

The impact of renal function on the prognostic value of N-terminal pro-B-type natriuretic peptide in patients with coronary artery disease

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Abstract

Background: *The impact of renal function on the prognostic value of N-terminal pro-B-type natriuretic peptide (NT-proBNP) remains unclear in coronary artery disease (CAD). This study sought to investigate the value of using NT-proBNP level to predict prognoses of CAD patients with different estimated glomerular filtration rates (eGFRs).*

Methods: *A retrospective analysis was conducted from a single registered database. 2087 consecutive patients with CAD confirmed by coronary angiography were enrolled. The primary endpoint was all-cause mortality.*

Results: *The mean follow-up time was 26.4 ± 11.9 months and death events occurred in 197 cases. The NT-proBNP levels increased with the deterioration of renal function, as well as the optimal cut-off values based on eGFR stratification to predict endpoint outcome (179.4 pg/mL, 1443.0 pg/mL, 3478.0 pg/mL, for eGFR ≥ 90, 60–90 and < 60 mL/min/1.73 m², respectively). Compared with the routine cut-off value or overall optimal one, stratified optimal ones had superior predictive ability for endpoint in each eGFR group (all with the highest Youden's J statistics). And the prognostic value became weaker as eGFR level decreased (eGFR ≥ 90 vs. 60–90 vs. < 60 mL/min/1.73 m², odds ratio [OR] 7.7; 95% confidence interval [CI] 1.7–33.9 vs. OR 4.8; 95% CI 2.7–8.5 vs. OR 3.0; 95% CI 1.5–6.2).*

Conclusions: *This study demonstrated that NT-proBNP exhibits different predictive values for prognosis for CAD patients with different levels of renal function. Among the assessed values, the NT-proBNP cut-off value determined using renal function improve the accuracy of the prognosis prediction of CAD. Moreover, lower eGFR is associated with a higher NT-proBNP cut-off value for prognostic prediction. (Cardiol J 2019; 26, 6: 696–703)*

Key words: coronary artery disease, renal function, N-terminal pro-B-type natriuretic peptide, prognosis

Introduction

N-terminal pro-B-type natriuretic peptide (NT-proBNP) level [1, 2] and estimated glomerular filtration rate (eGFR) [3, 4] are important

predictors of clinical prognosis in patients with coronary artery disease (CAD). Prior studies have shown that for such patients, NT-proBNP level is significantly correlated with eGFR; in particular, NT-proBNP level increases as eGFR decreases

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[5, 6]. Moreover, investigations have also revealed that the combined use of NT-proBNP level and eGFR can improve the identification of patients at high risk of acute myocardial infarction and heart failure (HF) [7–9]. Similarly, NT-proBNP levels are influenced by age [10]. Research has indicated that greater age is associated with a higher NT-proBNP cut-off value for diagnosing HF [11]. However, the predictive value of NT-proBNP measurements remains unclear for patients with different eGFRs.

This study sought to investigate the predictive value of using NT-proBNP level to predict prognoses of CAD patients with different eGFRs by analysing 2087 consecutive cases of patients with CAD.

Methods

Study population

The data source for this investigation was the West China Hospital CAD database. This single center database prospectively includes all patients undergoing coronary angiography with known or highly suspected CAD in West China Hospital affiliated to Sichuan University. For this analysis, consecutive patients with CAD were enrolled from July 2008 to January 2012. Patients with CAD were eligible for inclusion if they were restricted to participants with angiographic evidence of $\geq 50\%$ stenosis in ≥ 1 coronary vessels. The exclusion criteria included malignancies, pregnancy, end stage renal disease with hemodialysis or renal transplant and severe liver or hematological diseases. The above criteria were met by 3375 consecutive patients. After further removing those with loss of follow-up ($n = 312$) or incomplete follow-up data ($n = 61$), and patients without presence of NT-proBNP data at admission ($n = 915$), 2087 patients were included in this data analysis. The study protocol was approved by the local institutional review boards in accordance with the Declaration of Helsinki. All subjects provided written informed consent when they were included in the database.

Baseline characteristics

Demographic data, medical history, cardiovascular risk factor, vital signs at admission, medication at discharge, and final diagnosis were obtained from the patient electronic medical records and were reviewed by a trained study coordinator. Blood samples were collected before angiography, and blood biomarkers measured including NT-proBNP (measured with an electrochemiluminescence immunoassay kit, Roche Diagnostics,

Grenzach Wyhlen, Germany), liver and kidney function (including the admission serum creatinine levels), blood glucose, serum lipid, and other measurements were analyzed in the Department of Laboratory Medicine, West China Hospital, accredited by the College of American Pathologists. Hypertension was defined as those with systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg and/or those receiving anti-hypertensive medications. Diabetes mellitus was diagnosed in patients who had previously undergone dietary treatment for diabetes, had received additional oral antidiabetic or insulin medication or had a current fasting blood glucose level of ≥ 7.0 mmol/L or random blood glucose level ≥ 11.1 mmol/L. Patients received care according to usual practice; treatment was not affected by participation in this study.

Renal function assessment

Serum creatinine was finished before the angiography within first 24 h after admission and assessed by a nonkinetic alkaline picrate (Jaffe) method. The Modification of Diet in Renal Disease (MDRD) equation was used to eGFR rate in milliliters per minute per 1.73 m^2 [12]. Patients were divided into three eGFR groups: $\text{eGFR} \geq 90 \text{ mL/min/1.73 m}^2$ (normal renal function corresponding to strata used to define chronic kidney disease stages [13]), $60 \leq \text{eGFR} < 90 \text{ mL/min/1.73 m}^2$ (mildly impaired renal function), and $\text{eGFR} < 60 \text{ mL/min/1.73 m}^2$ (moderately or severely impaired renal function).

Follow-up and endpoint

The follow-up period ended on January 2013. Follow-up information was collected through contact with patients' physicians, patients or their family. All data were corroborated with hospital records. The primary endpoint in this study were all-cause mortality, as documented in the database. Cardiovascular mortality was not used as an endpoint outcome to perform analysis after preliminarily calculating statistics power, which was insufficient for further analysis due to low mortality in the limited follow-up time.

Statistical analysis

Post-hoc analysis was conducted on a retrospective basis. Baseline characteristics were compared among patients categorized by admission eGFR levels. Continuous variables were expressed as mean \pm standard deviation (SD) and categorical variables were reported as counts (percentages).

Analysis of t tests and Pearson χ^2 tests were used to compare the difference for baseline variables among eGFR groups, respectively. Kruskal-Wallis tests were applied to analyze the difference of NT-proBNP levels in patients across renal function status, as well as that between patients with and without endpoint in the same eGFR group. Trend χ^2 tests were used to evaluate tendency changes in all-cause mortality according to eGFR levels and NT-proBNP quartiles. For the investigation of overall optimal NT-proBNP cut-off value in the total population and stratified optimal ones in corresponding eGFR groups to predict the endpoint, receiving operating characteristic (ROC) analysis were conducted. And the following parameters: sensitivity, specificity, as well as Youden's J statistic, an index to measure the performance for these cut-off values to discriminate between low and high risk individuals in an objective manner [14], were calculated for overall and stratified optimal ones, and the non-optimal one (300 pg/mL, as proposed in the literature [15]) in each eGFR groups. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated based on Binary Logistic Regression models, which were used to investigate the risk effect of NT-proBNP levels (as categorical variables, under and above the optimal cut-off values or the non-optimal ones) on the outcome events in different eGFR groups. Two-sided p values of less than 0.05 indicated statistical significance. All analyses were performed with SPSS software (version 24.0).

Results

A total of 2087 patients with CAD were included in this study. Their mean age was 65.0 ± 10.7 years, 21.8% of the patients were female, and patients with $eGFR \geq 90$ mL/min/1.73 m² or < 60 mL/min/1.73 m² accounted for 29.6% and 19.1% of total population, respectively. Patients baseline characteristics varied as renal function deteriorated; in particular, compared with patients in a higher eGFR group, participants in the lower eGFR group tended to be older and had a higher proportion of female, smoke exposure, hypertension, diabetes, cardiac dysfunction, and complex coronary lesions at admission, and had a lower percentage of prescription of antiplatelet drugs and statins at discharge (Table 1).

Over a mean follow-up period of 26.4 ± 11.9 months, 197 endpoint outcomes occurred (all-cause mortality rate 9.4%), 107 of that were attributed to cardiovascular deaths (cardiac mortality rate 5.1%).

There was a strong association between renal function and all-cause or cardiovascular mortality, and a similar relationship was also observed between NT-proBNP quartiles and all-cause or cardiovascular mortality (all p values for trend < 0.01) (Fig. 1).

Meanwhile, there was a significant correlation between NT-proBNP levels and renal function. The NT-proBNP levels increased with the deterioration of renal function, median value ranging from 341.0 pg/mL at $eGFR \geq 90$ mL/min/1.73 m² to 1205.0 pg/mL at $eGFR < 60$ mL/min/1.73 m² in patients without all-cause death (p for trend < 0.01), and ranging from 900.0 pg/mL to 6086.5 pg/mL in patients with all-cause death (p for trend < 0.01), meanwhile, the NT-proBNP level of the dead was higher than that of survivors in each eGFR group (all p < 0.01) (Fig. 2, Table 2).

The overall optimal NT-proBNP cut-off value for all patients and the stratified optimal ones for patients with corresponding renal function status to predict all-cause death determined by ROC analysis were as follow: 1440.5 pg/mL for all patients, 179.4 pg/mL for $eGFR \geq 90$ mL/min/1.73 m², 1443.0 pg/mL for eGFR ranging 60–90 mL/min/1.73 m², and 3478.0 pg/mL for $eGFR < 60$ mL/min/1.73 m². Compared with non-optimal cut-off value (300 pg/mL) and overall optimal one, the stratified optimal one has a superior ability to discriminate the risk and predict all-cause mortality in each eGFR group (all the three with the highest Youden's J statistics) (Table 3).

After adjustment for potential confounders by multivariate logistic regression analysis, stratified optimal NT-proBNP cut-off value, not overall optimal one or non-optimal one, which increased with the deterioration of renal function status, was the first-rank one to predict endpoint in each eGFR group, and the prognostic values became weaker as eGFR level decreased ($eGFR \geq 90$ vs. 60–90 vs. < 60 mL/min/1.73 m², OR 7.7; 95% CI 1.7–33.9 vs. OR 4.8; 95% CI 2.7–8.5 vs. OR 3.0; 95% CI 1.5–6.2) (Table 4).

Discussion

This study has demonstrated that 1) NT-proBNP level is negatively correlated with eGFR in CAD patients; 2) the value of NT-proBNP level for predicting prognosis varies for CAD patients with different eGFRs: A lower eGFR level is indicative of decreased diagnostic value of NT-proBNP and a larger optimal NT-proBNP cut-off value for predicting prognosis.

The value of NT-proBNP level for predicting clinical prognosis in patients with cardiovascular

Table 1. Baseline characteristics of the study population.

Characteristics	eGFR [mL/min/1.73 m ²]				P
	Total	≥ 90	60–90	< 60	
No. of patients	2087	618	1071	398	
Age [years]	65.0 ± 10.7	59.1 ± 11.4	66.4 ± 9.6	70.7 ± 7.9	< 0.01
Gender, female	454 (21.8%)	101 (16.3%)	218 (20.4%)	135 (33.9%)	< 0.01
Medical history					
Current smoking	676 (34.1%)	227 (38.1%)	351 (35.0%)	98 (25.7%)	< 0.01
Pre-hypertension	1136 (54.6%)	268 (43.4%)	595 (55.8%)	273 (68.9%)	< 0.01
Pre-diabetes mellitus	472 (22.7%)	112 (18.2%)	228 (21.4%)	132 (33.3%)	< 0.01
At admission					
Systolic blood pressure [mmHg]	130.8 ± 23.6	128.8 ± 24.7	131.4 ± 22.4	132.4 ± 25.1	0.03
Diastolic blood pressure [mmHg]	76.3 ± 13.0	76.7 ± 12.9	76.7 ± 12.6	74.5 ± 14.3	0.01
Heart rate [bpm]	74.8 ± 14.7	74.0 ± 14.0	74.5 ± 14.1	76.9 ± 16.8	0.01
Killip classification ≥ II	268 (12.8%)	69 (11.2%)	123 (11.5%)	76 (19.1%)	< 0.01
Left ventricular ejection fraction [%]	59.4	59.7	60.2	56.7	< 0.01
Laboratory values					
eGFR [mL/min/1.73 m ²]	79.0 ± 24.1	106.3 ± 15.9	75.8 ± 8.3	45.4 ± 12.3	< 0.01
Blood glucose [mmol/L]	7.3 ± 3.5	6.9 ± 2.9	7.1 ± 3.1	8.2 ± 5.0	< 0.01
Diagnosis					
ACS	1552 (74.4%)	446 (72.2%)	803 (75.0%)	303 (76.1%)	0.30
STEMI	308 (14.8%)	98 (15.9%)	143 (13.4%)	67 (16.8%)	0.16
Severity of CAD					
Left main artery	215 (10.3%)	56 (9.1%)	114 (10.6%)	45 (11.3%)	0.50
Three vessel diseases	569 (27.3%)	143 (23.1%)	285 (26.6%)	141 (35.4%)	< 0.01
Discharge medication					
Acetylsalicylic acid	1931 (93.5%)	581 (94.8%)	1008 (95.1%)	342 (87.0%)	< 0.01
Clopidogrel	1886 (91.3%)	574 (93.6%)	974 (91.9%)	338 (86.0%)	< 0.01
Statin	1886 (91.3%)	562 (91.8%)	987 (93.1%)	337 (85.8%)	< 0.01
Beta-receptor blockers	1361 (65.9%)	398 (64.9%)	729 (68.8%)	234 (59.5%)	< 0.01
ACEI or ARBs	1200 (58.1%)	330 (53.8%)	642 (60.7%)	228 (58.0%)	0.02

Data are expressed as means ± standard deviation or counts and percentages, as appropriate. ACEI — angiotensin converting enzyme inhibitors; ACS — acute coronary syndrome; ARB — angiotensin receptor blockers; eGFR — estimated glomerular filtration rate; CAD — coronary artery disease; STEMI — ST-segment elevation myocardial infarction

diseases (CVD) has been proven. The use of NT-proBNP level in diagnosis has been recommended by guidelines for managing HF and acute coronary syndrome (ACS) in clinical practice [16, 17]. However, several studies have found that blood NT-proBNP levels may be significantly affected by renal function [6]. This study found that NT-proBNP level is negatively correlated with eGFR in CAD patients, and the level is significantly elevated in patients with eGFRs of less than 60 mL/min/1.73 m² compared with patients with eGFRs of at least 90 mL/min/1.73 m². This result is consistent with the findings of previous studies. Potential mechanisms to explain the relationship may be complex.

NT-proBNP is mainly excreted by the kidneys, decreases in eGFR lower the body's ability to clear NT-proBNP, resulting in NT-proBNP accumulation [18]; moreover, sodium and water retention in patients with renal dysfunction can cause an increase in ventricular wall tension, leading to increased secretion of NT-proBNP [19], and the underlying pathophysiology of concomitant CVD also make contribution to the elevation of NT-proBNP [20]. Additional renal-cardiac interactions can further complicate the relationship between NT-proBNP level and eGFR. Therefore, NT-proBNP levels in patients with renal insufficiency may not accurately reflect actual cardiac function and prognostic risk;

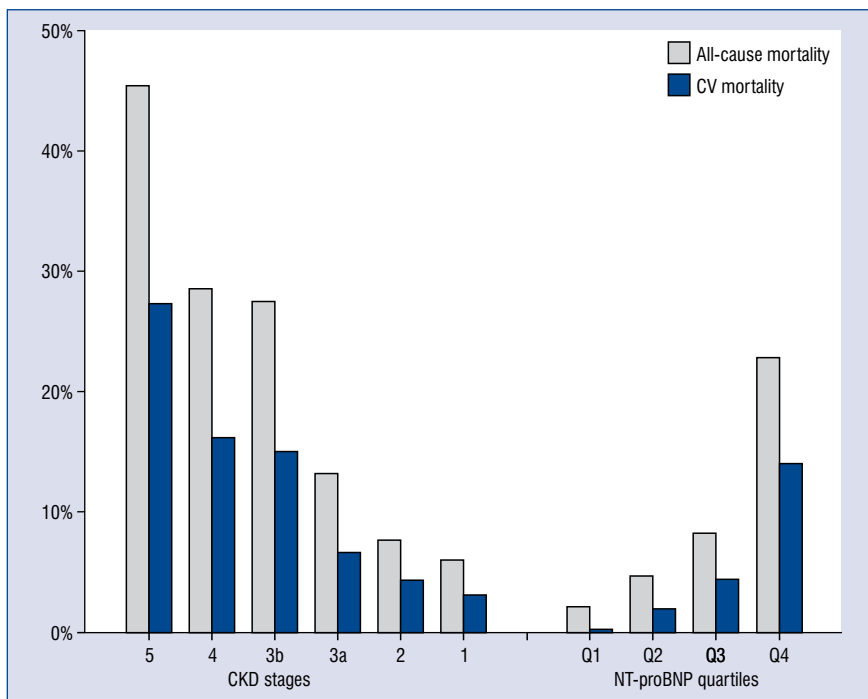


Figure 1. All-cause and cardiovascular (CV) mortality associated with renal function status and N-terminal pro-B-type natriuretic peptide (NT-proBNP) quartiles; eGFR — estimated glomerular filtration rate; CKD stages — chronic kidney disease stages: CKD 1 — eGFR ≥ 90 mL/min/1.73 m²; CKD 2 — $90 > \text{eGFR} \geq 60$ mL/min/1.73 m²; CKD 3a — $60 > \text{eGFR} \geq 45$ mL/min/1.73 m²; CKD 3b — $45 > \text{eGFR} \geq 30$ mL/min/1.73 m²; CKD 4 — $30 > \text{eGFR} \geq 15$ mL/min/1.73 m²; CKD 5 — $15 \text{ mL/min/1.73 m}^2 > \text{eGFR}$.

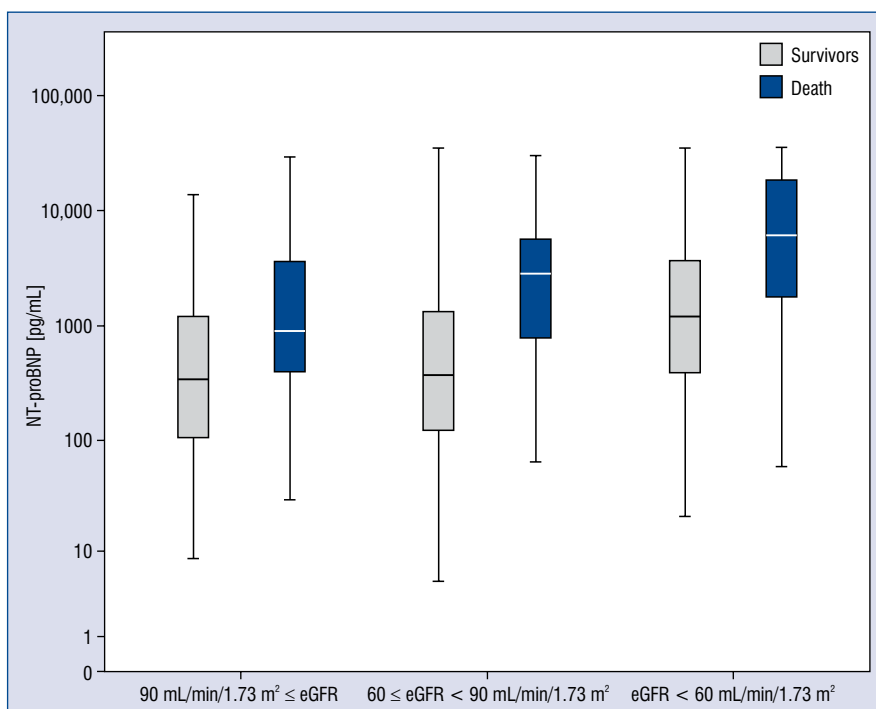


Figure 2. Distribution of N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels according to renal function in patients with or without all-cause death. The boxplots show the median, the lower and upper quartiles, and the range of data; eGFR — estimated glomerular filtration rate.

Table 2. N-terminal pro-B-type natriuretic peptide (NT-proBNP) concentrations in patients with or without all-cause death across estimated glomerular filtration rate (eGFR) groups.

NT-proBNP [pg/mL]	eGFR [mL/min/1.73 m ²]		
	90 ≤ eGFR	60 ≤ eGFR < 90	eGFR ≤ 60
Survivors	341.0 (106.0–1223.0)	371 (123–1330.0)	1205.0 (393.8–3720.0)
Deaths	900.0 (352.0–3753.5)	2875.0 (775.5–5735.8)	6086.5 (1752.5–18722.8)

Data are expressed as median (interquartile).

Table 3. The comparison among non-optimal, overall optimal and stratified optimal and predictive cut-off values of plasma N-terminal pro-B-type natriuretic peptide (NT-proBNP) to predict all-cause mortality.

eGFR [mL/min/1.73 m ²]	NT-proBNP [pg/mL]	Sensitivity	Specificity	Youden’s J statistic
Non-optimal predictive cut-off value of NT-proBNP [pg/mL]				
< 60	300.0	0.95	0.21	0.15
60–90	300.0	0.89	0.45	0.34
≥ 90	300.0	0.78	0.48	0.27
Overall optimal predictive cut-off value of NT-proBNP [pg/mL]				
< 60	1440.5	0.77	0.55	0.32
60–90	1440.5	0.67	0.76	0.43
≥ 90	1440.5	0.43	0.80	0.23
Stratified optimal predictive cut-off value of NT-proBNP [pg/mL]				
< 60	3478.0	0.65	0.75	0.40
60–90	1443.0	0.67	0.76	0.43
≥ 90	179.4	0.95	0.37	0.31

eGFR — estimated glomerular filtration rate

Table 4. Adjusted odds ratios for N-terminal pro-B-type natriuretic peptide (NT-proBNP) and the incidence of all-cause mortality.

eGFR [mL/min/1.73m ²]	Strata based on non-optimal cut-off value of NT-proBNP†			Strata based on overall optimal cut-off value of NT-proBNP			Strata based on stratified optimal cut-off value of NT-proBNP†		
	OR*	95% CI	P	OR*	95% CI	P	OR*	95% CI	P
< 60	1.9	0.6–5.8	0.28	2.4	1.1–4.9	0.02	3.0	1.5–6.2	< 0.01
60–90	4.0	1.8–8.8	< 0.01	4.8	2.7–8.5	< 0.01	4.8	2.7–8.5	< 0.01
≥ 90	2.5	1.1–6.0	0.04	1.8	0.8–4.1	0.19	7.7	1.7–33.9	< 0.01

†Non-optimal cut-off value of NT-proBNP = 300.0 pg/mL for all patients; overall optimal cut-off value of NT-proBNP = 1440.5 pg/mL for overall patients; stratified optimal cut-off value of NT-proBNP = 3478.0 pg/mL for patients with eGFR < 60 mL/min/1.73 m², 1443.0 pg/mL for patients with eGFR 60–90 mL/min/1.73 m², and 179.4 pg/mL for patients with eGFR ≥ 90 mL/min/1.73 m².

*Adjusted for age, sex, medical history (pre-hypertension and pre-diabetes mellitus), admission examination (systolic blood pressure, heart rate and Killip class), renal function (eGFR), diagnosis of acute coronary syndrome, and discharge medication (statin, angiotensin converting enzyme inhibitors or angiotensin receptor blockers and beta-receptor blockers)

CI — confidence interval; eGFR — estimated glomerular filtration rate; OR — odds ratio

in particular, “over elevation of NT-proBNP” may be observed.

Over elevated NT-proBNP levels in patients with renal dysfunction may affect the predictive

value of NT-proBNP for prognosis. This study showed that in patients with different renal function status, the optimal cut-off value of NT-proBNP determined via eGFR stratification had superior

predictive ability for clinical prognosis than the routine cut-off value (NT-proBNP = 300 pg/mL) or the overall optimal cut-off value for the entire population of CAD patients, simultaneously, a lower eGFR level is indicative of a larger optimal NT-proBNP cut-off value for predicting prognosis. Similarly, various NT-proBNP cut-off values determined for patients of different ages [7, 21, 22]. The underlying mechanism to explain this finding is that the increase of NT-proBNP level reflected not only impaired renal clearance but also the pathophysiological mechanisms of cardio-renal diseases [20], and this biomarker is still a useful indicator for clinical outcome even in patients with moderate or severe renal insufficiency although the prognostic value decreases as the deterioration of renal function. Accordingly, it is necessary to refer to appropriate NT-proBNP cut-off values to assess the prognoses of CAD patients with varying degrees of renal function. Unfortunately, there is a lack of sufficient evidence to determine which cut-off values are appropriate for CAD patients with renal insufficiency. Thus, NT-proBNP has limited utility for predicting prognosis in patients with renal insufficiency. Currently, the guidelines of management for ACS recommend using NT-proBNP level to stratify risk for patients with ACS. However, the Global Registry of Acute Coronary Events (GRACE) score and the Thrombolysis in Myocardial Infarction (TIMI) score, which are the stratification tools recommended by these guidelines, do not include NT-proBNP level as a parameter [16]. European Society of Cardiology (ESC) guidelines for managing HF issue a statement in 2016 that elevated NT-proBNP level is an important indicator of prognosis for patients with HF but does not recommend a definite NT-proBNP cut-off value for use as a reference. Moreover, these guidelines note that NT-proBNP level is affected by many factors, including age, renal function, atrial fibrillation and other complicating diseases. Therefore, patient clinical characteristics should be thoroughly considered when NT-proBNP levels are used to predict prognoses [17].

The strengths of this study: In clinical practice, NT-proBNP is an important indicator in the diagnosis, treatment and prognostic prediction of cardiac function for patients with CVD. The clinical significance of renal function and NT-proBNP measurement for prognosis for patients with CVD has been investigated by many prior studies; however, the findings of these studies only reflect the predictive value of NT-proBNP level and renal

function for clinical prognosis [4, 9, 23, 24]. In contrast, this study focused on evaluating different effects and optimal NT-proBNP cut-off values for prognostic prediction in CAD patients with various eGFRs. Thus, relative to prior findings, the results of this study are more practical with respect to clinical applicability. This study showed that the cut-off value of NT-proBNP significantly increases as eGFR decreases. The NT-proBNP cut-off value is nearly 20-fold higher in patients with moderate or severe renal failure than in patients with normal renal function. A similar result was obtained in a previous study of patients undergoing non-cardiac surgery [25].

Limitations of the study

This study was a single-centre observational study and had a few limitations. First, the registry made it difficult to completely avoid selection bias and confounding factors. Second, as the inherent limitation of the real-world study, the bias from the only one-time test of admission serum creatinine could not be ruled out completely. Third, objective echocardiography parameters for systolic and diastolic function were not completely collected in all participants, and the influence of cardiac function on NT-proBNP were not well adjusted, only when Killip was used as a functional classification in statistical analysis. Fourth, the samples in this single-center study were subject to geographical restrictions, which affected their representativeness and generalization. In summary, caution must be taken when analysing the results of this study. Moreover, NT-proBNP level is affected by many factors, including age, gender and other complicating diseases which make it hard to find out the optimal cut-off value for prognosis prediction. High-quality research reports are needed to provide more clinical evidence on this issue.

Conclusions

This study demonstrated that NT-proBNP exhibits different predictive values for prognosis for CAD patients with different levels of renal function. Among the assessed values, the NT-proBNP cut-off value determined using renal function improve the accuracy of the prognosis prediction of CAD. Moreover, lower eGFR is associated with a higher NT-proBNP cut-off value for prognostic prediction. These results indicate that in clinical practice, renal function must be adequately considered when using NT-proBNP level to assess clinical prognosis for patients with CAD.

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Conflict of interest: None declared

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