

Association between plasma NT-proBNP level and the risk of acute kidney injury: a retrospective cohort study

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Abstract

Background Acute kidney injury (AKI) is a serious complication in acute decompensated heart failure (ADHF). While N-terminal pro-brain natriuretic peptide (NT-proBNP) is a well-established biomarker for heart failure, its role in predicting AKI is less studied. This study investigated the association of plasma NT-proBNP levels and the risk of AKI and adverse renal outcomes in ADHF patients.

Methods This retrospective, single-centre, cohort study enrolled decompensated heart failure patients with measured plasma NT-proBNP levels from October, 2021 to September, 2022. The primary outcome was AKI during hospitalization per Kidney Disease Improving Global Outcomes (KDIGO) creatinine criteria. Secondary outcomes included AKI severity (defined by the maximal stage of AKI), renal recovery within 3 months, and hospitalization duration.

Results Of 669 patients studied, 289 (43%) developed AKI (stage 1: 53%, stage 2: 31%, stage 3: 16%). Multivariate analyses showed plasma NT-proBNP level was significantly associated with AKI risk (adjusted OR 1.470, [95% CI 1.347 to 1.604], $p < 0.001$), more severe AKI stages (adjusted OR of stage 1 AKI, 1.344; stage 2, 1.631; stage 3, 1.878; all $p < 0.001$) and prolonged hospitalization (adjusted IRR 1.087, $p < 0.001$). The association persisted in CKD stages 1 to 3 (adjusted OR among CKD stage 1 to 2, 1.488, $p < 0.001$; CKD stage 3, 1.376, $p = 0.001$). ROC analysis identified an NT-proBNP cut-off of 1450 pg/mL for AKI prediction (AUC 0.74, sensitivity 71.3%, specificity 65%).

Conclusion Elevated plasma NT-proBNP levels were independently associated with the risk of AKI and adverse renal outcomes in ADHF patients. These findings highlight the potential role of NT-proBNP in stratifying renal risk in heart failure patients.

Lay Summary

Acute kidney injury (AKI) is a serious problem that can happen in people whose heart failure suddenly worsens. NT-proBNP is a blood test used to assess heart failure severity, but whether it can predict kidney problems remains unclear. This study looked at whether NT-proBNP levels help predict the risk of AKI and other kidney issues in people with worsening heart failure. We recruited patients with worsening heart failure who had NT-proBNP levels checked between 2021 and 2022 at one hospital in Hong Kong and examined their kidney outcomes. Among 669 patients, we found that higher NT-proBNP levels were linked to increased AKI risk, more severe AKI and longer hospital stays. This held true even in those with pre-existing kidney problems. Our results suggested that NT-proBNP could help identify which heart failure patients are at higher risk for kidney complications, enabling more focused care to prevent kidney problems.

Introduction

Acute kidney injury (AKI) complicates 20 to 30% of hospitalizations for acute decompensated heart failure (ADHF) (1–3). An important cause of AKI in this setting is cardiorenal syndrome (CRS), where

dysfunction in either the heart or kidneys can trigger dysfunction in the other organ. The underlying pathophysiology of CRS is postulated to be related to hemodynamic changes, neurohormonal disturbances and inflammatory processes (3–6). Moreover, the presence of shared risk factors such as diabetes, hypertension and atherosclerosis in both cardiac and renal insufficiency may also explain the co-existing organ dysfunctions in CRS (3–8). Regardless of the underlying mechanism, the occurrence of AKI is independently associated with adverse clinical outcomes including increased mortality and prolonged hospitalization (1–3, 9). Those with AKI may also sustain permanent damage to the kidneys and potentially progressing to CKD or end-stage kidney disease (ESKD), which can further worsen clinical outcomes (10, 11). Therefore, it is important to identify patients at risk of developing AKI in ADHF with the aim to reduce morbidity and mortality.

Identification of a validated and reliable biomarker which predicts cardiac and/or kidney injury may be beneficial in the management of CRS because it allows timely implementation of renoprotective strategies and inform clinicians the risk of potential need for renal replacement therapy (RRT). Nevertheless, currently there is no established biomarker that can effectively predict both cardiac and kidney injury (3, 6–8, 12). NT-proBNP, a neurohormone secreted by cardiomyocytes during myocardial wall tension (12–14), may show promise as such a biomarker for the following key reasons. In CRS, ventricular dilatation in decompensated heart failure raises central venous pressure, leading to renal venous hypertension and impaired intrarenal blood flow. This ultimately results in renal dysfunction (3, 6–8, 15). By reflecting elevated ventricular wall tension, NT-proBNP may help identify individuals at risk of CRS and AKI. On the other hand, fluid resuscitation is a common practice in the initial management of AKI and studies have shown that volume overload in AKI is associated with adverse outcomes including increased mortality and decreased renal recovery (6, 16, 17). In this regard, NT-proBNP level may serve as a simple and minimally invasive surrogate marker of volume status, which may provide important prognostic information on renal recovery and survival. Moreover, as optimal volume status assessment and management has been the core target for treatment in CRS, NT-proBNP may also guide clinicians on appropriate fluid management and potentially improve clinical outcomes. Nevertheless, apart from myocardial stretch, plasma NT-proBNP level is also affected by renal function. As approximately 65 percent of natriuretic peptides are eliminated through renal clearance, NT-proBNP level has been found to be inversely correlated with renal function (7–9, 18). This may add uncertainty on the prognostic value of NT-proBNP in patients with background CKD.

Given these considerations, this study aimed to investigate the association between plasma NT-proBNP level and the development of AKI in a cohort of patients with acute decompensated heart failure. The cut-off threshold for NT-proBNP level in predicting AKI was determined. Furthermore, as pre-existing CKD may increase the risk of AKI in ADHF patients (9), we evaluated whether the predictive value of plasma NT-proBNP level was modified by baseline renal function. This study also explored the association between NT-proBNP levels with other adverse renal outcomes including severity of AKI, renal recovery and length of hospitalization. By establishing the role of NT-proBNP as a predictive biomarker for AKI and adverse renal outcomes in patients with acute decompensated heart failure, the findings can

potentially lead to improved risk stratification and targeted interventions that could mitigate adverse renal outcomes in these high risk patients.

Methods

This study was approved by the Joint Chinese University Hong Kong-New Territories East Cluster Clinical Research Ethics Committee (2024.716). All procedures in this study followed the guidelines outlined in the Declaration of Helsinki.

Setting and study population

This retrospective, single-centre, cohort study was conducted at Prince of Wales Hospital, a regional tertiary-care hospital with 1901 inpatient beds in Hong Kong (20). We enrolled consecutive adult patients aged 18 years old or older who presented between October, 2021 and September, 2022 with ADHF and measured plasma NT-proBNP levels. Diagnosis of ADHF was based on clinical evaluation by the attending medical team, supported by an admitting International Classification of Diseases, Tenth Revision (ICD-10) principal diagnosis code for heart failure. Each patient's plasma NT-proBNP level was determined by the first measurement obtained during hospitalization at our accredited laboratory. Baseline serum creatinine level was defined as the lowest measurement within 6 months pre-admission. It was then used to calculate the baseline estimated glomerular filtration rate (eGFR) using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) 2021 Eq. (19–21). Patients were excluded if they were younger than 18 years old, did not have NT-proBNP measurements available, or had no baseline serum creatinine level checked within 6 months before admission.

Data collection and availability

Clinical data were collected from the Clinical Data Analysis and Reporting System and the Electronic Patient Record system, which is a territory-wide computerized clinical data record system used across all hospitals under the Hospital Authority in Hong Kong. Information collected include patient demographics (age and gender), and baseline comorbidities that were derived using ICD-10 codes (diabetes, pre-existing cardiovascular disease, hypertension), as well as baseline serum creatinine level, eGFR, and CKD stage. Exposure to renin-angiotensin-aldosterone system (RAAS) inhibitors, sodium-glucose co-transporter 2 (SGLT-2) inhibitors, contrast agents, and the presence of sepsis during the hospitalization were also recorded. Research data was accessible only to the principal investigators and would be stored for 10 years after the study by Hospital Authority encrypted storage device and destroyed afterwards. Data otherwise kept by the Hospital Authority would be managed according to institutional standards. The study was approved for retrospective data collection by the Clinical Research Ethics Committee, which oversees all clinical studies conducted by Hospital Authority personnel to ensure the protection of rights and well-being of study subjects. Informed consent was

waived due to the retrospective nature of analysis and patient identities were masked using unique reference keys distinct from Hong Kong identity card number.

Study outcome

The primary outcome of the study was the development of AKI during hospitalization, defined by creatinine criteria of the Kidney Disease Improving Global Outcomes (KDIGO) classification (10). AKI staging was determined by comparing the highest inpatient creatinine level to baseline. Stage 1 AKI was defined as a serum creatinine increase of 1.5 to 1.9 times the baseline or ≥ 26.5 $\mu\text{mol/L}$, while stage 2 AKI was classified as an increase in serum creatinine by 2 to 2.9 times the baseline. Stage 3 AKI referred to those with either serum creatinine increase of 3 times the baseline, a serum creatinine > 353.6 $\mu\text{mol/L}$ (with a rise of ≥ 26.5 $\mu\text{mol/L}$ or 1.5 times the baseline) or start of RRT. Secondary outcomes included AKI severity, the degree of renal recovery, and hospitalization duration. AKI severity was defined as the maximal AKI stage attained during the admission. Renal recovery was defined as the return of renal function to within 50 percent of baseline eGFR within 3 months after discharge.

Statistical Analysis

Descriptive statistics of continuous variables were presented as the mean $\pm$ standard deviation (SD) or the median and interquartile range (IQR) if the data were not normally distributed. Categorical variables were summarized as frequency (percentage). Baseline demographics and clinical characteristics of individuals with AKI were compared to those without AKI using the independent t-test or Mann-Whitney U test depending on the normality of data. Chi-square test was used to compare categorical variables between patients with and without AKI.

To investigate the primary outcome of the study, multivariate logistic regression model was constructed to examine the association between plasma NT-proBNP levels and the development of AKI with adjustment for gender, age, baseline eGFR, use of RAAS inhibitors, use of SGLT-2 inhibitors, diabetic status, pre-existing cardiovascular disease, hypertension, sepsis, and contrast exposure. As plasma NT-proBNP level showed a highly skewed distribution, the data was first log-transformed (with a base of 2) before incorporation into the statistical models. The potential modification effect of baseline renal function on predictive value of plasma NT-proBNP level on AKI risk was also investigated by including an interaction term between plasma NT-proBNP and baseline CKD stages in the logistic regression. Further subgroup analyses according to the baseline CKD stage were performed if the interaction was significant. To identify the cut-off threshold of NT-proBNP levels for predicting AKI development, receiver operation characteristic (ROC) curves were constructed. Different diagnostic cut-off values with their corresponding sensitivities and specificities were evaluated for patients with different baseline CKD stages respectively.

For secondary outcomes analyses, the association between plasma NT-proBNP level and AKI severity was evaluated using multivariate multinomial regression. The degree of renal recovery was assessed by

multivariate logistic regression, and the duration of hospitalization was analysed by the negative binomial regression due to over-dispersion of data. All models adjusted for the same covariates as the primary analysis, with an additional adjustment for AKI stages in the model analysing hospitalization duration.

All statistical analyses were performed by SPSS version 28 (IBM corporation, Armonk, NY) with significance set at $p\text{-value} < 0.05$. All probabilities were two-tailed.

Results

During the study period, a total of 1533 patients were admitted for acute decompensated heart failure, of which 842 were excluded due to missing plasma NT-proBNP measurements, and 22 were excluded as they lacked baseline serum creatinine level within 6 months before admission. As a result, the final analysis included 669 patients. Table 1 summarized the baseline characteristics of the study cohort. Among these patients, 289 (43%) developed AKI. The severity of AKI was categorized as stage 1 in 154 patients (53%), stage 2 in 90 patients (31%), and stage 3 in 45 patients (16%), respectively. The median NT-proBNP level was significantly higher in patients with AKI than those without. AKI patients were older, more often to have diabetes, pre-existing cardiovascular disease, sepsis, and more frequently on RAAS inhibitors and SGLT-2 inhibitors, while their baseline eGFR were similar.

Table 1
Demographics and baseline characteristics of patients with or without AKI

No. of cases	All cases	AKI	No AKI	p-value
	669	289	380	
Age, years	72 (64 to 80)	74 (65 to 83)	71.5 (63 to 79)	0.003
Male gender, n (%)	374 (55.9)	154 (53.3)	220 (57.9)	0.234
Baseline serum creatinine, umol/L	79 (63 to 101)	76 (59.5 to 101.5)	81 (64 to 101)	0.084
Baseline eGFR, mL/min/1.73m ²	78.2 (57.5 to 104.3)	79.2 (54.8 to 112.6)	77.8 (59.6 to 99.0)	0.525
Plasma NT-proBNP, pg/mL	1522 (359.5 to 4613.5)	3245 (1299 to 8342.5)	761 (186 to 2322)	< .001
Baseline CKD stage, n (%)				0.015
Stage 1	249 (37.2)	119 (41.2)	130 (34.2)	
Stage 2	233 (34.8)	82 (28.4)	151 (39.7)	
Stage 3	141 (21.1)	61 (21.1)	80 (21.1)	
Stage 4	28 (4.2)	18 (6.2)	10 (2.6)	
Stage 5	18 (2.7)	9 (3.1)	9 (2.4)	
Concurrent medical problems, n (%)				
Diabetes	120 (17.9)	65 (22.5)	55 (14.5)	0.007
Hypertension	566 (84.6)	252 (87.2)	314 (82.6)	0.105
Cardiovascular disease	542 (81)	258 (89.3)	284 (74.7)	< .001
Active infection	217 (32.4)	137 (47.4)	80 (21.1)	< .001
RAAS blocker	529 (79.1)	252 (87.2)	277 (72.9)	< .001
SGLT-2 inhibitors	234 (35)	117 (40.5)	117 (30.8)	0.009
Contrast exposure	187 (28)	85 (29.4)	102 (26.8)	0.463
Values are median (interquartile range) unless otherwise specified.				
eGFR, estimated glomerular filtration rate; CKD, chronic kidney disease; AKI, acute kidney injury; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; RAAS, renin angiotensin aldosterone system; SGLT2 inhibitors, sodium-glucose co-transporter 2 inhibitors.				

Association between NT-proBNP and risk of AKI development

In univariate analysis, log-transformed plasma NT-proBNP level showed a significant association with the risk of AKI (odds ratio [OR] 1.437, [95% CI 1.334 to 1.547], $p < 0.001$), with every doubling in NT-proBNP level associated with 43.7% increased risk of AKI. After adjusting for gender, age, use of RAAS inhibitors, SGLT-2 inhibitors, diabetic status, hypertension, cardiovascular disease, sepsis, contrast exposure and baseline eGFR by multivariable logistic regression, NT-proBNP level remained significantly associated with AKI risk (adjusted OR 1.470, [95% CI 1.347 to 1.604], $p < 0.001$) (Table 2).

Table 2
Logistic regression model for the association between plasma NT-proBNP and risk of AKI

	no. of case	unadjusted	<i>p</i> value	adjusted	<i>p</i> value
		OR (95% CI) ^a		OR (95% CI) ^b	
Total	289	1.437 (1.334–1.547)	< 0.001	1.470 (1.347–1.604)	< 0.001
Stratify by baseline CKD stage					
CKD stage 1 and 2	201	1.564 (1.416–1.727)	< 0.001	1.488 (1.337–1.655)	< 0.001
CKD stage 3	61	1.363 (1.157–1.606)	< 0.001	1.376 (1.133–1.671)	0.001
CKD stage 4 and 5	27	1.157 (0.895–1.495)	0.266	1.344 (0.982–1.838)	0.064
NT-proBNP, N-terminal prohormone of brain natriuretic peptide; AKI, acute kidney injury; OR, odds ratio; CI, confidence interval; CKD, chronic kidney disease.					
^a Odds ratios (OR) are estimated using logistic regression or multinomial regression with NT-proBNP level log transformed. ORs represent the change in odds of outcome associated with every doubling in NT-proBNP level. ^b Adjusted for gender, age, use of renin-angiotensin-aldosterone system inhibitors, use of sodium-glucose co-transporter 2 inhibitors, diabetic status, hypertension, cardiovascular disease, sepsis, contrast exposure and baseline eGFR. NT-proBNP values were log-transformed for analysis.					

There was a significant interaction between plasma NT-proBNP level and baseline CKD stages in predicting AKI risk (p for interaction = 0.023). Further subgroup analysis was therefore performed according to the baseline CKD stage as pre-specified. Among CKD stage 1 and 2 patients, plasma NT-proBNP level was significantly associated with risk of AKI in univariate analysis (OR 1.564, [95% CI 1.416 to 1.727], $p < 0.001$). A similar association was found for those with CKD stage 3 (OR 1.363, [95% CI 1.157 to 1.606], $p < 0.001$). However, the association was not significant in CKD stage 4 and 5 (OR 1.157,

[95% CI 0.895 to 1.495], $p = 0.266$). After multivariate adjustment for confounders as shown in Table 2, plasma NT-proBNP level remained significantly associated with AKI risk in CKD stage 1 to 2 (adjusted OR 1.488, [95% CI 1.337 to 1.655], $p < 0.001$) and stage 3 (adjusted OR 1.376, [95% CI 1.133 to 1.671], $p = 0.001$) (Table 2).

ROC curves were further constructed to determine the cut-off NT-proBNP levels for predicting AKI development. For the entire cohort, the area-under-curve (AUC) of the ROC curve was 0.739 ($p < 0.001$), and a cut-off NT-proBNP level at 1450 pg/ml was found to have a sensitivity and specificity of 71.3% and 65%, respectively, in predicting AKI (Fig. 1). When stratified by baseline CKD stages, among CKD stage 1 to 2, a cut-off NT-proBNP level of 1000 pg/mL has the sensitivity and specificity of 75.1% and 63.7%, respectively (Fig. 2A). For CKD stage 3 patients, the optimal cut-off value of NT-proBNP was 2000 pg/ml, which yielded a sensitivity of 70.5% and specificity of 60% (Fig. 2B). No reliable cut-off value could be identified for CKD stage 4 to 5 due to insufficient patient numbers (Fig. 2C).

Association between NT-proBNP and AKI severity

For secondary outcomes, log-transformed plasma NT-proBNP level was associated with AKI severity (OR of stage 1 AKI 1.320, [95% CI 1.215 to 1.435], $p < 0.001$; OR of stage 2 AKI 1.540, [95% CI 1.378 to 1.722], $p < 0.001$; OR of stage 3 AKI 1.859, [95% CI 1.584 to 2.182], $p < 0.001$), with higher NT-proBNP level associated with more severe AKI stage. After adjusting for the confounders as shown in Table 3 by multivariable multinomial regression, the association remained significant (adjusted OR of stage 1 AKI 1.344, [95% CI 1.218 to 1.483], $p < 0.001$; adjusted OR of stage 2 AKI 1.631, [95% CI 1.424 to 1.867], $p < 0.001$; adjusted OR of stage 3 AKI 1.878, [95% CI 1.549 to 2.278], $p < 0.001$). In other words, each doubling of plasma NT-proBNP level was associated with a 34.4%, 63.1% and 87.8% increase in odds for developing stage 1, 2 and 3 AKI, respectively.

Table 3

Association between plasma NT-proBNP levels and the severity of AKI, renal recovery, and duration of hospitalization

	Unadjusted		Adjusted	
	OR or IRR ^a (95% CI)	<i>p</i> value	OR ^b or IRR ^c (95% CI)	<i>p</i> value
Stage of AKI ^d				
stage 1	1.320 (1.215–1.435)	< 0.001	1.344 (1.218–1.483)	< 0.001
stage 2	1.540 (1.378–1.722)	< 0.001	1.631 (1.424–1.867)	< 0.001
stage 3	1.859 (1.584–2.182)	< 0.001	1.878 (1.549–2.278)	< 0.001
Renal recovery	0.925 (0.744–1.151)	0.484		
Duration of hospitalization	1.157 (1.120–1.196]	< 0.001	1.087 (1.049 to 1.126)	< 0.001
^a Odds ratios (OR) were estimated using logistic regression or multinomial regression with NT-proBNP level log transformed. ORs represent the change in odds of outcome associated with every doubling in NT-proBNP level. Incidence rate ratio (IRR) was estimated using negative binomial regression with NT-proBNP level log transformed. IRR represents the change in incident rate ratio for every doubling in NT-proBNP level.				
^b Adjusted for gender, age, use of renin-angiotensin-aldosterone system (RAAS) inhibitors, use of sodium-glucose co-transporter 2 (SGLT-2) inhibitors, diabetic status, hypertension, cardiovascular disease, sepsis, contrast exposure and baseline eGFR.				
^c Adjusted for gender, age, use of RAAS inhibitors, use of SGLT-2 inhibitors, diabetic status, hypertension, cardiovascular disease, sepsis, contrast exposure, baseline eGFR and stage of AKI.				
^d As compared to no AKI.				

Association between NT-proBNP and duration of hospitalization

In our cohort, the median length of stay was 7 days (IQR 3 to 13). Among those with AKI, the median hospitalization stay was 11 days (IQR 6 to 21), while that of those without AKI was 4 days (IQR 1 to 8) ($p < 0.001$). Log-transformed plasma NT-proBNP level was significantly correlated with longer hospitalization (Incidence rate ratio [IRR] 1.157, [95% CI 1.120 to 1.196], $p < 0.001$), with higher NT-proBNP level corresponding to longer length of stay. The association persisted after adjusting for confounders as specified in Table 3 by multivariable negative binomial regression (adjusted IRR 1.087, [95% CI 1.049 to 1.126], $p < 0.001$).

Association between NT-proBNP and renal recovery

Of the 289 AKI patients, 271 (93.8%) had recovery of kidney function. There was no significant association between NT-proBNP level and renal recovery (OR 0.925, [95% CI 0.744 to 1.151], $p = 0.484$), even after adjusting for confounding variables (adjusted OR 0.935, [95% CI 0.743 to 1.177], $p = 0.570$) (Table 3).

Discussion

Our study demonstrated that in patients with acute decompensated heart failure, higher plasma NT-proBNP level was independently associated with increased risk of AKI development. This association remained significant for those with pre-existing CKD (stages 1 to 3). Overall, the NT-proBNP threshold for AKI prediction was 1450 pg/mL, with moderate sensitivity and specificity. The threshold for baseline CKD stage 1 or 2 was 1000 pg/mL, and for stage 3 patients was 2000 pg/mL. Additionally, higher plasma NT-proBNP level correlated with increased AKI severity and longer hospitalization, but showed no significant association with renal recovery.

NT-proBNP is an established biomarker for heart failure diagnosis, prognostication and volume status (22–25). Our study adds to evidence supporting its role in predicting adverse renal outcomes. In a retrospective cohort study of 3811 patients with stage 2 and 3 AKI, higher NT-proBNP level was independently associated with increased risk of dialysis requirement, dialysis dependence and in-hospital mortality (26). Notably, this study included particularly ill AKI subjects comparing to other studies (27–29), with 66% required urgent RRT, 42% were dialysis dependent and 35% died during hospitalization. Patients in the highest NT-proBNP quartile had worse outcomes, with dialysis rate up to 78% and mortality rate reaching 39%. These findings may be explained by the study design, as it only included patients who required renal consultation during hospitalization, potentially introducing selection bias toward sicker patients. Moreover, the exclusion of pre-existing ESRD or CKD stage 5 patients may limit result generalizability. Nevertheless, this large cohort suggests NT-proBNP's potential in predicting severe renal outcomes.

Another prospective study of 138 intensive care unit patients admitted for non-cardiac reasons showed that higher admission NT-proBNP level was independently associated with increased AKI risk, severity and need for acute RRT (15). This association persisted after excluding patients who developed acute myocardial infarction in a sensitivity analysis. However, the study did not adjust for baseline CKD stage, a potential confounder that could create a spurious association.

Consistent with these studies, we observed that elevated NT-proBNP level was associated with adverse renal outcomes and longer stay in ADHF patients, suggesting its potential in renal risk stratification. Furthermore, we observed a significant interaction between plasma NT-proBNP level and baseline CKD stages in predicting AKI risk (p for interaction = 0.023), indicating baseline kidney function modifies this relationship. This aligns with previous research, which showed that baseline CKD is a risk factor for AKI

in heart failure patients (9, 12, 30), and that NT-proBNP, being primarily cleared by the kidneys, has an inverse relationship with kidney function (7–9, 12, 18). Specifically, when stratified by CKD stages, NT-proBNP maintained significant prognostic value for AKI risk in CKD stage 1 through 3 even after adjusting for confounders (CKD stage 1 or 2: adjusted OR 1.488, $p < 0.001$; CKD stage 3: adjusted OR 1.376, $p = 0.001$). This enables important risk stratification in these at-risk patients. Meanwhile, the insignificant association in CKD stage 4 and 5 may be attributed to the small number of patients in these subgroups. Additionally, in severe renal insufficiency, reduced renal clearance may play a more dominant role in elevating NT-proBNP levels than cardiac function does. Consequently, NT-proBNP becomes less reflective of cardiac stress and volume status, potentially limiting its value as a cardiac biomarker and CRS risk predictor in advanced CKD. Larger studies in this subgroup are needed for clarification.

Our study identified the NT-proBNP threshold for predicting AKI as 1450 pg/mL, with lower cut-offs of 1000 pg/mL in CKD stage 1 or 2 and a higher cut-off of 2000 pg/mL in CKD stage 3. To the best of our knowledge, evidence on NT-proBNP threshold for predicting AKI in ADHF is limited, and this study is the first to establish these thresholds. Our findings of different cut-off levels across CKD stages align with previous research, which showed that natriuretic peptides thresholds for heart failure diagnosis were 2–3 times higher in patients with $eGFR < 60$ mL/min/m² (31, 32). This is likely explained by the reduced renal clearance of NT-proBNP as kidney function declines, creating an inverse correlation between NT-proBNP levels and baseline renal function.

On the other hand, our study did not find a significant association between NT-proBNP level and renal recovery. By contrast, Chou et al's study of 163 critically ill patients showed renal recovery from AKI was associated with changes in natriuretic peptides level between day of admission and 24 hours later (33). They also demonstrated that changes in natriuretic peptides level were significantly correlated with changes in central venous pressure (33). Unlike their approach, we examined NT-proBNP level at a single time point. As changes in natriuretic peptides level has been demonstrated as a marker of decongestion, they better reflect volume status and thus may correlate more closely with renal recovery (33, 34). This methodological difference might explain our contrasting results. Further research will help verify these observations.

Our study has several limitations. Firstly, due to the retrospective study design, routine echocardiogram, left ventricular systolic function assessment and anthropometric parameters such as body mass index were not available for every patient. Thus, their potential interactions with NT-proBNP level and renal outcomes could not be assessed. Nevertheless, we have made efforts to adjust for key confounders as specified. Secondly, as with any retrospective study, unmeasured confounders could not be entirely excluded and thus may have influenced findings. We acknowledge that the retrospective study design may only suggest associations rather than causation. Thirdly, our outcome definition of AKI relied solely on KDIGO creatinine criteria, as urine output data was unavailable. Consequently, AKI cases identified by urine output criteria were not captured, potentially underestimating AKI rates. Moreover, the exact aetiology of AKI was not always documented, which may have confounded our findings. Finally, since this retrospective study only captured plasma NT-proBNP level at one time-point, and changes in NT-

proBNP levels have been proposed to correlate with volume status and renal outcomes (33), longitudinal measurements represent an area for future research that may enhance NT-proBNP's value in renal risk stratification.

Conclusion

In ADHF patients, higher plasma NT-proBNP levels were independently associated with increased risk of AKI development. NT-proBNP was also a significant predictor for more severe AKI stages and longer hospitalizations. When patients were stratified by baseline CKD stages, plasma NT-proBNP remained a significant predictor of AKI risk in those with CKD stages 1 to 3. These findings highlight NT-proBNP's potential for renal risk assessment in heart failure patients, extending beyond its use as a heart failure biomarker. Larger prospective studies would be valuable to confirm NT-proBNP's role as a predictive biomarker in CRS.

Declarations

Author contribution

Research idea and study design: PWLH, CCS; data acquisition: PWLH, JKCN, WWSF, GCSC; data analysis/interpretation: PWLH, JKCN, CCS; statistical analysis: JKCN, CCS; supervision or mentorship: KMC, WFP; manuscript preparation: PWLH, JKCN, CCS. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved.

Ethics Statement

This study was approved by the Joint Chinese University Hong Kong-New Territories East Cluster Clinical Research Ethics Committee (2024.716). All procedures in this study followed the guidelines outlined in the Declaration of Helsinki.

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Competing Interests

The authors declare no conflict of interest.

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Data availability

The original data supporting the findings of this study are openly available in Github repository at: https://github.com/szetocc/BNP_AKI

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Figures

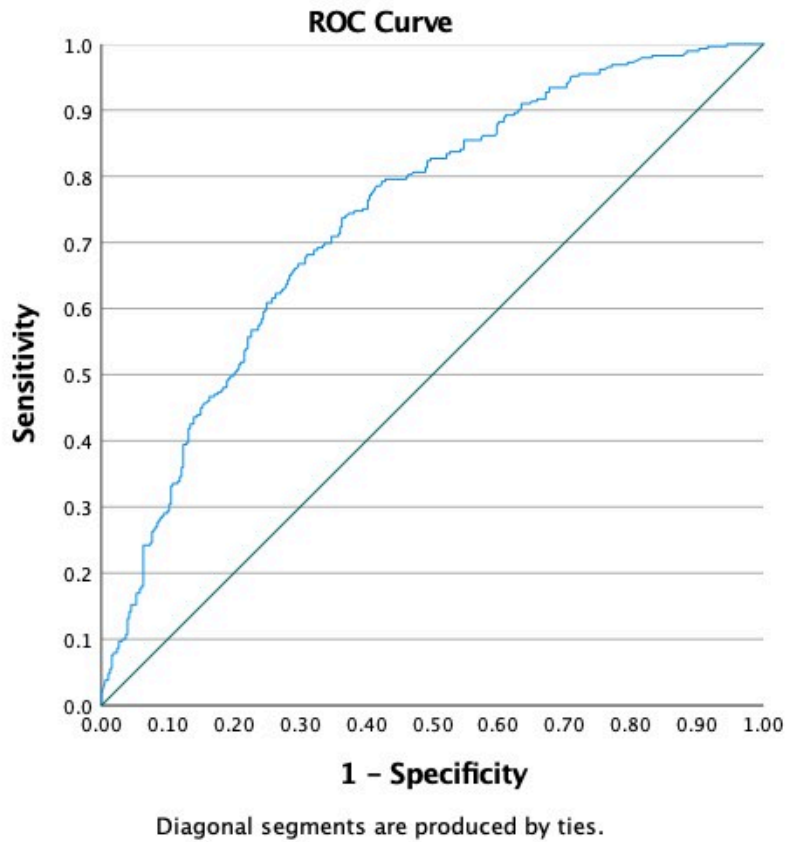


Figure 1

Receiver operating characteristics (ROC) curve of plasma NT-proBNP level as a predictor of acute kidney injury (AKI) development. For the entire cohort, the area-under-curve (AUC) of the ROC curve was 0.739 ($p < 0.001$). A cut-off NT-proBNP level at 1450 pg/ml has a sensitivity of 71.3% and specificity of 65% in predicting AKI.

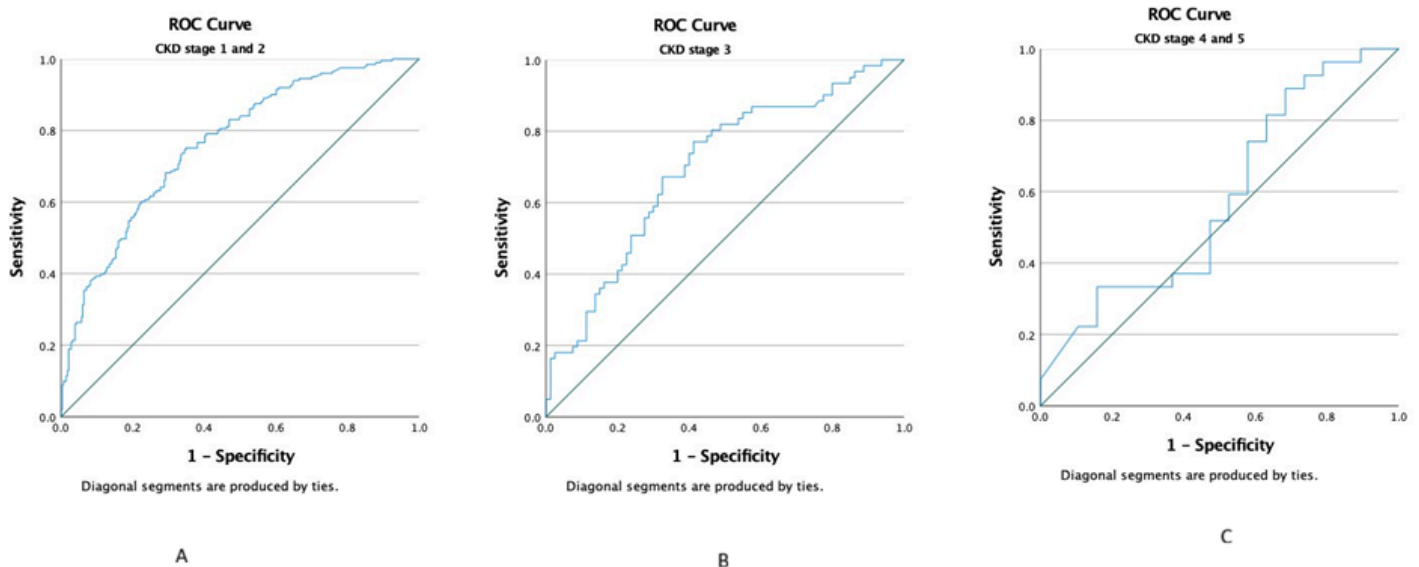


Figure 2

Receiver operating characteristics (ROC) curve of plasma NT-proBNP level as a predictor of AKI development in patients stratified by baseline chronic kidney disease (CKD) stages: (A) stage 1 and 2; (B) stage 3; and (C) stage 4 and 5. For CKD stage 1 to 2, a cut-off NT-proBNP level of 1000 pg/mL has the sensitivity and specificity of 75.1% and 63.7%, respectively. For CKD stage 3 patients, the optimal cut-off value was 2000 pg/ml, with a sensitivity of 70.5% and specificity of 60%. For CKD stage 4 to 5, no reliable cut-off value could be established.