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Original Article

Optimizing NT-proBNP and Left Ventricular Filling Pressure for Accurate Diagnosis of Acute Decompensated Heart Failure in Chronic Kidney Disease Patients

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Abstract

Objectives: Diagnosing Acute Decompensated Heart Failure (ADHF) in patients with Chronic Kidney Disease (CKD) is challenging due to the complexities in interpreting N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels. This study aimed to determine an optimal NT-proBNP cutoff value in CKD patients with ADHF confirmed by elevated left ventricular filling pressure (LVFP).

Methodology: In this retrospective, cross-sectional study conducted at Doctors Hospital, Lahore, between May 1, 2018, and April 30, 2019, 85 hospitalized patients were evaluated, of which 66 had CKD. All participants presented with clinical evidence of volume overload. NT-proBNP levels and estimated glomerular filtration rate (eGFR) were assessed, while LVFP was measured to confirm the diagnosis of ADHF.

Results: Median NT-proBNP levels were significantly higher in the CKD patients with elevated LVFP compared to those with normal LVFP (12,186 pg/mL vs. 2,528 pg/mL, $p < 0.003$). The NT-proBNP cutoff for CKD patients with clinical volume overload was determined to be 1,750 pg/mL. For all patients with high LVFP (including both CKD and non-CKD), the cutoff was 2,760 pg/mL. However, in CKD patients with clinical volume overload confirmed by high LVFP, the optimal NT-proBNP cutoff value was 3,737 pg/mL.

Conclusion: Elevated NT-proBNP levels correlate with CKD and high LVFP. Utilizing a higher NT-proBNP cutoff value improves diagnostic accuracy for ADHF in CKD patients, aiding in more reliable clinical decision-making.

Keywords: NT-proBNP, Left Ventricular Filling Pressure, Acute Decompensate Heart Failure, Chronic Kidney Disease

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INTRODUCTION

Chronic Kidney Disease (CKD) and Heart Failure (HF) are common and interrelated conditions. CKD affects approximately 15% of the U.S [1]. population, with global estimates reaching 850 million individuals. Similarly, HF affects around 64.3 million people worldwide. Both conditions share common risk factors, including diabetes mellitus, advanced age, hypertension, and coronary artery disease [2]. The prevalence of HF in CKD is notably high, at 27.7%, and increases with advancing CKD stages. Additionally, 30–60% of HF patients exhibit moderate to severe kidney impairment, which further complicates management and prognosis [3].

CKD exacerbates mortality risk in HF patients. According to the United States Renal Data System (USRDS), the probability of 24-month survival for patients over 66 years with both HF and CKD stage 4–5 is 0.512, compared to 0.669 in patients without CKD [4]. Worsening HF is often associated with acute kidney injury (AKI), leading to higher risks of hospitalization and mortality [5].

Diagnosing acute decompensated heart failure (ADHF) in CKD patients poses unique challenges. While history and physical examination are cornerstones of HF diagnosis, they are often insufficient in CKD patients. Objective measures, particularly to assess volume status, are essential for accurate diagnosis and optimal management [6].

Natriuretic peptides, including B-type natriuretic peptide (BNP) and N-terminal pro-B-type natriuretic peptide (NT-proBNP), are valuable biomarkers for diagnosing ADHF. Cardiac ventricular distension triggers the release of prohormone pro-BNP, which is cleaved into the active BNP and the inactive NT-proBNP. Guidelines from the American College of Cardiology (2013), the Heart Failure Society of America (2010), and the European Society of Cardiology recommend measuring NT-proBNP in evaluating ADHF [7].

The Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference in 2019 highlighted the utility of BNP and NT-proBNP in diagnosing ADHF in CKD patients. However, this application is challenging because normal cutoff levels for NT-proBNP were established in non-CKD populations, and impaired renal clearance elevates NT-proBNP levels in CKD patients. Additionally, the NT-proBNP to BNP ratio rises with worsening renal function, making interpretation more complex [8].

The International Collaborative of NT-proBNP (ICON) study established that an NT-proBNP cutoff of 900 pg/mL provides diagnostic accuracy comparable to a BNP level of 100 pg/mL. Meanwhile, the PARADIGM-HF trial found a higher NT-proBNP to BNP ratio of 6.25:1 in patients with reduced ejection fraction (EF), which deviates from earlier guidelines. Cutoff values for natriuretic peptides also vary based on ejection fraction, CKD stage, age, gender, obesity, sepsis, pulmonary hypertension, and hepatic dysfunction.

Echocardiography provides critical insights into ventricular systolic function, wall thickness, valve function, chamber volumes, and left ventricular filling pressure (LVFP). Elevated LVFP is a key indicator of ADHF, particularly in CKD patients, and echocardiography has been recommended by the KDIGO Controversies Conference as an adjunct to diagnose ADHF. Despite its importance, the relationship between NT-proBNP and LVFP in CKD patients with ADHF remains inadequately documented.

This study aims to establish a reliable NT-proBNP cutoff value in acutely dyspneic CKD patients when ADHF is confirmed by elevated LVFP. By addressing this knowledge gap, we hope to improve diagnostic accuracy and guide tailored management for this high-risk population.

METHODOLOGY

Study Design: This was a retrospective, cross-sectional study aimed at investigating the association between chronic kidney disease (CKD) and heart failure with preserved ejection fraction (HFpEF), midrange ejection fraction (HFmrEF), and reduced ejection fraction (HFrEF) in patients presenting with acute dyspnea and potential acute decompensated heart failure (ADHF). The study analyzed patient records from the Emergency Department of Doctors Hospital Lahore, covering the period from May 1, 2018, to April 30, 2019.

Ethics: The study was approved by the Institutional Review Board (IRB) of Doctors Hospital Lahore. All methods were performed in accordance with

relevant ethical guidelines and regulations. Since this was a retrospective study utilizing existing medical records, informed consent was not required. The study adhered to privacy and confidentiality protocols during data collection and analysis.

Setting: The study was conducted at Doctors Hospital Lahore, a tertiary care hospital with a comprehensive Emergency Department. The hospital provides care for patients with a wide range of medical conditions, including acute heart failure.

Participants: The study included a total of 85 patients who met the following criteria:

- **Inclusion Criteria**: Patients aged 18 years and older, who presented to the Emergency Department with acute dyspnea and potential ADHF between May 1, 2018, and April 30, 2019. All participants had simultaneous echocardiography, NT-proBNP measurement, and clinical evidence of volume overload, which included pulmonary edema, pleural effusion, peripheral edema, raised jugular venous pressure (JVP), and a positive response to diuretics.
- **Exclusion Criteria**: Patients who were undergoing dialysis were excluded from the study to avoid confounding due to renal replacement therapy.

Patients were categorized into two groups based on the presence or absence of CKD:

- **CKD Group**: 66 patients with chronic kidney disease (classified using the eGFR criteria).
- **Non-CKD Group**: 19 patients without chronic kidney disease.

Further stratification was made based on left ventricular ejection fraction (LVEF) [9]:

- **HFrEF**: Patients with LVEF <40%
- **HFmrEF**: Patients with LVEF 40-50%
- **HFpEF**: Patients with LVEF >50%

Variables: The main variables examined in the study included both dependent and independent factors, as well as clinical outcomes. Dependent variables focused on the type of heart failure, categorized as heart failure with reduced ejection fraction (HFrEF), heart failure with mid-range ejection fraction (HFmrEF), or heart failure with preserved ejection fraction (HFpEF). Additionally, left ventricular ejection fraction (LVEF) and NT-proBNP levels were measured as key indicators of heart failure severity. Independent variables included the presence of chronic kidney disease (CKD), as well as demographic and clinical factors such as age, gender, hypertension, diabetes mellitus, and left ventricular filling pressure (LVFP). Clinical outcomes assessed in the study included fluid overload, as evidenced by signs of volume overload like pulmonary edema or pleural effusion, and the patient's response to diuretic treatment.

Data Sources/Measurement: Data were collected from the medical records of patients admitted to the Emergency Department during the study period. Various data sources were reviewed to ensure comprehensive patient information. Physician notes were examined, providing detailed documentation of symptoms, signs, and diagnoses. Laboratory results were also reviewed, including serum NT-proBNP levels, measured using the Elecsys ProBNP II assay, and estimated glomerular filtration rate (eGFR), which was calculated using the Chronic Kidney Disease Epidemiology (CKD-Epi) equation. Additionally, diagnostic imaging reports, particularly echocardiography, were analyzed to assess left ventricular function, including diastolic function, left ventricular filling pressure (LVFP), and left ventricular ejection fraction (LVEF). The algorithm used to assess LVFP included Doppler measurements such as the E/A ratio, E/e' ratio, tricuspid regurgitation velocity, and the left atrial maximal volume index [10].

Bias: To minimize bias, data were collected from a standardized review of medical records. The analysis was limited to patients with available complete data, including echocardiography, NT-proBNP levels, and clinical signs of fluid overload. Since the study was retrospective, there was no direct control over the clinical management, and thus, potential treatment variations may introduce confounding.

Study Size: The study included 85 patients meeting the inclusion criteria, with a total of 66 patients in the CKD group and 19 patients in the non-CKD group. The sample size was determined based on available records from the study period, and the analysis was powered to detect significant associations between heart failure type and CKD status.

Quantitative Variables: The quantitative variables in the study included several key measures related to

kidney function, biomarkers, and echocardiographic findings. Estimated glomerular filtration rate (eGFR) was calculated using the CKD-Epi equation to assess renal function. NT-proBNP levels, a crucial biomarker for heart failure, were measured using the Elecsys ProBNP II immunoassay. Additionally, echocardiographic measurements were obtained to assess cardiac function, including left ventricular ejection fraction (LVEF), left ventricular filling pressure (LVFP), and other Doppler parameters that provide insights into diastolic function and overall heart performance.

Statistical Methods: Data were entered and analyzed using IBM-SPSS version 23.0. Descriptive statistics, including frequencies and percentages, were used to summarize categorical variables such as age group, gender, and clinical conditions (e.g., hypertension, diabetes mellitus, LVFP, fluid overload). For continuous variables such as eGFR and NT-proBNP levels, medians and interquartile ranges were reported.

Associations between categorical variables (CKD status, heart failure type, and clinical parameters) were tested using Pearson's Chi-Square test. For variables with low counts, Fisher's exact test was used. Group comparisons based on CKD status and LVFP were performed using the Kruskal-Wallis test, and pairwise comparisons were made using the Mann-Whitney U test. A p-value of less than 0.05 was considered statistically significant.

RESULTS

Participants: A total of 85 patients were included in this study, consisting of 66 Chronic Kidney Disease (CKD) patients and 19 non-CKD patients. The participants were selected based on the inclusion criteria of presenting with acute dyspnea and potential acute decompensated heart failure (ADHF) between May 1, 2018, and April 30, 2019. All included patients had undergone simultaneous echocardiography, NT-pro BNP measurement, and exhibited clinical evidence of volume overload (such as pulmonary edema, pleural effusion, peripheral edema, raised jugular venous pressure, and a positive response to diuretics). The exclusion criteria ruled out patients on dialysis.

The baseline characteristics of these patients are shown in Table 1. The median age for the CKD group was higher than that of the non-CKD group, though there was no significant difference in age distribution between the groups (p=0.10). The gender distribution was comparable between CKD and non-CKD patients (50% male, 50% female in both groups), with no significant association between gender and CKD status (p=0.84). Hypertension was present in 57.8% of CKD patients and 36.8% of non-CKD patients, though this difference was not statistically significant (p=0.10). A notable finding was the higher prevalence of diabetes mellitus in CKD patients (60.9%) compared to non-CKD patients (31.6%), which was statistically significant (p=0.024).

Table 1: Baseline Characteristics of Studied Samples (N=85)

	CKD	Non-CKD	p-value
Age Group¥			
≤75 years	51(77.3)	18(94.7)	0.1
>75 Years	15(22.7)	1(5.3)	
Gender			
Female	33(50)	9(47.4)	0.84
Male	33(50)	10(52.6)	
Hypertension			
None	27(42.2)	12(63.2)	0.1
Present	37(57.8)	7(36.8)	
Diabetes Mellitus			
None	25(39.1)	13(68.4)	0.024*
Present	39(60.9)	6(31.6)	
LV Filling Pressure			
Normal <14	30(45.5)	8(42.1)	0.79
Increased >14	36(54.5)	11(57.9)	
Fluid Overload			
None	0(0)	0(0)	N.A
Present	66(100)	19(100)	
EF¥			
<40%	24(36.4)	7(36.8)	
40 -50%	9(13.6)	1(5.3)	0.78
>50%	33(50)	11(57.9)	
GFR£			
Median (Q3-Q1)	34.05 (44.42-20)	83 (91-71)	<0.01*

**p<0.05 was considered statistically significant using Pearson Chi Square test*
¥: P-value based on Fisher's Exact test
£: p-value based on Mann Whitney U test

Descriptive Data: The study included patients with a range of left ventricular (LV) ejection fraction (EF) categories: 36.4% of CKD patients and 36.8% of non-CKD patients had an EF <40% (HFrEF), while 13.6% of CKD patients and 5.3% of non-CKD patients had a mid-range EF (40-50%, HFmrEF), and 50% of CKD patients and 57.9% of non-CKD patients had an EF >50% (HFpEF). There was no significant difference between the two groups in terms of LV ejection fraction (EF) distribution (p=0.78).

All patients in both the CKD and non-CKD groups presented with clinical signs of fluid overload. There

was no difference in the prevalence of fluid overload between the groups (p=N.A). The distribution of LV filling pressure (LVFP) was also similar between the two groups, with 54.5% of CKD patients and 57.9% of non-CKD patients showing elevated LVFP (p=0.79).

The median eGFR for CKD patients was significantly lower than for non-CKD patients (34.05 vs. 83, p<0.01), consistent with the presence of chronic kidney disease in the former group.

Table 2: Comparison of NT Pro BNP with CKD and High LVFP

Groups	NT-proBNP Median (IQR)	p-values for Comparisons of ¥		Multiple
		Non CKD + high LVFP	CKD + high LVFP	Non CKD + normal LVFP
Non CKD + high LVFP (n=11)	829 (10588-258)			
CKD + high LVFP (n=36)	12186 (31037-2164)	0.001*		
Non CKD + normal LVFP (n=8)	865 (984.5-215.25)	0.49	<0.01*	
CKD +normal LVFP (n=30)	2528 (7687-955)	0.20	0.003*	0.006*

**NT-ProBNP considered statistically significant using Kruskal Wallis Test*

¥:Multiple Comparison between groups was made using Mann Whitney U test

Outcome Data: The primary outcome of interest was the NT-pro BNP levels, which were measured to assess the severity of heart failure. Table 2 presents the comparison of NT-pro BNP levels across different combinations of CKD status and LVFP. The NT-pro BNP levels were significantly higher in CKD patients compared to non-CKD patients. Among those with high LVFP, the median NT-pro BNP was markedly elevated in CKD patients (12,186 pg/mL) compared to non-CKD patients (829 pg/mL), with a p-value of 0.001, indicating a statistically significant difference. Similarly, when comparing NT-pro BNP levels in patients with normal LVFP, CKD patients had a significantly higher NT-pro BNP level (2528 pg/mL) compared to non-CKD patients (865 pg/mL), with a p-value of 0.006.

The NT-pro BNP levels also differed when categorized by LVFP status. Among patients with high LVFP, the median NT-pro BNP levels were significantly different between CKD and non-CKD groups (p<0.01), with the CKD group exhibiting notably higher levels.

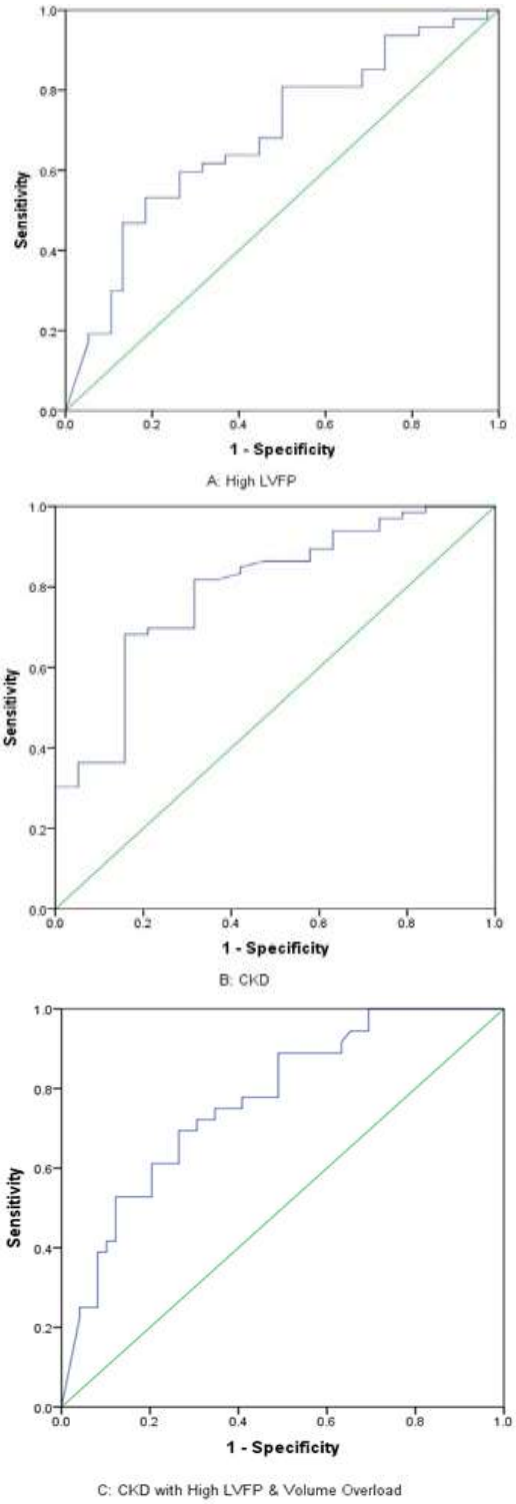

Figure 1: Receiver Operating Curve Analysis and Recommended Cut offs

Main Results: The Kruskal-Wallis test revealed a significant difference in NT-pro BNP levels across the four subgroups defined by CKD status and LVFP ($p<0.01$). Multiple comparisons using the Mann-Whitney U test confirmed that the difference between CKD + high LVFP and non-CKD + high LVFP was highly significant ($p=0.001$). Other significant comparisons included CKD + high LVFP vs. non-CKD + normal LVFP ($p<0.01$), CKD + high LVFP vs. CKD + normal LVFP ($p<0.003$), and non-CKD + normal LVFP vs. CKD + normal LVFP ($p=0.006$).

Furthermore, Figure 1 presents the Receiver Operating Characteristic (ROC) curve analysis to determine the optimal NT-pro BNP cutoff values for predicting high LVFP in both CKD and non-CKD patients.

- Graph A shows the ROC analysis for high LVFP across both CKD and non-CKD patients, with an area under the curve (AUC) of 67.7% (CI 0.56-0.79). The optimal NT-pro BNP cutoff for predicting high LVFP in these patients was 2760 pg/mL, with sensitivity and specificity values of 63.8% and 64%, respectively ($p<0.005$).
- Graph B demonstrates the ROC analysis for NT-pro BNP in CKD patients, with an AUC of 79% (CI 0.68-0.9), sensitivity of 69.7%, and specificity of 69%. The optimal NT-pro BNP cutoff for CKD patients was 1750 pg/mL ($p<0.01$).
- Graph C presents the ROC analysis for NT-pro BNP in CKD patients with high LVFP and clinical volume overload, showing an AUC of 77% (CI 0.67-0.86), sensitivity of 69%, and specificity of 70%. The optimal NT-pro BNP cutoff for these patients was 3737 pg/mL.

DISCUSSION

Brain natriuretic peptide (BNP) and N-terminal pro-brain natriuretic peptide (NT-proBNP) are invaluable biomarkers, particularly for ruling out heart failure (HF), even in patients with chronic kidney disease (CKD). Research indicates that normal NT-proBNP and BNP levels are more effective in excluding HF than confirming it. For instance, in a study of 142 euvolemic CKD patients with a mean GFR of 38 ± 14 mL/min/1.73 m² [11], the median NT-proBNP and BNP levels were 311 pg/mL and 59 pg/mL, respectivelyy, NT-proBNP levels below 1,000 pg/mL were used to confirm the resolution of volume overload in another study of 151 patients [12].

Severa influence NT-proBNP and BNP levels, including renal function, age, and left ventricular ejection fraction (EF). Elevated NT-proBNP levels are commonly observed in CKD patients, even in the absence of HF. In the Breathing Not Properly study, a BNP cutoff of <200 pg/mL was suggested to rule out HF in patients with an eGFR <60 mL/min/1.73 m² [13]. Another study of s identified a NT-proBNP cutoff of 1,200 pg/mL for individuals with GFR <60 mL/min/1.73 m², demonstrating a sensitivity of 89% and specificity of 72% [14]. A meta-analysis involving 4ts also reported higher NT-proBNP levels in CKD patients with acute decompensated heart failure (ADHF), with a median cutoff of 1,980 pg/mL [15]. Similarly, in patients with severe retion (mean GFR 27.7 ± 14 mL/min/1.73 m²), an NT-proBNP cutoff of 4,502 pg/mL was associated with an EF of 42.9 ± 6.8% [16].

In our study, the NT-proBNP cutoff for CKD pat, 750 pg/mL, lower than other reports. This discrepancy may reflect our cohort's lower mean GFR (32.06 mL/min/1.73 m²) and the presence of reduced EF (<50%) in half of the patients. Moreover, we observed that the NT-proBNP cutoff increased to 3,737 pg/mL in patients with clinical volume overload and elevated left ventricular filling pressure (LVFP). The combination of clinical volume overload and high LVFP in our study yielded a sensitivity of 69%, specificity of 70%, and an AUC of 0.77. These findings underscore the importance of integrating clinical, biochemical, and echocardiographic parameters for diagnosing ADHF [17].

The relationship between NT-proBNP levels and declining renal function has been well established. A study of 213 CKD patients demonstrated a 37.7% increase in NT-proBNP for every 10 mL/min/1.73 m² decline in GFR, compared to a 20.6% increase in BNP [18]. NT-proBNP/BNP ratios also increased with CKD severity. Fo NT-proBNP cutoffs rose from 1,360 pg/mL in patients with eGFR 60-89 mL/min/1.73 m² to 6,550 pg/mL in Stage 4 CKD [19].

The integration of echocardiography to measure LVFP further enhancic accuracy. Echocardiographic parameters such as E/e' ratios provide non-invasive insights into elevated LVFP, aiding in the differentiation of HF from other causes of dyspnea [20]. Studies have shown that combining elevated BNP levels with an E/e' ratio >15sk prediction in acute myocardial infarction [21]. BNP-guided management strategies and ultrasound-based LVFP assessments

have demonstrated improveds, including reduced acute kidney injury rates [22-25].

In our study, CKD patients with elevated LVFP had significantly higher NT-proBNP levels (median 12,186 pg with normal LVFP (2,528 pg/mL, p=0.003). The observed cutoff values, especially 3,737 pg/mL for CKD patients with high LVFP, align with prior research while reflecting the unique characteristics of our population. These findings emphasize the diagnostic and prognostic utility of NT-proBNP, particularly when used alongside echocardiographic LVFP measurements.

This study supports the use of higher NT-proBNP thresholds for diagnosing ADHF in CKD patients, especially those with elevated LVFP. These findings could help refine patient management strategies, improve diagnostic accuracy, and optimize clinical outcomes in this challenging patient population. Future research should focus on standardizing NT-proBNP cutoffs across different CKD stages and validating these thresholds in larger, diverse cohorts.

Limitations: This study has several limitations. First, the sample size was small, and the retrospective design inherently limits causal inferences. We did not adjust NT-proBNP levels for potential confounding factors such as body weight and pulmonary, neurologic, and hepatic comorbidities, which could have influenced the results. Follow-up evaluations of NT-proBNP and echocardiograms were not performed, preventing us from monitoring biomarker and clinical changes with treatment. Additionally, correlations between NT-proBNP and New York Heart Association (NYHA) stages were not assessed, which might have provided valuable insights into disease severity.

Our data showed a skewed distribution, leading to a higher median NT-proBNP value than the calculated cutoff. Due to the limited sample size, we could not stratify NT-proBNP levels across different CKD stages or analyze them based on heart failure subtypes, such as heart failure with preserved ejection fraction (HFpEF) versus reduced ejection fraction (HFrEF). These limitations highlight the need for larger, prospective studies to validate our findings and address these gaps.

CONCLUSION

NT-proBNP is a rapid and reliable biomarker for the early and accurate diagnosis of acute decompensated heart failure (ADHF). In CKD patients, the cutoff value for NT-proBNP is higher than in non-CKD populations, underscoring the need to adjust thresholds based on renal function for optimal diagnostic accuracy.

Our findings suggest that incorporating NT-proBNP measurements alongside high left ventricular filling pressure (LVFP) can aid in the definitive diagnosis of ADHF in CKD patients. Importantly, we identified a higher NT-proBNP cutoff than previously reported, which could reflect the unique characteristics of our study population, such as advanced CKD and reduced ejection fraction in many patients. These results support the use of tailored NT-proBNP thresholds for CKD patients to improve diagnostic precision and guide management strategies. Further research is warranted to validate these findings and refine clinical protocols for this high-risk group.

AUTHORS' CONTRIBUTION

AM, SHZ, SS, ZR, and SS: Concept and design, data acquisition, interpretation, drafting, final approval, and agree to be accountable for all aspects of the work. AM, SHZ, SS, ZR, and SS: Data acquisition, interpretation, drafting, final approval and agree to be accountable for all aspects of the work.

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