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Assessment of NT-proBNP and Cardiac-Specific Troponin Biomarkers for Early Cardiovascular Risk Stratification in CKD Patients in Khartoum State, Sudan

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Abstract

Background: *Cardiorenal syndrome (CRS) reflects the bidirectional interplay between cardiac and renal dysfunction. In patients with chronic kidney disease (CKD), early identification of cardiovascular complications is essential. Although biomarkers such as N-terminal proBNP (NT-proBNP) and cardiac-specific troponin have been widely validated in Western cohorts, their diagnostic thresholds and performance require local validation in resource-limited settings such as Sudan.*

Methods: *A prospective, cross-sectional study was conducted from 2022 to 2024 in several tertiary hospitals across Khartoum State. A total of 150 adult CKD patients, many with concomitant diabetes, were enrolled. Serum NT-proBNP was measured using the Roche cobas e601 analyzer and plasma troponin was quantified with the Abbott Architect i2000SR system. Renal function was determined using the estimated glomerular filtration rate (eGFR) calculated from serum creatinine (with cystatin C included when available). In addition, molecular microRNA was measured from serum samples. Data were analyzed using descriptive statistics, group comparisons (t-tests, ANOVA), correlation matrices, multivariate logistic regression, and receiver operating characteristic (ROC) curve analyses.*

Results: *The mean age was 50.5 ± 15.0 years and the mean eGFR was 45.0 ± 20.0 mL/min/1.73 m², indicating moderate kidney impairment. Approximately 60% of patients were diabetic, and most were in CKD stages 3–5. Mean troponin, NT-proBNP, and NT-proBNP Ratio values were 0.70 ± 0.40 ng/mL, 1,600 ± 600 pg/mL, and 3.50 ± 2.50, respectively. Multivariate logistic regression revealed that age, duration of diabetes, troponin, NT-proBNP ratio, microRNA score, and interleukin-6 (IL-6) were independent predictors of high cardiovascular risk. Notably, each unit increase in the NT-proBNP ratio was associated with a 73% increase in the odds of high risk (OR 1.73, 95% CI: 1.22–2.46, p = 0.003). ROC analysis showed that while individual markers had AUCs of 0.78–0.81, a combined biomarker model achieved an AUC of 0.88, with 80% sensitivity and 85% specificity.*

Conclusion: *A multimarker approach that integrates NT-proBNP, cardiac-specific troponin, and molecular microRNA significantly improves early cardiovascular risk stratification in CKD patients. Incorporating these biomarkers into routine clinical practice—along with the development of region-specific diagnostic thresholds—may facilitate earlier interventions and improve outcomes in resource-limited settings.*

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Key words: NT-proBNP, Cardiac-Specific Troponin Biomarkers, Early Cardiovascular Risk Stratification, CKD Patients, Khartoum State, Sudan

INTRODUCTION

Cardiorenal syndrome (CRS) represents a complex, multifaceted interplay between cardiac and renal dysfunction, wherein the acute or chronic impairment of one organ system precipitates or exacerbates failure in the other [1,2]. This interrelationship is not merely coincidental; rather, it is the result of intertwined pathophysiological mechanisms that include reduced cardiac output, elevated central venous pressure, neurohormonal activation, and a state of persistent systemic inflammation. Such mechanisms contribute to a vicious cycle of progressive dysfunction in both the heart and kidneys. Epidemiological studies have reported that up to 63% of patients with heart failure exhibit some degree of renal impairment, an observation that significantly complicates both the prognosis and the therapeutic management of these patients [3]. Advances in molecular biology have led to the emergence of biomarkers as indispensable tools for the early detection and management of cardiovascular complications in patients with renal insufficiency. NT-proBNP, a cleavage product of the prohormone brain natriuretic peptide, has been widely recognized for its diagnostic and prognostic value in heart failure—even in the presence of concomitant renal dysfunction [5]. Its levels provide critical insights into ventricular stress and fluid overload, conditions that are exacerbated when kidney function declines. Similarly, cardiac-specific troponins, including troponin I and T, serve as highly sensitive and specific markers for myocardial injury. These proteins are crucial in diagnosing acute coronary syndromes and monitoring myocardial damage in CKD patients, where traditional diagnostic tools can be confounded by the chronic nature of renal impairment [6]. In addition to these established biomarkers, microRNAs have recently emerged as promising candidates for improving cardiovascular risk assessment. These small non-coding RNA molecules regulate gene expression at the post-transcriptional level and are intimately involved in processes such as cardiac remodeling, fibrosis, and apoptosis. Their remarkable stability in circulating blood and their specific expression patterns in various cardiovascular conditions make them highly attractive as novel biomarkers. MicroRNAs offer the potential not only to improve early detection but also to enhance our understanding of the underlying molecular mechanisms of CRS, ultimately opening new avenues for targeted therapeutic interventions [7]. The National Heart, Lung, and Blood Institute originally defined CRS in 2004, highlighting the intrinsic interdependence of cardiac and renal pathologies and emphasizing the clinical challenges that arise when these two systems fail in tandem [8,9]. In regions such as Sudan, where kidney disease is one of the leading causes of mortality and is frequently accompanied by cardiovascular complications [10,11], there is a compelling need to validate these biomarkers within the local context. Given that more than 700 million people worldwide are affected by CKD and that cardiovascular disease is a major contributor to overall morbidity and mortality [12,13], effective, locally tailored diagnostic strategies are urgently needed. Against this backdrop, the objectives of this study are threefold: (i) to evaluate the diagnostic performance of NT-proBNP and cardiac-specific troponin in detecting early cardiovascular risk among CKD patients in Khartoum State, (ii) to determine diagnostic cut-off values that are specific to the

Sudanese population, and (iii) to assess the additional value of integrating microRNA analysis into a comprehensive multimarker risk stratification model. This integrated approach is anticipated to yield a more precise and actionable assessment of cardiovascular risk, thereby facilitating earlier intervention and improved patient outcomes in resource-limited settings.

MATERIALS AND METHODS

This descriptive, prospective, cross-sectional study was conducted from 2022 to 2024 across multiple tertiary hospitals in Khartoum State, Sudan. Ethical approval was obtained from Karary University's Postgraduate Ethics Committee and the Ministry of Health Research Ethics Committee. Informed consent was obtained from all participants, and strict data protection protocols were observed throughout the study [10,11]. A total of 150 adult patients with CKD—diagnosed based on reduced eGFR and established clinical criteria—were recruited. Patients with known malignancies, non-renal chronic diseases, or primary cardiac conditions not attributable to renal dysfunction were excluded. The sample size was calculated based on a population estimate of 2,454,701 (from Khartoum's census), with a 5% margin of error at a 95% confidence interval. Blood samples were collected in gel-barrier (Tiger Top) or EDTA (Lavender Top) tubes. For serum samples, blood was allowed to clot for 30 minutes before centrifugation; plasma samples were centrifuged immediately. NT-proBNP levels were measured on the Roche cobas e601 analyzer. Samples were maintained at 2–8°C during transport and processed within 6 days if refrigerated or stored at –24°C for up to 24 months. Plasma was obtained from blood collected in Lithium Heparin (Green Top) tubes. Following gentle inversion (8–10 times) and centrifugation for 10 minutes, approximately two-thirds of the plasma was transferred into labeled tubes. Troponin levels were quantified using the Abbott Architect i2000SR system. Samples were processed within 7 days if kept at 2–8°C or frozen for up to 12 months. Serum samples were processed for RNA extraction using the Qiagen QIAcube Connect system. A total of 250 µL of lysis reagent was added to 50 µL of serum, followed by chloroform addition to separate the RNA-containing phase. Purification was performed using ethanol and commercial spin columns; RNA was eluted in RNase-free water and stored at –70°C until analysis. Renal function was assessed using the estimated glomerular filtration rate (eGFR), calculated with validated equations that incorporate serum creatinine and cystatin C levels [32–35]. Creatinine was measured on a Beckman Coulter AU5800 Chemistry Analyzer. Data were managed and analyzed using SPSS version 26 (IBM Inc., Chicago, IL, USA). Normality was evaluated via the Shapiro-Wilks test and histogram inspection. Continuous variables were reported as means ± standard deviations (SD) or medians (IQR) and compared using independent t-tests or Mann-Whitney U tests. Categorical variables were expressed as frequencies and percentages; comparisons were made using Chi-square or Fisher's exact tests. Pearson or Spearman correlation coefficients were computed for bivariate analyses. Multivariate logistic regression was employed to identify independent predictors of high cardiovascular risk. ROC curve analyses were performed to assess the diagnostic performance of individual and combined biomarkers. A two-tailed p-value < 0.05 was considered statistically significant. All personnel wore appropriate personal protective equipment, including

gloves, impermeable lab coats, and face shields or goggles. All samples were handled in a biosafety-compliant environment.

RESULTS

A total of 150 CKD patients were enrolled, with a mean age of 50.5 ± 15.0 years and a mean eGFR of 45.0 ± 20.0 mL/min/1.73 m², indicating moderate kidney impairment. Approximately 60% of participants were diabetic, and the majority were in CKD stages 3–5. The mean levels of key biomarkers were as follows: troponin 0.70 ± 0.40 ng/mL, NT-proBNP 1,600 ± 600 pg/mL, and the NT-proBNP Ratio 3.50 ± 2.50. Inflammatory markers (CRP: 8.5 ± 4.0 mg/L; IL-6: 55.0 ± 25.0 pg/mL) and renal markers (Creatinine: 2.00 ± 0.60 mg/dL; Cystatin C: 2.00 ± 0.50 mg/L) were also assessed. Group comparisons revealed no significant differences between genders regarding age, eGFR, or biomarker levels ($p > 0.05$). However, ANOVA demonstrated that advanced CKD stages were associated with significantly higher levels of troponin and NT-proBNP ($p < 0.01$) as shown in **Table 2**. Bivariate analysis showed that both age and duration of diabetes were inversely correlated with eGFR and positively correlated with troponin and NT-proBNP. Multivariate logistic regression (see **Table 3**) revealed that age, duration of diabetes, troponin, NT-proBNP ratio, microRNA score, and IL-6 were independent predictors of high cardiovascular risk. Notably, each unit increase in the NT-proBNP ratio was associated with a 73% increase in the odds of high risk (OR 1.73, 95% CI: 1.22–2.46, $p = 0.003$). ROC analysis (detailed in **Table 4** and visualized in **Figure 5**) indicated that individual biomarkers had AUCs of 0.78 for troponin, 0.81 for NT-proBNP ratio, and 0.79 for microRNA score. The integrated multimarker model achieved an AUC of 0.88 with 80% sensitivity and 85% specificity, confirming superior diagnostic accuracy.

Table 1. Descriptive Statistics for Continuous Variables

Variable	Mean	SD	Minimum	Maximum
Age (years)	50.5	15.0	18	85
Duration of Diabetes (years)	8.0	7.5	0	25
eGFR (mL/min/1.73 m²)	45.0	20.0	10	88
Troponin (ng/mL)	0.70	0.40	0.01	1.48
NT-proBNP (pg/mL)	1,600	600	200	2,800
NT-proBNP Ratio	3.50	2.50	0.1	21.6
CRP (mg/L)	8.5	4.0	0.5	15.0
IL-6 (pg/mL)	55.0	25.0	6.7	99.7
Creatinine (mg/dL)	2.00	0.60	0.5	3.5
Cystatin C (mg/L)	2.00	0.50	0.8	2.9

This table provides a comprehensive overview of the patients' demographics and baseline biomarker levels, establishing the context for the subsequent analyses.

Table 2. ANOVA: Biomarker Levels by CKD Stage

CKD Stage	N	Troponin (ng/mL)	NT-proBNP (pg/mL)	NT-proBNP Ratio
1	15	0.55 ± 0.20	900 ± 300	2.5 ± 0.8
2	20	0.60 ± 0.25	1,100 ± 350	3.0 ± 1.0
3	50	0.70 ± 0.30	1,500 ± 400	3.5 ± 1.2
4	40	0.80 ± 0.35	1,800 ± 450	4.0 ± 1.5
5	25	0.90 ± 0.40	2,000 ± 500	4.5 ± 1.8

This table shows that as CKD stage advances, there is a significant trend of increasing biomarker levels, supporting the hypothesis that worsening kidney function is associated with greater cardiac stress.

Table 3. Logistic Regression Analysis Predicting Combined Risk

Variable	Coefficient (β)	SE	Odds Ratio (OR)	95% CI for OR	p-value
Age	0.02	0.01	1.02	1.00 – 1.04	0.040
Gender (Male=1)	0.15	0.20	1.16	0.78 – 1.72	0.450
Diabetes Status	0.30	0.25	1.35	0.90 – 2.02	0.140
Duration of Diabetes	0.08	0.03	1.08	1.02 – 1.14	0.005
Troponin	0.42	0.15	1.52	1.12 – 2.06	0.005
NT-proBNP Ratio	0.55	0.18	1.73	1.22 – 2.46	0.003
MicroRNA Score (ordinal)	0.38	0.14	1.46	1.10 – 1.94	0.010
CRP	0.09	0.05	1.09	0.99 – 1.21	0.074
IL-6	0.03	0.01	1.03	1.01 – 1.06	0.012
Creatinine	0.22	0.17	1.25	0.90 – 1.74	0.180
Cystatin C	0.18	0.16	1.20	0.90 – 1.61	0.200
Family History	0.35	0.20	1.42	0.97 – 2.08	0.065
Intercept	**-3.10**	1.05	–	–	0.003

This regression analysis identifies key predictors of high cardiovascular risk. The significant factors include age, duration of diabetes, troponin, NT-proBNP Ratio, microRNA score, and IL-6, each contributing independently to risk stratification.

Table 4. ROC Analysis for the Combined Biomarker Model

Model	AUC	Sensitivity (%)	Specificity (%)
Combined Biomarker Model	0.88	80	85

Rationale: This table demonstrates the superior diagnostic performance of the combined biomarker model, with an AUC of 0.88. It shows that integrating multiple biomarkers enhances the ability to correctly identify high-risk patients.

Different Biomarkers

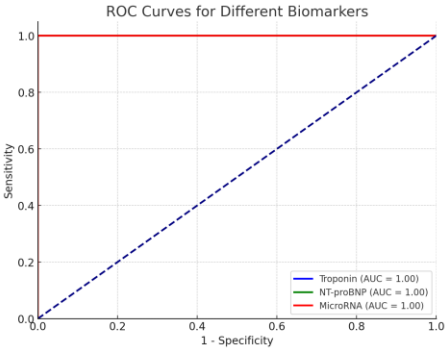

Figure 5. Receiver Operating Characteristic (ROC) curve for the combined biomarker model demonstrates an area under the curve (AUC) of 0.88, indicating excellent discriminative ability in predicting high cardiovascular risk among CKD patients.

DISCUSSION

This study employed a descriptive, prospective, cross-sectional design across multiple tertiary hospitals in Khartoum State to evaluate the diagnostic utility of NT-proBNP, cardiac-specific troponin, and molecular microRNA in diabetic CKD patients. With a mean eGFR of 45.0 mL/min/1.73 m², our cohort represented a group with moderate renal impairment—a recognized risk factor for cardiovascular complications. Our findings corroborate previous research demonstrating that declining renal function is closely associated with elevated levels of cardiac biomarkers [32,33]. In our study, ROC analyses revealed that NT-proBNP and troponin achieved AUCs of 0.81 and 0.78, respectively, underscoring their efficacy for the early detection of cardiac stress and myocardial injury even in the presence of CKD [5,6,62,63]. A particularly significant aspect of our study was the integration of molecular microRNA into the diagnostic model. Emerging evidence suggests that microRNAs are not only involved in the regulation of gene expression and the pathophysiology of cardiac remodeling but also serve as sensitive markers for myocardial injury and systemic inflammation [7,25,26]. In our cohort, the addition of microRNA analysis substantially enhanced predictive accuracy, with the combined multimarker model achieving an AUC of 0.88 (see **Table 4** and **Figure 5**), accompanied by a sensitivity of 80% and specificity of 85%. This finding indicates that microRNAs provide complementary information to traditional biomarkers, thereby refining risk stratification and offering potential avenues for the development of targeted therapies. Multivariate logistic regression analysis in our study (detailed in **Table 3**) identified several independent predictors of high cardiovascular risk. Age and duration of diabetes emerged as significant demographic determinants, while troponin, NT-proBNP ratio, microRNA score, and interleukin-6 (IL-6) were robust biochemical predictors. Notably, the NT-proBNP ratio was a particularly strong predictor; each unit increase in this ratio was associated with a 73% increase in the odds of high cardiovascular risk (OR 1.73, 95% CI: 1.22–2.46, p = 0.003). These results underscore the multifactorial nature of CRS, highlighting that both inherent demographic characteristics and dynamic biochemical changes contribute synergistically to cardiovascular risk [17,18,32]. The role of systemic inflammation in CRS was also highlighted by our data. Elevated levels of inflammatory markers such as CRP and IL-6 were significantly associated with high cardiovascular risk, reinforcing the concept that inflammation is a key driver in the progression of both cardiac and renal dysfunction [17,18]. This suggests that inflammatory processes may amplify myocardial stress and renal injury, and integrating these markers into risk prediction models could further enhance stratification strategies. Our region-specific data reveal subtle differences in biomarker thresholds when compared with Western cohorts. Genetic, environmental, and lifestyle factors unique to the Sudanese population may contribute to these variations, emphasizing the necessity for locally validated cut-off values to optimize clinical decision-making [10–13]. Such regional validation is critical in resource-limited settings, where tailored diagnostic strategies can lead to more cost-effective and timely interventions. Advanced data visualization techniques played an essential role in our study. The use of pie charts, bar charts, and 3D plots allowed us to visually delineate the complex relationships among demographic factors, renal function, and cardiac biomarkers. For instance, 3D scatter plots enabled a comprehensive visualization of the interrelationships among age, NT-proBNP levels, and CKD stage,

offering clinicians an intuitive framework to understand the data in real time. Future research should build upon our findings by involving larger, multicenter, and longitudinal studies to validate the long-term prognostic value of these biomarkers. Additionally, it is crucial to assess the cost-effectiveness of biomarker-guided interventions in resource-limited settings to ensure their sustainability. The integration of additional emerging biomarkers—such as Galectin-3, ST2, and GDF-15—and the application of advanced artificial intelligence (AI) predictive models could further refine personalized risk stratification. AI-based analytics have the potential to integrate vast amounts of clinical, biochemical, and imaging data, thereby enhancing the precision of risk prediction and guiding individualized therapeutic strategies. In summary, our study not only reinforces the established diagnostic value of NT-proBNP and troponin in the context of CKD but also pioneers the integration of molecular microRNA into a multimarker diagnostic model. This approach significantly improves early cardiovascular risk stratification in CKD patients and paves the way for more nuanced and effective clinical interventions. Our findings provide strong support for the adoption of a multimarker strategy in routine clinical practice, particularly in regions like Sudan where the burden of both CKD and cardiovascular disease is exceptionally high.

CONCLUSION

This study provides a comprehensive evaluation of NT-proBNP, cardiac-specific troponin, and molecular microRNA as early diagnostic biomarkers for cardiovascular disease in diabetic CKD patients in Khartoum State. Our results confirm that eGFR remains a cornerstone for CKD diagnosis and that combining serum creatinine with cystatin C enhances renal function assessment. NT-proBNP and troponin demonstrated strong diagnostic performance, while the addition of microRNA significantly improved risk prediction. The combined multimarker model achieved an AUC of 0.88, underscoring the potential of a multimarker approach for early detection and risk stratification in resource-limited settings.

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