(A)** and the interventional phase **(B)**. LUS, lung ultrasound; BIA, bioelectrical impedance analysis; IVC, inferior vena cava; BLS, B-line score; DW, dry weight; h, hours.

Observational phase

Pulmonary congestion was frequent both before and after dialysis in both sessions regardless of the inter-dialytic interval (pre-dialysis, 16±5.53, and post-dialysis, 15.3±6.63; pre-dialysis, 16.3±5.27, and post-dialysis, 13.6±5.83, respectively).

Systemic congestion was also frequent, as mean pre- and post-dialysis IVC dimensions and dynamics were quite elevated in both sessions, with a higher level of systemic congestion in the first HD session (diameter and collapsibility of 2.1 cm and 23%, and 2.01 cm and 19%, respectively) compared with the second session (1.98 cm and 17.5%, and 1.9 cm and 22%, respectively), without reaching statistical significance.

Systolic (left ventricular ejection fraction) and diastolic cardiac function (e/è ratio) parameters from one side and pulmonary congestion (BLS) from the other were not always correlated. BLS was correlated to the e/è ratio before HD (session 1) (R^2 = 0.476, p = 0.002) and after HD (session 2) (R^2 = 0.193, p = 0.034) (Figure 2).

Pulmonary congestion reflected by BLS was correlated to the global volume state reflected by BIA only in the second HD session (HD2) (R^2 = 0.374, p = 0.007) (Figure 3).

NT-ProBNP levels and BLS were correlated before both sessions (R^2 = 0.421, p = 0.004; R^2 = 0.505, p = 0.001, respectively).

IVC dimensions and global volume status measured by BIA were correlated in the second dialysis session (R^2 = 0.260, p = 0.031). No correlation was found between IVC dimensions and diastolic cardiac function (e/è ratio) parameters or with NT-proBNP levels.

No correlation was found between pulmonary congestion represented by LUS and systemic congestion represented by IVC.

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TABLE 1 Patients' basic and biological characteristics.

Variable	Value
Number	18
Age (year)	68 (24–88)
Female/male ratio	3/15
Diabetes, *n* (%)	6 (33%)
Hypertension, *n* (%)	16 (89%)
Heart failure, *n* (%)	3 (17%)
AVF, *n* (%)	10 (55%)
Central catheter, *n* (%)	8 (45%)
HD, *n* (%)	8 (45%)
HDF, *n* (%)	10 (55%)
Mean BMI, kg/m^2 (min–max)	25.6 (15–34)
Haemoglobin mean, g/dl (min–max)	10.8 (7.4–12.7)
Kt/V, mean (± SD)	1.74 (± 0.38)
Dialysis vintage, mean (months)	65.9
Residual urine volume (ml)	437
Albumin (g/dl), mean (± SD)	40.6 (± 4.1)
Calcium (mmol/L), mean	2.36
Potassium (mmol/L), mean	5
Phosphorus (mmol/L), mean	1.53
Pre-dialysis urea (mg/dl), mean	123
Post-dialysis urea (mg/dl), mean	29.4

AVF, arteriovenous fistula; HD, hemodialysis; HDF, haemodiafiltration; BMI, body mass index.

Basic echocardiographic findings from cardiologists' reports made in the year before the study were similar to our findings with no significant differences (Table 2).

Interventional phase

On day 30, a significant reduction in BLS was observed before (17.4 *vs.* 8.5, $p < 0.0001$, effect size (ES) = 2.63) and after (13.3 *vs.* 5, $p < 0.001$, ES = 2.1) HD in the active group, whereas no difference was found in the control group before (14.9 *vs.* 12.1, $p = 0.16$) and after (14 *vs.* 10.6, $p = 0.122$) HD (Figure 4).

This reduction in pulmonary congestion in the active group was not associated with a statistically significant reduction in systemic congestion (IVC) or global volume status (BIA).

Discussion

This study reveals that there is a weak correlation between systemic and pulmonary congestion in addition to volume status in hemodialysis patients.

Also, it shows that a LUS-guided management was able to reduce pulmonary congestion in a significant way. However, no real impact was observed on systemic congestion or global volume status.

Pulmonary congestion was quite frequent. It was reduced after the dialysis session by ultrafiltration (UF). However, it remained relatively high even when patients reached their estimated dry weight. This is in line with the work of Noble et al., who demonstrated that UF induces a concomitant reduction of the B lines during dialysis treatment (6).

Volume status measured by BIA was not always correlated to pulmonary congestion or systemic congestion. Volume redistribution through a damaged alveolar–capillary barrier may explain why pulmonary congestion estimated by LUS is not always related to body water volume estimated by BIA. This structure damage may be the result of inflammation, oxidative stress, or other causes related to uraemia. Interstitial space congestion caused by the chronic nature of ESKD may explain the weak correlation between the global volume status and systemic congestion.

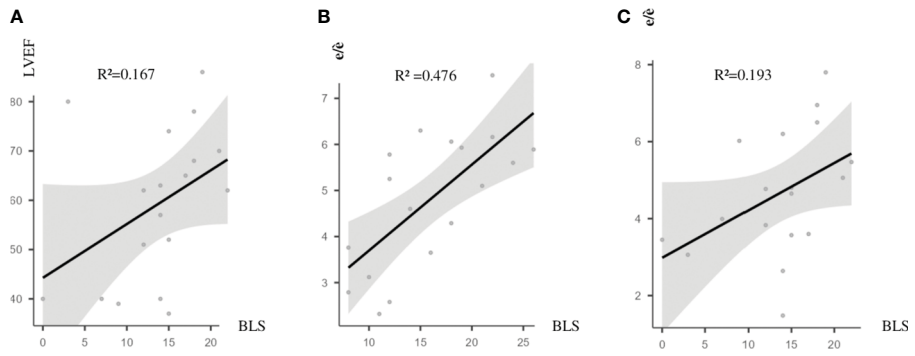

FIGURE 2
Correlations between PC (reflected by BLS) and cardiac functional markers. **(A)** BLS and LVEF after HD2; $R^2 = 0.167$, $p = 0.046$. **(B)** BLS and e/è before HD1; $R^2 = 0.476$, $p = 0.002$. **(C)** BLS and e/è after HD2; $R^2 = 0.193$, $p = 0.034$. BLS, B-line score; PC, pulmonary congestion; LVEF, left ventricular ejection fraction; HD2, second hemodialysis session; HD1, first hemodialysis session.

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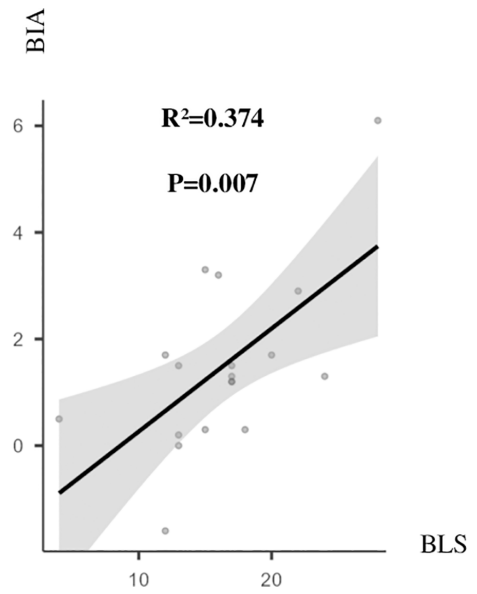

FIGURE 3
BLS and BIA before HD2. R^2 = 0.374, p = 0.007. BIA, bioelectrical impedance analysis in litre; BLS, B-line score; HD2, second hemodialysis session.

TABLE 2 Basic and echocardiographic features.

	Basic EF	Mean EF	Basic e/è	Mean e/è
N	17	18	18	18
Mean	50.9	56.7	10.1	4.45
Median	51	56.6	9.13	4.32
Standard deviation	11.3	10.2	6.22	1.04

EF, ejection fraction.

Supporting our findings, two studies found that BLS and total body water by BIA measured together were very weakly associated (7, 8).

Along the same lines, studies conducted on patients with acute decompensated heart failure concluded that patients' clinical improvement did not correlate with a change in their weight. This confirms the idea that symptoms resulting from volume expansion are secondary to redistribution rather than the accumulation of fluids (9).

Numerous trials and epidemiological studies have demonstrated the prevalence of pulmonary congestion in patients with chronic heart failure (HF). The *post hoc* analysis of the LUS-HF trial revealed that up to 40% of patients considered "dry" according to pulmonary auscultation presented LUS-evidenced pulmonary congestion at hospital discharge. These patients also experienced worse prognoses at 6-month follow-up (10).

In the interventional phase, our simplified LUS-guided management was able to reduce pulmonary congestion in a significant way. This reduction in PC was not associated with a reduction in total body volume estimated by BIA or systemic congestion represented by IVC, which encourages us to investigate further the intercommunication between the interstitial volume expansion, vascular volume expansion, and pulmonary alveolar water and how these volumes interact. We hypothesize that chronic interstitial volume expansion caused by ESKD is difficult to reverse and may even be irreversible, whereas vascular volume expansion and even more pulmonary alveolar water are easier to manage and reduce. This pathophysiological hypothesis may be one of the factors explaining why a slight reduction in the dry weight guided by BLS compared with the standard of care has a real impact on pulmonary congestion.

This congestion in multiple compartments (systemic, interstitial, and pulmonary) and fluid movement speed between them may be different from one patient to another, which makes the use of every available tool to evaluate every space and its dynamic a

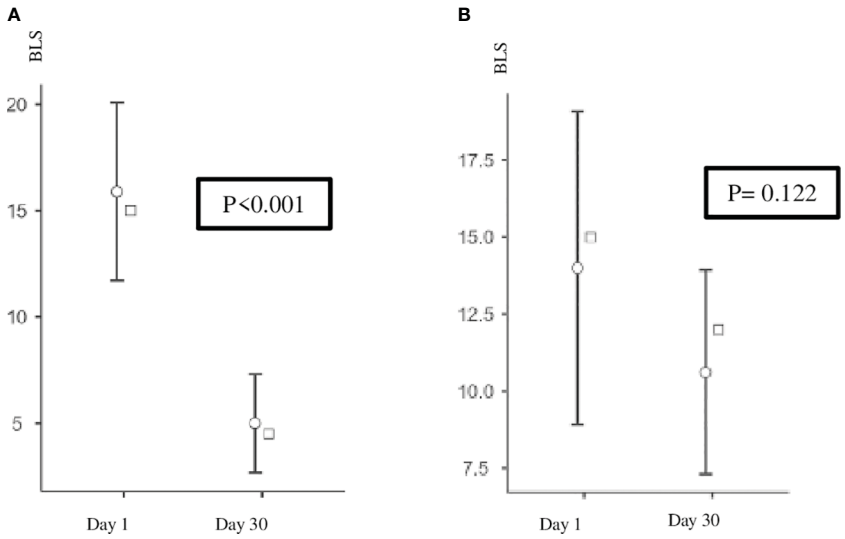

FIGURE 4
(A) Active group: BLS after HD on days 1 and 30. p < 0.001. **(B)** Control group: BLS after HD on days 1 and 30. BLS, B-line score; HD, hemodialysis.

crucial element to reach a personalized approach in the management of HD patients on a case-by-case basis.

Building a protocol that integrates these tools will possibly provide better objective markers to establish the best management for HD patients.

In conclusion, the correlation between pulmonary congestion, systemic congestion, and global volume status in hemodialysis patients is weak and independent of variable inter-dialytic intervals. Our simplified LUS-guided management approach was very useful in reducing pulmonary congestion when it was added to the standard of care. However, the effect on systemic and global volume status was weak, encouraging us to find a more complete protocol integrating BIA and IVC in the management of hemodialysis patients.

This study has limitations. As a pilot study, it had a low sample size and a monocentric nature.

Data availability statement

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found below: DOI 10.6084/m9.figshare.24099672.

Ethics statement

The studies involving humans were approved by the Brugmann University Hospital ethics committee. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

SK: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Writing – original draft, Writing – review & editing. BP: Data curation, Software, Writing – review & editing. MM: Writing – review & editing. FC: Writing – review & editing. JN: Conceptualization, Methodology, Supervision, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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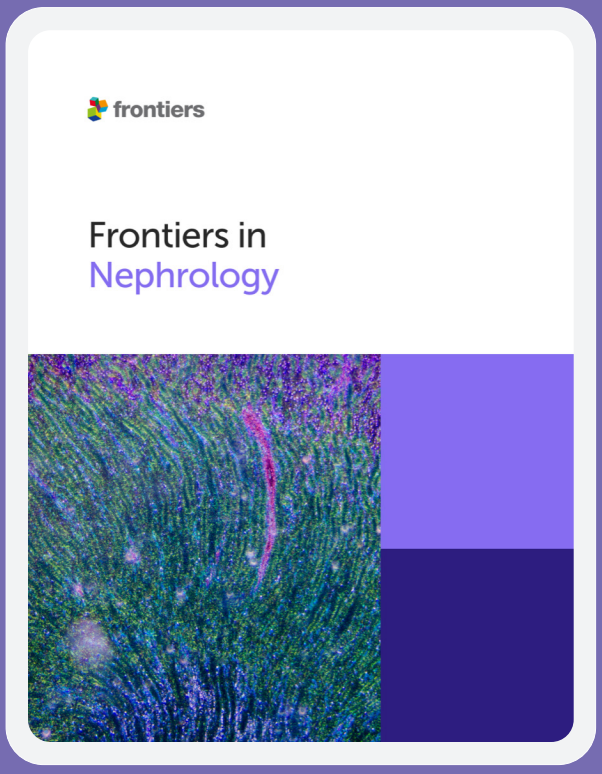

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