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Original Article

ORIGINAL ARTICLE

N-terminal pro-B-type natriuretic peptide, eGFR, and progression of kidney disease in chronic kidney disease patients without heart failure

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ABSTRACT

Background. Cardiorenal syndrome highlights the bidirectional relationship between kidney and heart dysfunction. N-terminal pro-B-type natriuretic peptide (NT-proBNP), which is the gold standard biomarker in heart failure (HF), may be an important biomarker for chronic kidney disease (CKD) progression. However, NT-proBNP is negatively related with estimated glomerular filtration rate (eGFR). In this study, we investigated the association of NT-proBNP, eGFR, and progression of kidney disease in CKD patients without HF.

Methods. This multicentric retrospective cohort study recruited 23 860 CKD patients without HF, who had at least one NT-proBNP record from China Renal Data System database. Linear regression model evaluated the relationship between eGFR and NT-proBNP. Cox regression analysis assessed the association between NT-proBNP and CKD progression. Sensitivity analysis examined the robustness of the main findings.

Results. This study involved 23 860 CKD patients without HF, distributed across different CKD stages: 10 526 in stages G1-2, 4665 in G3a, 3702 in G3b, 2704 in G4, and 2263 in G5. NT-proBNP was negatively correlated with eGFR, particularly in stages 4–5 CKD. A 15-unit decrease in eGFR was associated with increases in log (NT-proBNP) levels by 1.04-fold, 1.27-fold, 1.29-fold, 1.80-fold, and 3.50-fold for stages 1–2, 3a, 3b, 4, and 5, respectively. After excluding patients who developed CKD progression within 1 year, the Cox regression analysis revealed that the relationship between NT-proBNP and CKD progression was not significant in stages 4 and 5. However, for stages 1–3, each standard deviation increase in log (NT-proBNP) was associated with a 26%, 36%, and 28% higher risk of CKD progression, with *P* interaction $\leq$.001. The hazard ratios were 1.26 (95% confidence intervals (CI), 1.18 to 1.35), 1.36 (95% CI, 1.22 to 1.51), and 1.28 (95% CI, 1.14 to 1.43) for stages 1–2, stage 3a, and stage 3b, respectively.

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Conclusions. Despite its strong inverse association with eGFR, NT-proBNP was positively associated with the risk of progression of kidney disease in CKD patients with stages 1–3 without HF. Future studies should investigate the effectiveness of NT-proBNP as a predictive biomarker for the progression of kidney disease across diverse racial groups and healthcare settings.

Keywords: chronic kidney disease, estimated glomerular filtration rate, heart failure, N-terminal pro-B-type natriuretic peptide, progression of kidney disease

KEY LEARNING POINTS

What was known:

- Previous studies have demonstrated that cardiac dysfunction is linked with the decline in kidney function.
- However, there is currently limited research on whether NT-proBNP, a biomarker reflecting cardiac stress and volume overload, is associated with the risk of progression of kidney disease in CKD patients without heart failure.

This study adds:

- Compared with individuals with better kidney function, CKD patients with poorer kidney function have a stronger negative correlation between the NT-proBNP and eGFR.
- In patients with stages 1–3 CKD without HF, NT-proBNP was independently positively associated with the risk of CKD progression, regardless of age, gender, history of hypertension, or any use of antihypertensive drugs.
- In patients with stages 4–5 CKD without HF, elevated NT-proBNP level strongly related with impaired baseline kidney function.

Potential impact:

- In CKD patients without HF, plasma NT-proBNP level increases with the worsening of kidney function, and this increase is more pronounced in advanced CKD patients.
- Routine NT-proBNP measurements may be useful to evaluate the risk of CKD progression for stages 1–3 CKD patients, even for those with no history of heart failure.
- Future studies should investigate the effectiveness of regular monitoring of NT-proBNP to assess the risk of CKD progression in patients with CKD across diverse racial groups and healthcare settings.

INTRODUCTION

Chronic kidney disease (CKD) is characterized by persistent reduced glomerular filtration rate or markers of kidney damage such as elevated proteinuria, abnormal urine sediment, or radiographic findings [1]. CKD patients face a heightened risk of progressing to end-stage kidney disease (ESKD) and heart failure (HF) [2, 3]. Additionally, the concept of cardiorenal syndrome highlights the bidirectional relationship between kidney and heart, where each can exacerbate the development of the other [4–9].

N-terminal pro-B-type natriuretic peptide (NT-proBNP), which is the gold standard biomarker in the diagnosis and prognosis of HF, is released by cardiac muscle cells in response to pressure and volume overload [10, 19]. In CKD patients, the ability of the kidneys to effectively remove NT-proBNP from the bloodstream is diminished, leading to an accumulation of NT-proBNP in the plasma [11]. Furthermore, Bige Ozkan *et al.* identified an inverse relationship between kidney function and NT-proBNP, highlighting variations in this correlation among CKD patients without cardiovascular disease across different eGFR categories [12].

Previous studies have reported an association between elevated NT-proBNP levels and poor long-term renal outcomes in community populations aged 45–64 years [13], as well as in patients with diabetes mellitus [14–16], stable ischemic heart disease [17], and those with restricted estimated glomerular filtration rate (eGFR) levels ranging from 20 to 70 ml/min [18, 19] recruited from cohort studies or clinical trials. However, most participants in these studies were not of Asian descent [13, 18, 19], and many of the studies were limited by small sample sizes [15–17], or included individuals with preexisting HF [13, 14]. The association between NT-proBNP and progression of kidney disease in CKD patients without HF in different eGFR spectrums remains uncertain. A large and multicentric cohort study is needed.

Therefore, we aimed to investigate the association of NT-proBNP, eGFR, and progression of kidney disease in different eGFR spectrums of CKD patients without HF recruited from China Renal Data System (CRDS).

MATERIALS AND METHODS

Data source

A multicentric retrospective cohort study was conducted based on the CRDS, including 23 860 CKD patients from 24 clinical centers, covering the period from January 2000 to August 2023. The CRDS contains data gathered from inpatients and outpatients, encompassing details such as patient demographics, vital signs, medication prescriptions, medical diagnoses, laboratory tests, surgical procedures, and other findings acquired as part of standard clinical care. The data collected from all collaborating centers underwent consolidation and refinement at the National Clinical Research Center for Kidney Disease in Guangzhou, China. Previous research has validated the accuracy and comprehensiveness of this database [20–22].

Our study adhered to the Declaration of Helsinki, with approval number 2021-BC0037 granted by CRDS through the Chinese Office of Human Genetic Resources for Data Preservation and the Ministry of Science and Technology of China.

Study population

We included CKD patients, both outpatients and inpatients, aged ≥18 years, without a history of heart failure, and with at least one NT-proBNP record in the database. CKD was identified using the International Classification of Diseases, 10th Revision (ICD-10) code N18, or based on an eGFR <60 ml/min/1.73 m², urinary albumin-to-creatinine ratio (UACR) ≥30 mg/g, sustained for a minimum of 90 days. HF was defined by ICD-10 code of I50 or cardiac systolic dysfunction reported by echocardiographic assessment.

Exclusion criteria included: (i) pregnancy at the index date; (ii) patients lacking serum creatinine (Scr) measurement within 3 months before the index date; (iii) patients who underwent renal replacement therapy (including maintenance dialysis or kidney transplantation) prior to the index date; (iv) patients diagnosed with malignant tumors, underwent emergency treatment (including electric defibrillation, cardiopulmonary resuscitation, mechanical ventilation, intra-aortic balloon pump, and intensive care unit hospitalization), and surgical operation within 3 months before the index date; and (v) patients who were followed up for <30 days, or lacked Scr measurements during follow-up.

Participants were categorized according to eGFR levels (G1-2, eGFR ≥ 60; G3a, 45 ≤ eGFR < 60; G3b, 30 ≤ eGFR < 45; G4, 15 ≤ eGFR < 30; G5, eGFR <15 ml/min/1.73 m²), in accordance with the Kidney Disease Improving Global Outcomes (KDIGO) clinical practice guideline [1].

Exposure and outcome

Blood specimens were collected from patients during their hospitalization or outpatient visit. NT-proBNP levels were measured using either electrochemiluminescence immunoassay, chemiluminescence assay, or immunofluorescence assay method.

The index date was defined as the date of the earliest NT-proBNP record in the database. Consequently, we organized the data by the date of the initial NT-proBNP measurement, designated the earliest date as the index date, and eliminated duplicate records. The endpoint event was progression of kidney disease, encompassing a composite of either a 50% increase in Scr or a 40% decrease in eGFR from baseline, initiation of maintenance hemodialysis/peritoneal dialysis, or undergoing a kidney transplant. The follow-up period commenced on the index date and extended until the incidence of the defined outcome, the date of the final record in CRDS, or loss to follow-up (1 August 2023), whichever occurred first.

Covariates

Demographic characteristics, medical history, medication usage, and laboratory variables were extracted from the CRDS, with demographic information and medical history collected prior to the index date. Medication information was gathered from a 1-year observational period prior to the index date and categorized according to the Anatomical Therapeutic Chemical classification system, as stipulated in a previous study [20]. Demographic characteristics, such as blood pressure, weight, and height, were obtained from the medical records at each clinical center. Body mass index (BMI) was calculated as the ratio of weight (kg) to height (m) squared.

Hypertension (HTN) was defined by ICD-10 code I10. Diabetes mellitus (DM) was determined by the ICD-10 code E11 or any use of antidiabetic medications. Cardiovascular disease (CVD) included previously diagnosed acute coronary syndrome (myocardial infarction or unstable angina), stable angina, and stroke before the index date. Additional comorbidities, including peripheral vascular disease (PVD), arrhythmia, hyperuricemia, chronic obstructive pulmonary disease (COPD), pulmonary heart disease (PHD), valvular heart disease (VHD) (including mitral valve, tricuspid valve, pulmonary artery valve, or aortic valve disease) and cardiomyopathy (including dilated cardiomyopathy, hypertrophic cardiomyopathy, and amyloidosis), were confirmed using ICD-10 codes. Cardiac systolic or diastolic dysfunction were determined by echocardiography assessment before the index date [20].

Laboratory parameters were gathered within the 3 months preceding the index date. Proteinuria was determined by a positive urine protein test. UACR was assessed using a morning urine sample. Charlson Comorbidity Index (CCI) was calculated by summing the scores assigned to various comorbidities [23]. The eGFR was computed using the CKD Epidemiology Collaboration equation based on Scr measurement [24].

Statistical analysis

All analyses were performed using R v.4.1.1 (R Foundation for Statistical Computing, Vienna, Austria), a significance level of $P < .05$ (two-sided) was considered statistically significant. We assumed the missing data happened randomly and dealt with it by multiple imputations. Analysis of variance compared normally distributed continuous variables, Kruskal–Wallis tested non-normally distributed continuous variables, and the chi-square test examined categorical variable distribution across NT-proBNP quantiles.

NT-proBNP was $\log_e$-transformed due to its skewed nature. Linear regression model was conducted to evaluate the relationship between eGFR and NT-proBNP. The β coefficients and their 95% confidence intervals (CIs) were calculated after adjusting for reported confounders which may affect NT-proBNP, including age, gender, systolic blood pressure, diastolic blood pressure, BMI, HTN, DM, CVD, COPD/PHD, arrhythmia, PVD, VHD, cardiomyopathy, cardiac diastolic dysfunction, white blood cell (WBC), proteinuria, low-density lipoprotein (LDL), glycated hemoglobin (HbA1c), hemoglobin (Hb), uric acid (UA), albumin (Alb), and CCI.

Cox proportional hazards regression model was used to investigate the association between NT-proBNP and progression of kidney disease stratified by CKD stages. Hazard ratios (HR) with a 95% CI were estimated after adjusting for age, gender, BMI, systolic blood pressure, diastolic blood pressure, HTN, DM, CVD, COPD/PHD, arrhythmia, PVD, VHD, cardiomyopathy, cardiac diastolic dysfunction, use of renin-angiotensin system inhibitor (RASi), β-blockers, diuretics, calcium channel blockers (CCB), statins, insulin, metformin, sulfonylureas, sodium glucose co-transporter 2 inhibitor (SGLT2i), and dipeptidyl peptidase-4 inhibitor (DPP4i), LDL, CCI, UA, Alb, Hb, HbA1c, WBC, eGFR, proteinuria. The effect modification of eGFR on the relationship between NT-proBNP and a decline in kidney function was also determined, with interactions considered significant at $P \leq .05$.

We conducted a series of sensitivity analyses to assess the robustness of our main findings. First, we excluded participants who had endpoint events within 1 year to reduce bias related to unclear causality. Second, a competing risk model was used to address potential bias from all-cause mortality by calculating a sub-distribution HR, where death was treated as a competing endpoint. Third, we excluded individuals with CVD, VHD, cardiomyopathy, and/or cardiac diastolic dysfunction to remove

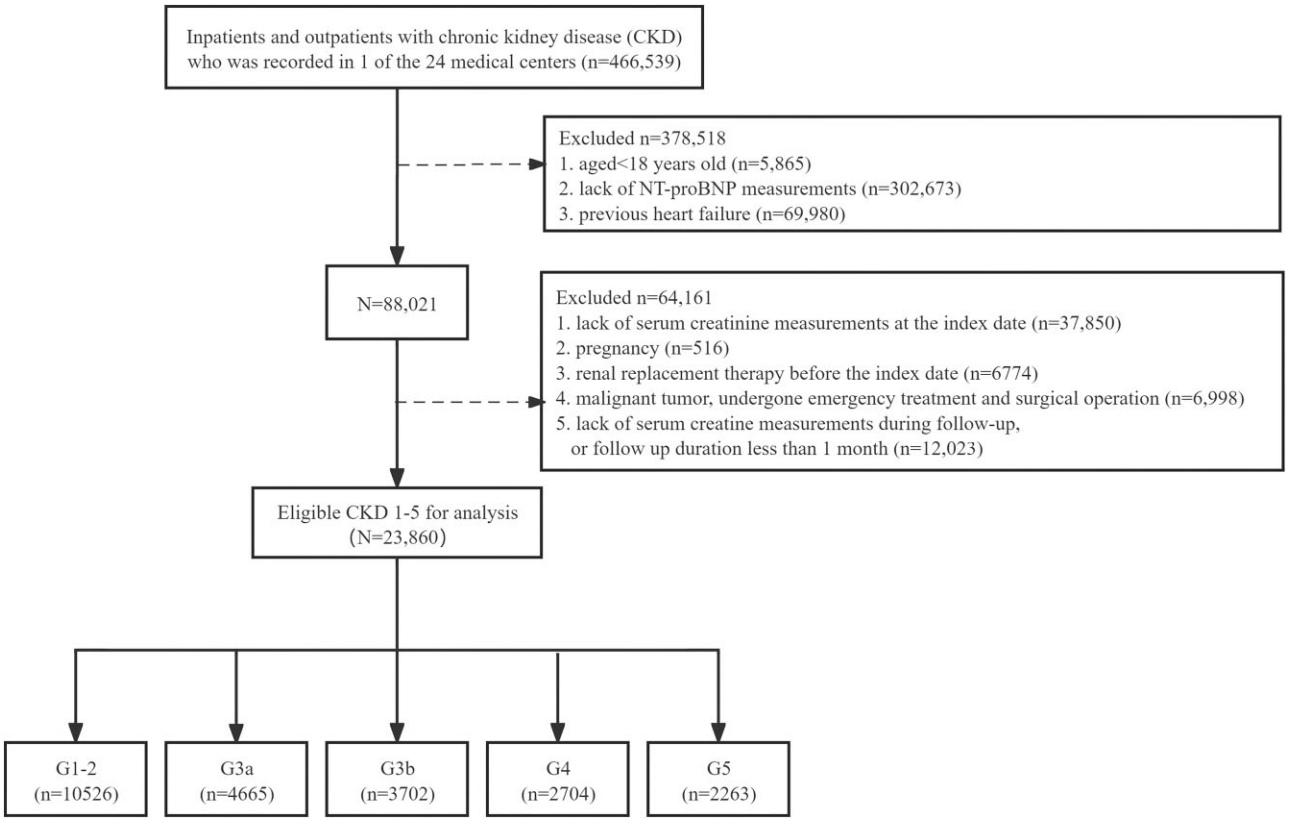

Figure 1: Flow chart of study population. Emergency treatment included electric defibrillation, cardiopulmonary resuscitation, mechanical ventilation, intra-aortic balloon pump and intensive care unit hospitalization. Participants were grouped based on the levels of eGFR (G1-2, eGFR ≥ 60; G3a, 45 ≤ eGFR < 60; G3b, 30 ≤ eGFR < 45; G4, 15 ≤ eGFR < 30; G5, eGFR < 15 ml/min/1.73 m^2), according to the KDIGO clinical practice guideline.

potential confounders. Fourth, to reduce the bias from single measurement, we calculated the association between the average level of NT-proBNP and CKD progression in population who had at least two measurements of NT-proBNP during the 1-year follow-up period. Finally, we calculated the *E* value to mitigate potential bias arising from unmeasured confounders.

Non-linear associations of NT-proBNP and progression of kidney disease were examined using restricted cubic spline (RCS) analysis with four knots (5th, 35th, 65th, 95th percentiles of NT-proBNP) across eGFR categories. If non-linearity was identified, threshold effect analysis and a two-segment Cox regression model using the "segmented" package were applied to calculate the inflection points.

Additional analysis

Additional analyses were conducted to investigate the association between NT-proBNP and progression of kidney disease stratified by age (>75 vs. ≤75), gender, history of hypertension, or use of RASi, β-blocker, diuretics and CCB.

RESULTS

Population characteristics

As illustrated in Fig. 1, this study included 23 860 CKD patients, with varying stages: 10 526 in stages G1-2, 4665 in G3a, 3702 in G3b, 2704 in G4, and 2263 in G5. Among all participants, 13 392 (56%) were male, and 11 612 (48.6%) were diagnosed with proteinuria. The median age was 66 (53, 77) years, with median eGFR was 55 (35, 82) ml/min/1.73 m², median UACR was 466 (66, 1955) mg/g and median level of NT-proBNP was 316 (100, 1331) pg/ml (Supplemental Table S1). Participants with higher levels of NT-proBNP were older and had lower eGFR, and higher UACR values (Table 1).

The relationship between the levels of NT-proBNP and eGFR

As shown in Table 2, the level of NT-proBNP showed a progressive increase from stage 1–2 to stage 5, with the median of 149 (61, 523), 355 (123, 1276), 541 (189, 2068), 900 (279, 3290), and 1860 (564, 6596) pg/ml in G1-2, G3a, G3b, G4, and G5, respectively.

After multivariable adjustment, NT-proBNP was independently negatively correlated with eGFR, which was more pronounced in patients with advanced kidney disease. Each decrease of 15 ml/min/1.73 m² in eGFR was associated with a 1.04-, 1.27-, 1.29-, 1.80-, and 3.50-fold higher level of log (NT-proBNP) in CKD patients with stages 1–2, 3a, 3b, 4, and 5, respectively.

The predictive role of NT-proBNP for progression of kidney disease

During a median follow-up duration of 33.5 (13.1, 67.1) months, a total of 5810 cases of progression of kidney disease were observed.

Table 1: Baseline characteristics of participants by quantiles of NT-proBNP level among CKD patients with stages 1–5.

Characteristics	NT-proBNP level				SMD	*P* value
	Quantile 1 ($n = 5965$)	Quantile 2 ($n = 5965$)	Quantile 3 ($n = 5965$)	Quantile 4 ($n = 5965$)		
Demographics						
Age, years	56 (44, 68)	67 (54, 77)	71 (58, 80)	71 (58, 80)	0.40	<.001
Male, %	3595 (60)	3242 (54)	3304 (55)	3249 (54)	0.08	<.001
BMI, median (IQR), kg/m^2	23.9 (21.6, 26.5)	23.4 (20.9, 26.0)	23.1 (20.7, 25.6)	22.6 (20.1, 25.2)	0.19	<.001
SBP, median (IQR), mmHg	130 (118, 142)	134 (120, 150)	137 (121, 153)	138 (120, 156)	0.23	<.001
DBP, median (IQR), mmHg	80 (72, 88)	79.0 (70, 87)	79.0 (70, 87)	80.0 (70, 90)	0.07	<.001
Comorbidities, (%)						
Hypertension	3040 (51.0)	3532 (59.2)	3708 (62.1)	3512 (58.9)	0.12	<.001
Diabetes mellitus	1777 (29.8)	1899 (31.8)	1813 (30.4)	1752 (29.4)	0.03	.02
Cardiovascular disease	1533 (25.7)	1970 (33.0)	2000 (33.5)	1879 (31.5)	0.09	<.001
PVD	799 (13.4)	857 (14.3)	779 (13.1)	634 (10.6)	0.06	<.001
Arrhythmia	284 (4.8)	468 (7.8)	629 (10.5)	927 (15.5)	0.20	<.001
Hyperuricemia	1465 (24.6)	1478 (24.8)	1450 (24.3)	1362 (22.8)	0.06	.02
COPD/PHD	677 (11.3)	818 (13.7)	786 (13.2)	755 (12.7)	0.04	<.001
VHD	79 (1.3)	136 (2.3)	281 (4.7)	653 (10.9)	0.23	<.001
Cardiomyopathy	9 (0.2)	30 (0.5)	70 (1.2)	284 (4.8)	0.17	<.001
Cardiac diastolic dysfunction	604 (10.1)	780 (13.1)	695 (11.7)	483 (8.1)	0.10	<.001
Medication, (%)						
Insulin	879 (14.7)	997 (16.7)	990 (16.6)	956 (16.0)	0.03	.01
Metformin	566 (9.5)	497 (8.3)	343 (5.8)	257 (4.3)	0.12	<.001
Sulfonylureas	332 (5.6)	328 (5.5)	284 (4.8)	235 (3.9)	0.04	<.001
SGLT2 inhibitor	17 (0.3)	14 (0.2)	18 (0.3)	11 (0.2)	0.01	.57
DPP4 inhibitor	142 (2.4)	124 (2.1)	111 (1.9)	79 (1.3)	0.04	<.001
CCB	1367 (22.9)	1722 (28.9)	1821 (30.5)	1824 (30.6)	0.09	<.001
RAASi	1599 (26.8)	1694 (28.4)	1593 (26.7)	1501 (25.2)	0.04	.002
β-blocker	741 (12.4)	995 (16.7)	1171 (19.6)	1440 (24.1)	0.17	<.001
Diuretic	839 (14.1)	1217 (20.4)	1623 (27.2)	2476 (41.5)	0.35	<.001
Statin	1634 (27.4)	1889 (31.7)	1776 (29.8)	1731 (29.0)	0.05	<.001
Laboratory parameters, median (IQR)						
NT-proBNP, pg/ml	51 (28, 72)	173 (128, 233)	600 (428, 876)	3609 (2139, 7741)	1.96	<.001
eGFR, ml/min/1.73 m^2	79 (57, 107)	60 (42, 85)	49 (30, 69)	37 (17, 57)	0.68	<.001
UACR, mg/g	198 (30, 878)	531 (67, 2067)	798 (108, 2693)	1367 (270, 3490)	0.28	<.001
Proteinuria, %	2636 (44.2)	2657 (44.5)	3023 (50.7)	3282 (55.0)	0.16	<.001
Bun, mmol/l	5.6 (4.5, 7.2)	6.7 (5.1, 9.2)	8.0 (5.7, 12.0)	10.3 (6.8, 16.7)	0.58	<.001
Hemoglobin, g/l	132.0 (119.0, 145.0)	121.0 (106.0, 134.0)	112.0 (94.0, 127.0)	104.0 (84.0, 123.0)	0.62	<.001
Alb, g/l	39.5 (35.5, 42.8)	37.2 (32.3, 40.6)	35.4 (30.4, 39.2)	34.0 (29.2, 38.0)	0.38	<.001
UA, μmol/l	380 (308, 466)	388 (310, 479)	405 (321, 502)	450 (352, 556)	0.27	<.001
HbA1c, %	6.0 (5.5, 7.3)	6.1 (5.6, 7.5)	6.1 (5.6, 7.3)	6.1 (5.5, 7.1)	0.06	<.001
HDL-C, mmol/l	1.09 (0.89, 1.34)	1.09 (0.87, 1.37)	1.05 (0.83, 1.31)	1.02 (0.80, 1.29)	0.14	<.001
LDL-C, mmol/l	2.84 (2.17, 3.59)	2.72 (2.05, 3.60)	2.54 (1.90, 3.38)	2.39 (1.77, 3.21)	0.19	<.001
TG, mmol/l	1.59 (1.09, 2.43)	1.49 (1.03, 2.22)	1.37 (0.97, 2.00)	1.24 (0.89, 1.80)	0.21	<.001
TC, mmol/l	4.71 (3.93, 5.73)	4.63 (3.75, 5.76)	4.34 (3.52, 5.45)	4.12 (3.27, 5.17)	0.22	<.001
Serum sodium, mmol/l	140 (138, 142)	140 (137, 142)	140 (137, 142)	139 (136, 142)	0.14	<.001
Serum potassium, mmol/l	4.0 (3.7, 4.3)	4.0 (3.7, 4.4)	4.1 (3.7, 4.5)	4.1 (3.7, 4.6)	0.09	<.001
WBC, $\times 10^9$l	7.1 (5.7, 8.8)	7.1 (5.7, 9.1)	7.4 (5.7, 9.8)	7.4 (5.7, 10.0)	0.09	<.001
CCI, median (IQR)	4 (3, 6)	5 (3, 6)	5 (4, 6)	5 (4, 6)	0.20	<.001

Note: Continuous variables were presented as mean (SD) or median (25th percentile to 75th percentile). Categorical variables were expressed as number (percentage). The percentages of comorbidities and medication history were be retained one decimal place to better visualize the distribution differences between groups. Abbreviations: IQR, interquartile range; SMD, standardized mean difference; SBP, systolic blood pressure; DBP, diastolic blood pressure; Bun, blood urea nitrogen; HbA1c, glycated hemoglobin; HDL-C, high density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglyceride.

Cox proportional hazards regression model revealed that NT-proBNP was positively associated with a heightened risk of progression of kidney disease among CKD patients with stages 1–5 (HR, 1.37; 95% CI, 1.32, 1.42), with a stronger association among CKD stages 3a and 3b (3a: HR of 1.42 with 95% CI of 1.31 to 1.54; 3b: HR of 1.43 with 95% CI of 1.31 to 1.55; *P* for interaction <.001).

We did several sensitivity analyses to examine the stability of the main results. The *E* value, ranging from 2.21 to 2.81 in different CKD stages, suggested that unmeasured confounders would need an HR of at least 2.21 to change the current conclusion. As shown in Supplemental Tables S2–S7, when applying the competing risk model, excluding individuals with a history of specific conditions, such as cardiovascular disease, cardiomyopathy, VHD, and cardiac diastolic dysfunction, and exploring the association between the mean level of NT-proBNP during the 1-year follow-up period and CKD progression, the main findings

Table 2: Distributions of NT-proBNP and the correlation between eGFR and log (NT-proBNP) in CKD patients across eGFR category.

	G1-2	G3a	G3b	G4	G5
Distributions of NT-proBNP in CKD patients across eGFR category					
NT-proBNP (pg/ml)	149 (61, 523)	355 (123, 1276)	541 (189, 2068)	900 (279, 3290)	1860 (564, 6596)
The correlation between each 15-ml/min/1.73 m^2 lower eGFR and log (NT-proBNP) in CKD patients across eGFR category.					
β coefficients (SE)	0.040 (0.007)	0.239 (0.073)	0.252 (0.084)	0.586 (0.092)	1.254 (0.160)
exp (β coefficients) (95% CI)	1.04 (1.03, 1.06)	1.27 (1.10, 1.46)	1.29 (1.09, 1.52)	1.80 (1.50, 2.16)	3.50 (2.56, 4.80)
P values	<.001	.001	.001	<.001	<.001

Distributions of NT-proBNP were described by median and interquartile range values; β coefficients were calculated from linear regression model after adjusting for confounders as described in methods; exp (β coefficients) was calculated as exponentiated (β coefficients).

Table 3: Association of log (NT-proBNP) and progression of kidney disease among stage 1–5 CKD patients across eGFR category.

	Total population		Excluding participants who developed CKD progression within 1 year	
Group	No. of events/participants	Per SD HR (95% CI)	No. of events/participants	Per SD HR (95% CI)
G1-2	2115/10 526	1.26 (1.20, 1.33)	1197/9608	1.26 (1.18, 1.35)
G3a	845/4665	1.42 (1.31, 1.54)	479/4299	1.36 (1.22, 1.51)
G3b	801/3702	1.43 (1.31, 1.55)	458/3377	1.28 (1.14, 1.43)
G4	900/2704	1.21 (1.12, 1.31)	439/2243	1.09 (0.97, 1.23)
G5	1149/2263	1.09 (1.02, 1.17)	318/1432	1.06 (0.93, 1.21)

HRs were estimated after adjusting for age, sex, BMI, systolic blood pressure, diastolic blood pressure, hypertension, DM, chronic obstructive pulmonary disease/PHD, arrhythmia, PVD, cardiovascular disease, VHD, cardiomyopathy, cardiac diastolic dysfunction, eGFR, proteinuria, LDL, CCI, UA, glycated hemoglobin, albumin, hemoglobin, WBC, use of renin-angiotensin system inhibitor, β-blockers, diuretics, CCB, statins, insulin, metformin, sulfonylureas, sodium glucose co-transporter 2 inhibitor and dipeptidyl peptidase-4 inhibitor.

remained consistent. However, when excluding participants who developed the progression of kidney disease within 1 year, the association between NT-proBNP and CKD progression was insignificant in stages 4 and 5 CKD patients [HR (95% CI): stage 4, 1.09 (0.97, 1.23), $P = .16$; stage 5, 1.06 (0.93, 1.21), $P = .36$]. As shown in Table 3, each standard deviation (SD) increase in log (NT-proBNP) was linked to a 26%, 36%, and 28% higher risk of kidney disease progression in CKD stages 1–2, 3a, and 3b, respectively [HR (95% CI): stage 1–2, 1.26 (1.18, 1.35); stage 3a, 1.36 (1.22, 1.51); stage 3b, 1.28 (1.14, 1.43)].

The RCS analysis revealed a non-linear relationship between NT-proBNP and progression of kidney disease in stages 1–4 CKD patients, except for stage 5 CKD patients (G1-4: $P_{\text{non-linear}} < .001$; G5: $P_{\text{non-linear}} = .47$). Additionally, among stages 1–4 CKD patients, a reversed L-shaped relationship was observed between NT-proBNP and CKD progression (Fig. 2). Utilizing a two-segment Cox regression model, inflection points were identified at 250, 750, 653, and 526 pg/mL for G1-2, G3a, G3b, and G4, respectively. Below these inflection points, increased NT-proBNP was significantly associated with a higher risk of declining kidney function. However, above the inflection points, a less significant correlation between NT-proBNP and CKD progression risk was observed (Supplemental Table S8).

Additional analysis

This study found a significant association between higher NT-proBNP levels and an increased risk of CKD progression in patients with stages 1–3 CKD, even after adjusting for confounding factors and accounting for reverse causation. Subsequently, we performed additional analyses in stages 1–3 CKD patients to explore the association of NT-proBNP and CKD progression stratified by age, gender, history of hypertension, or any use of RASi, β-blocker, diuretics or CCB subgroups. As shown in Supplementary Figure S1–S3, elevated NT-proBNP levels were associated with an increased risk of progression of kidney disease in stage 1–3 CKD patients across various subgroups. This association was particularly stronger in CKD 3a and 3b patients aged ≥75, as well as in male patients with CKD 3b.

DISCUSSION

This large sample, multicentric cohort study has provided several novel insights. First, in CKD patients without HF, the negative correlation between NT-proBNP and eGFR was more pronounced in advanced CKD. Second, the plasma level of NT-proBNP could predict the risk of CKD progression in stages 1–3 CKD without HF, regardless of age, gender, hypertension, or any use of antihypertensive drugs. However, this correlation was insignificant among patients with CKD stages 4–5 after accounting for reverse causation.

Our study demonstrated an inverse correlation between NT-proBNP levels and kidney function in CKD patients, with a more pronounced effect observed in those with worsened renal impairment. This finding aligns with existing studies. A study involving 229 patients admitted to the cardiology department reported a negative correlation between NT-proBNP and eGFR ($r = -0.579$, $P < .05$) [25]. Furthermore, a more recent cross-sectional analysis from the National Health and Nutrition Examination Survey included 11 456 American adults without prior CVD [19]. This analysis observed that the negative association between NT-proBNP and eGFR was stronger in CKD patients with worsening kidney function [12]. The reduced clearance rate of

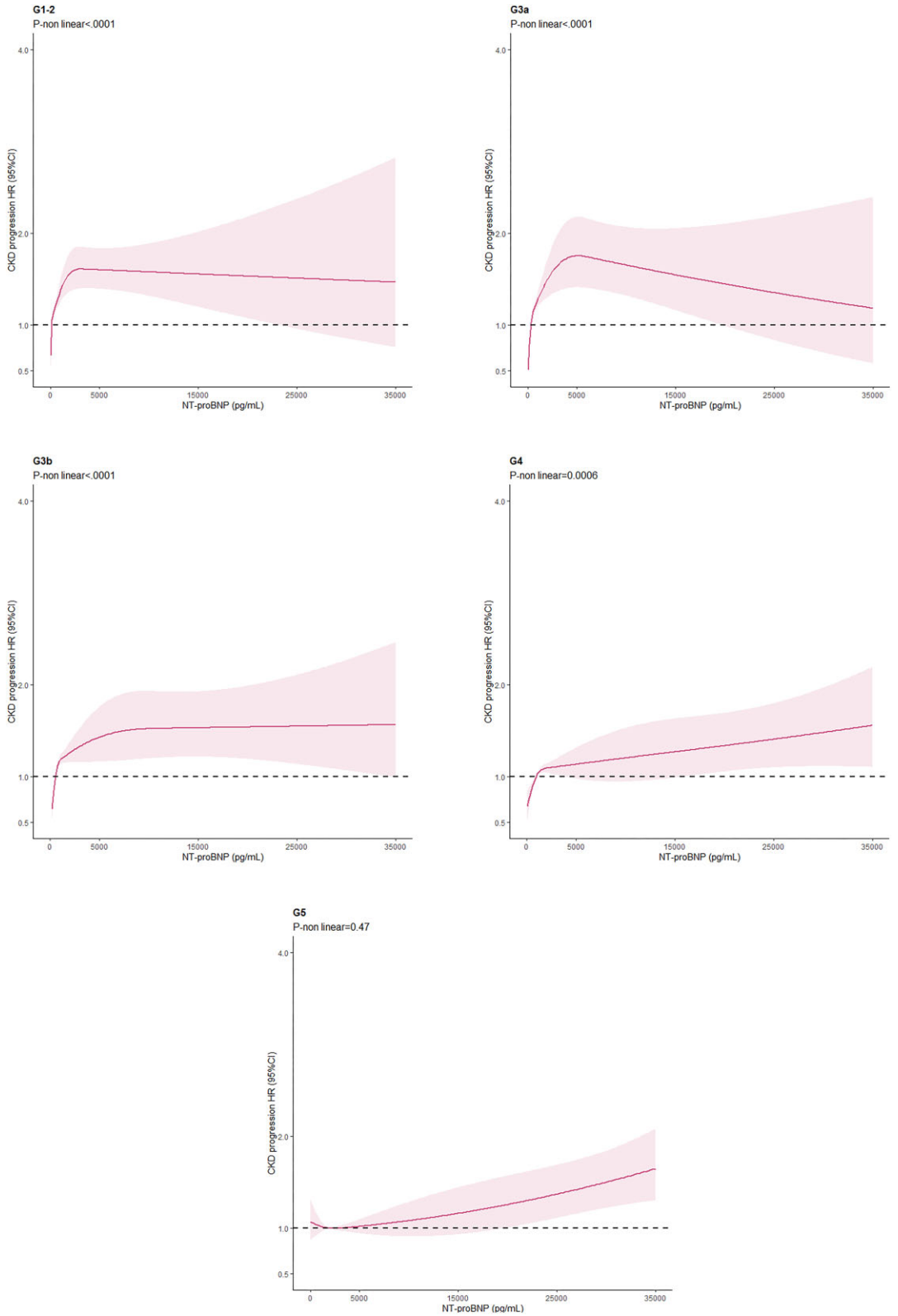

Figure 2: Association of NT-proBNP and progression of kidney disease in CKD patients across eGFR categories using RCS analyses with four knots. Adjusted for age, gender, BMI, systolic blood pressure, diastolic blood pressure, hypertension, DM, cardiovascular disease, chronic obstructive pulmonary disease/PHD, arrhythmia, PVD, VHD, cardiomyopathy, cardiac diastolic dysfunction, eGFR, proteinuria, LDL, CCI, UA, glycated hemoglobin, albumin, hemoglobin, WBC, use of renin-angiotensin system inhibitor, β-blockers, diuretics, CCB, statins, insulin, metformin, sulfonylureas, sodium glucose co-transporter 2 inhibitor, and dipeptidyl peptidase-4 inhibitor. The red area represents the 95% confidence interval. (a) G1-2, (b) G3a, (c) G3b, (d) G4, and (e) G5.

NT-proBNP in those with worsened renal impairment likely explains this negative relationship [26].

In response to stretch, cardiomyocytes secrete pro B-type natriuretic peptide (BNP), which is promptly cleaved into BNP and NT-proBNP [27]. NT-proBNP is a widely utilized biomarker for diagnosing and managing HF. American Heart Association (AHA) guidelines proposed regarding NT-proBNP as an indication of pre-HF [28]. NT-proBNP does not solely correlates to left ventricular (LV) systolic function and volume expansion. Several factors can affect its concentration, including LV hypertrophy, cardiac diastolic dysfunction, cardiovascular disease, VHD, and cardiomyopathy [28–30]. Despite all this, NT-proBNP has a well-defined role in the risk stratification of cardiovascular disease and adverse outcomes [11].

Oka T *et al.* linked BNP monitoring with the risk of acute kidney injury among 2998 CKD patients before dialysis [31]. However, the study did not specifically clarify the relationship between NT-proBNP and long-term renal outcomes. Our study provided further affirmation of the significance of NT-proBNP as a prognostic biomarker for CKD progression. The association between increased level of NT-proBNP and decline in kidney function has been established in stages 1–4 CKD, observed in both small and specific populations [13, 14, 17–19], which is consistent with our findings. In CKD patients with mild to moderate impaired kidney function, irrespective of diabetes history, individuals with elevated NT-proBNP levels are more likely to experience a reduction of eGFR by half or the need to initiate kidney replacement therapy [18]. In the context of CKD with type 2 diabetes, a *post hoc* analysis confirmed the predictive value of NT-proBNP for both renal and cardiac outcomes [32]. Furthermore, NT-proBNP demonstrated strong prognostic significance for the progression to ESKD in a cohort of 227 nondiabetic patients with a concentration of Scr $<$531 μmol/l [33]. These findings collectively emphasize the potential importance of regularly measuring NT-proBNP for monitoring progression of kidney disease in CKD patients.

As a further point, our result underscores the robust predictive role of NT-proBNP for the risk of progression of kidney disease in CKD 1–3 patients without symptomatic HF. Some mechanisms may be correlated with high NT-proBNP levels and the progression of kidney disease. First, CKD is frequently accompanied by the long-term activation of the RAAS, leading to the production of angiotensin II and aldosterone, which have vasoconstrictive and sodium-retaining effects. This, in turn, prompts the synthesis and release of NT-proBNP, which may serve as a biomarker for CKD progression [34]. Second, patients with CKD often have coexisting cardiovascular disease, which can exacerbate the decline in renal function. Additionally, myocardial injury or disease increases the tension in the myocardium, which can lead to elevated plasma NT-proBNP levels [34].

Ascher *et al.* recently explored the association between 1-year changes in NT-proBNP levels and declines in kidney function among participants in the Systolic Blood Pressure Intervention Trial [35]. This study demonstrated that reductions in NT-proBNP during blood pressure treatment are independently associated with a lower risk of decline in kidney function, especially in individuals with eGFR of 20-59 ml/min/1.73 m², which is consistent with our findings. Our study addresses the data gap concerning Chinese patients with stages 4–5 CKD and revealed that in these stages, elevated NT-proBNP levels were correlated with baseline impaired kidney function but were not associated with CKD progression. Various reasons proposed to explain this. First, a significant number of this population may experience mortality before advancing to ESKD [36]. Besides, it has been reported that eGFR decreases by 0.26 $\pm$ 0.47 ml/min/1.73 m² per month in CKD patients with stages 4–5 [37], and they are more prone to requiring dialysis treatment. These factors may introduce bias into the results. Second, as kidney function deteriorates, the correlation between NT-proBNP and eGFR may strengthen [12]. This suggests that the effect of decreased renal clearance on NT-proBNP could surpass the excessive production of NT-proBNP in patients with advanced kidney disease. Last, multiple factors such as anemia and hypoalbuminemia might mask the role of NT-proBNP as a biomarker for the decline in kidney function [38]. These considerations highlight the complexity of the relationship between NT-proBNP and CKD progression, especially in patients with advanced CKD.

This study revealed that stage 3 CKD patients aged 75 years and older, as well as male patients with stage 3b CKD, exhibited a stronger correlation between NT-proBNP levels and CKD progression. These findings align with existing knowledge, as supported by the Heart Failure Association of the European Society of Cardiology, which advocates for age-specific interpretations of NT-proBNP [39]. These factors highlight the necessity for a nuanced and personalized interpretation of NT-proBNP levels, considering the unique characteristics and clinical context of each patient.

Our study was the first to evaluate the non-linear correlation between NT-proBNP and CKD progression, underscoring the complexity of NT-proBNP dynamics and its potential clinical implications. RCS and threshold effect analysis revealed a reversed L-shaped relationship between NT-proBNP and risk of kidney function progression, with inflection points observed in stage 1–4 CKD patients. Once the plateau was reached, even if the value of NT-proBNP increased, its association with the maximum risk of CKD progression did not change any more. This observation aligns with prior research, which demonstrated a reversed L-shaped association of NT-proBNP with all-cause mortality until reaching an inflection point at 3231.4 pg/mL among HF patients [40]. Additionally, our study findings offer evidence for maintaining NT-proBNP levels as low as possible to mitigate the progression of CKD. On reaching the inflection point, the correlation between NT-proBNP and kidney function progression did not change greatly even if the level of NT-proBNP increased. For instance, the CKD progression risk in CKD patients with a NT-proBNP level of 35 000 pg/ml is equivalent to that of a NT-proBNP level of 30 000 pg/ml. However, our study did not find a significant non-linear relationship between NT-proBNP and progression of kidney disease in CKD stage 5. The RCS model might not fully characterize the complex relationships between NT-proBNP and CKD progression in this stage.

Our findings carried several important clinical implications and strengths. First, we firstly demonstrated that the association of NT-proBNP, eGFR and progression of kidney disease in CKD patients varied by baseline renal function. Thus, the NT-proBNP should be interpreted carefully across different eGFR levels. Second, our findings are the first to highlight the predictive role of NT-proBNP in assessing the decline in kidney function in Chinese patients with stages 1–3 CKD. This finding suggests that early screening for NT-proBNP in CKD patients could aid in the management of CKD, even in individuals with an eGFR of $\geq$30 ml/min/1.73 m² who had no history of HF. Future research should investigate the relationship between longitudinal changes in NT-proBNP and kidney function in populations with diverse racial backgrounds or healthcare settings to assess the generalizability of the findings from this study.

This study should be deciphered in the context of the following limitations. First, due to the retrospective nature, we identified the endpoint outcome of kidney replacement therapy using diagnostic codes and operative prescriptions from collaborative medical centers. Thus, individuals undergoing dialysis or kidney transplants at other hospitals were omitted. Second, patients with impaired renal function may have a higher probability of experiencing endpoint events, potentially introducing some bias to the results. Third, it is important to note that only 22.5% of participants had a record of echocardiography assessment in the CRDS dataset, which may have resulted in the misclassification of some patients as not having HF. Therefore, this study should be interpreted as focusing on CKD patients without symptomatic HF, rather than those with presymptomatic HF. A more accurate interpretation would be possible if all included patients had undergone a complete echocardiogram assessment. Furthermore, the small number of patients with echocardiography assessments may lead to misdiagnosis of certain conditions, such as cardiac valve disorders and myocardial disorders, and detailed information about the severity of these diseases was unavailable in the database. Fourth, the use of different methods for measuring NT-proBNP, along with the unclear timing of these measurements, could introduce bias, potentially influenced by the clinical reasons for ordering the test. Last, in the present study, we were unable to obtain the medication history of patients not recorded in the CRDS. As a result, medication information for individuals prescribed outside the collaborative hospital was not included in our analysis.

In summary, we demonstrated that NT-proBNP may predict CKD progression for stages 1–3 CKD patients without HF, while for stage 4–5 CKD patients, NT-proBNP may be more related with baseline kidney function. The association of NT-proBNP, eGFR, and CKD progression varied in different CKD stages, highlighting the importance of a prudent interpretation of the cardiorenal biomarker NT-proBNP among CKD patients.

SUPPLEMENTARY DATA

Supplementary data are available at *Clinical Kidney Journal* online.

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DATA AVAILABILITY STATEMENT

The CRDS datasets generated and analyzed in the present study are available from the corresponding author on reasonable request.

CONFLICT OF INTEREST STATEMENT

None declared.

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