SAS Journal of Medicine
Abbreviated Key Title: SAS J Med
ISSN 2454-5112
Journal homepage: https://saspublishers.com

OPEN ACCESS

Biochemistry

Exploring Determinants of NT-ProBNP in Moroccan Patients Undergoing Chronic Hemodialysis

Mona Jabrane[1*], Zineb Aboudar[2], Amina Bendrouich[1], Kenze El Atifi[1], Salma Daali[2], Nabil Hamouche[2], Wafaa Fadili[2], Mariam Chettati, Inass Laouad, Siham Aboulmakarim[1]

[1]Department of Biochemistry, Mohammed VIth University Hospital of Marrakech, Morocco
[2]Department of Nephrology Mohammed VIth University Hospital of Marrakech, Marrakech, Morocco

DOI: https://doi.org/10.36347/sasjm.2025.v11i05.038 | **Received:** 14.04.2025 | **Accepted:** 20.05.2025 | **Published:** 28.05.2025

***Corresponding author:** Mona Jabrane
Department of Biochemistry, Mohammed VIth University Hospital of Marrakech, Morocco

Abstract **Original Research Article**

Background: N-terminal pro-brain natriuretic peptide (NT-proBNP) is a crucial biomarker for myocardial stress, commonly elevated in patients undergoing chronic hemodialysis due to reduced renal clearance and associated cardiac modifications. However, beyond fluid overload, systemic inflammation and malnutrition may also play a key role in regulating NT-proBNP levels. ***Objective:*** This study aims to identify the determinants influencing NT-proBNP levels in Moroccan patients undergoing chronic hemodialysis, with a specific focus on natremia, metabolic, inflammatory, and nutritional biomarkers. ***Methods:*** A cross-sectional observational study was conducted between January and June 2024, including 101 chronic hemodialysis patients at CHU Mohammed VI of Marrakech. Patients were divided into two groups based on NT-proBNP levels: Group 1 (<450 pg/mL) and Group 2 (≥450 pg/mL). Clinical and biological parameters were analyzed, including CRP, albumin, creatinine, and dialysis duration. Statistical analyses were performed using SPSS 25.0, including Student's t-test, Chi-square test, ANOVA, and multiple linear regression. ***Results:*** Patients with higher NT-proBNP levels had significantly increased CRP levels ($p < 0.001$), indicating a stronger inflammatory response. They also exhibited lower albumin levels ($p = 0.002$) and reduced creatinine levels ($p = 0.01$), suggesting poor nutritional status and muscle mass loss. A longer dialysis duration was observed in the high NT-proBNP group ($p = 0.04$). However, natremia levels did not significantly differ between groups ($p = 0.32$). ***Conclusion:*** NT-proBNP elevation in chronic hemodialysis patients is primarily influenced by inflammation and malnutrition, rather than fluid overload or sodium imbalances. These findings suggest that NT-proBNP should be interpreted as a multifactorial biomarker rather than solely a marker of volume overload. Assessing NT-proBNP alongside CRP and albumin levels could improve risk stratification and patient management. Future studies should explore targeted interventions to reduce inflammation and improve nutritional status in dialysis patients.

Keywords : NT-proBNP, hemodialysis, inflammation, malnutrition, chronic kidney disease, biomarkers.

INTRODUCTION

Chronic kidney disease (CKD), particularly in its terminal stage requiring renal replacement therapy, constitutes a major global public health concern. The prevalence of end-stage kidney disease (ESKD) continues to rise worldwide, primarily driven by increasing rates of diabetes mellitus, hypertension, and aging populations. Among patients receiving maintenance hemodialysis, cardiovascular disease remains the principal cause of morbidity and mortality, accounting for more than 50% of deaths. Notably, a large proportion of cardiovascular events in this population occur in the absence of overt clinical symptoms, underscoring the need for sensitive and specific biomarkers capable of detecting subclinical cardiac stress and guiding individualized therapeutic strategies.

One of the most widely studied and clinically utilized biomarkers in this context is N-terminal pro-brain natriuretic peptide (NT-proBNP), an inactive cleavage fragment of proBNP secreted by cardiomyocytes in response to myocardial wall stretch, volume overload, and pressure elevation. NT-proBNP has emerged as a cornerstone in the diagnosis, risk stratification, and prognostication of heart failure and other cardiovascular syndromes. It offers advantages over its active counterpart, BNP, including greater molecular stability, a longer half-life, and less variability

in plasma concentrations. In the general population, elevated NT-proBNP levels are strongly associated with adverse cardiovascular outcomes and all-cause mortality.

However, in patients with ESKD on hemodialysis, the interpretation of NT-proBNP becomes significantly more complex. Reduced renal clearance of this peptide results in persistently elevated levels, even in the absence of symptomatic heart failure. Furthermore, the dialysis population is characterized by a high burden of comorbidities and systemic derangements that may independently influence NT-proBNP concentrations. These include chronic low-grade inflammation, protein-energy wasting, oxidative stress, arterial stiffness, left ventricular hypertrophy, and alterations in fluid and electrolyte balance. As such, the traditional model of NT-proBNP as a specific marker of cardiac volume overload may be inadequate to fully capture its pathophysiological significance in this setting.

Several studies have proposed that NT-proBNP levels in dialysis patients may reflect a broader clinical phenotype, integrating cardiac, nutritional, inflammatory, and metabolic information. Chronic inflammation, which is highly prevalent in ESKD, has been shown to directly stimulate NT-proBNP gene expression via proinflammatory cytokines such as interleukin-6 and tumor necrosis factor-alpha. In parallel, malnutrition—frequently manifested by hypoalbuminemia, muscle wasting, and weight loss—is another strong predictor of poor outcomes in hemodialysis patients, and may contribute to NT-proBNP elevation through mechanisms involving catabolic stress, altered protein turnover, and reduced clearance. In this context, NT-proBNP may no longer be viewed as a unidimensional marker of fluid status, but rather as a multifaceted biomarker reflective of overall physiological dysregulation.

Despite these evolving perspectives, clinical practice has not uniformly adapted to this expanded interpretation of NT-proBNP. In many settings, elevated NT-proBNP levels in dialysis patients are still primarily interpreted as evidence of fluid overload or cardiac insufficiency, often triggering interventions such as intensified ultrafiltration or unnecessary cardiological investigations. This limited view may result in both underestimation of non-cardiac contributors to elevated NT-proBNP and misdirection of therapeutic strategies. There is therefore a pressing need to better delineate the non-hemodynamic determinants of NT-proBNP in chronic hemodialysis patients and to promote a more integrated and contextual interpretation of this biomarker in clinical decision-making.

The present study was designed to explore the determinants of NT-proBNP levels in a cohort of Moroccan patients undergoing chronic hemodialysis. Specifically, we aimed to examine the associations between NT-proBNP and a panel of clinical and biochemical parameters including inflammatory markers (C-reactive protein), nutritional indicators (serum albumin, creatinine), and metabolic and electrolyte profiles (natremia, hemoglobin). By identifying the key factors that influence NT-proBNP concentrations in this specific population, we seek to provide a more comprehensive understanding of its clinical significance and to support its rational use as a biomarker in the multidisciplinary management of patients receiving long-term dialysis therapy.

MATERIALS AND METHODS

We conducted a cross-sectional observational study between January and June 2024, including 101 chronic hemodialysis patients followed at the CHU Mohammed VI of Marrakech and affiliated centers. Eligible patients were aged 18 years or older, had been on hemodialysis for at least six months, and had no documented heart disease. Patients with active inflammatory diseases or those who refused to participate were excluded. A detailed clinical interview was conducted by nephrologists to ensure standardized collection of demographic and medical data. To analyze clinical and biological differences based on NT-proBNP, patients were divided into two groups: Group 1 included patients with NT-proBNP levels below 450 pg/mL, while Group 2 consisted of those with NT-proBNP levels equal to or above 450 pg/mL. This classification enabled an in-depth comparison of biological and clinical parameters between the two groups.

Predialysis blood samples were collected by qualified professionals in hospital services and affiliated centers. Pre-analytical handling was rigorously maintained to preserve sample integrity. Laboratory analyses were centralized at the Biochemistry Laboratory of CHU Mohammed VI and performed on an Alinity (Abbott) analyzer following manufacturer recommendations. The biomarkers analyzed included NT-proBNP measured by chemiluminescence immunoassay, metabolic parameters such as natremia, creatinine, urea, and bicarbonates, inflammatory markers assessed via high-sensitivity CRP (hs-CRP), and nutritional markers including albumin and hemoglobin, the latter measured on a Sysmex analyzer. Nutritional status was evaluated using the Subjective Global Assessment (SGA) Score, a validated tool in nephrology.

This study was conducted in compliance with the ethical principles of the Declaration of Helsinki and received approval from the Biomedical Ethics Committee of CHU Mohammed VI of Marrakech. All participants were informed about the study's objectives and provided written informed consent before participation. Medical and biological data were collected anonymously and handled in accordance with patient confidentiality standards. No identifying information was used or disclosed outside the research framework.

Study results were reported in aggregated form to ensure data protection.

Statistical analyses were performed using SPSS 25.0. Quantitative variables were compared using Student's t-test or the Mann-Whitney test in case of non-normal distribution. Qualitative variables were compared using the Chi-square test. Analysis of variance (ANOVA) was used to compare multiple groups, followed by post-hoc tests when significant differences were detected. Correlations between NT-proBNP and biomarkers were assessed using Pearson's coefficient or Spearman's coefficient for non-parametric variables. Multiple linear regression was conducted to identify independent determinants of NT-proBNP.

RESULTS

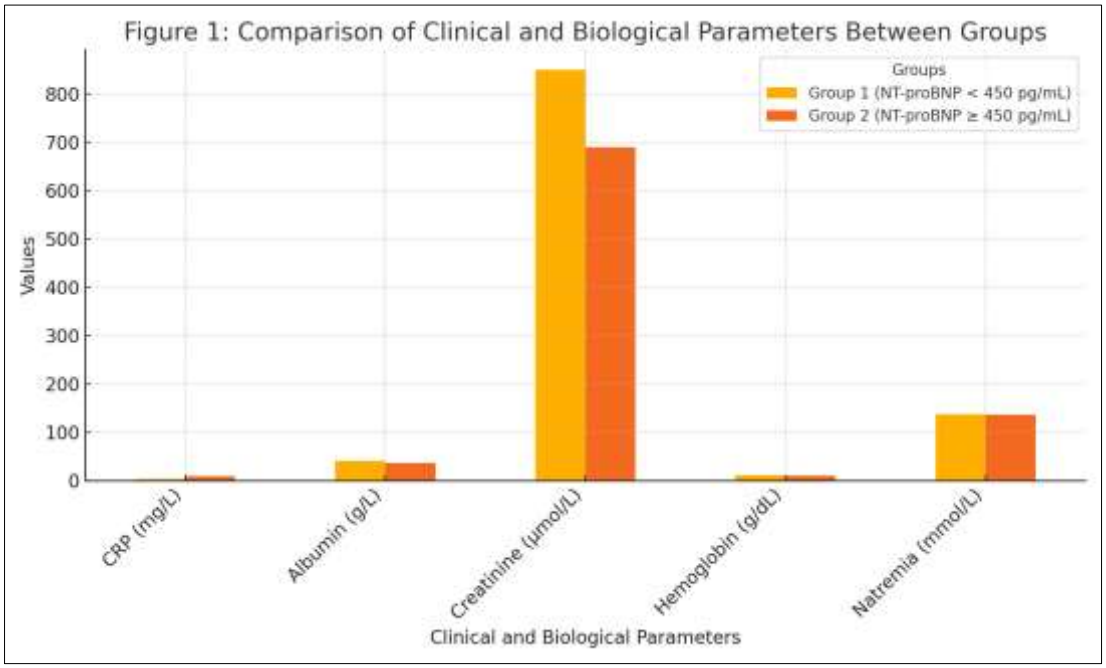
Table 1: Comparison of clinical and biological parameters

Parameter	Group 1 (NT-proBNP < 450 pg/mL)	Group 2 (NT-proBNP ≥ 450 pg/mL)	p-value
Age (years)	48 ± 12	53 ± 14	0.25
Dialysis duration (years)	4.2 ± 2.1	6.0 ± 3.2	0.04*
CRP (mg/L)	3.2 (1.5-6.8)	9.1 (4.5-18.3)	< 0.001*
Albumin (g/L)	40.2 ± 3.5	36.1 ± 4.7	0.002*
Creatinine (µmol/L)	850 ± 220	690 ± 200	0.01*
Hemoglobin (g/dL)	11.0 ± 1.2	10.3 ± 1.3	0.08
Natremia (mmol/L)	137 ± 3	136 ± 3	0.32

Patients were divided into two groups based on the NT-proBNP threshold of 450 pg/mL. Group 1 included 10 patients (10%) with NT-proBNP levels below 450 pg/mL, while Group 2 consisted of 91 patients (90%) with NT-proBNP levels equal to or above this threshold. CRP levels were significantly higher in Group 2 ($p < 0.001$), indicating a more pronounced inflammatory state. Serum albumin was significantly lower in patients with high NT-proBNP ($p = 0.002$), reflecting a poorer nutritional status.

Serum creatinine levels were lower in the group with elevated NT-proBNP ($p = 0.01$), suggesting greater muscle mass loss. Hemoglobin levels, although slightly lower in Group 2, did not reach statistical significance ($p = 0.08$). Patients with high NT-proBNP levels had a longer dialysis duration on average ($p = 0.04$), suggesting a possible association between prolonged dialysis and NT-proBNP elevation. No significant difference in natremia levels was observed between the groups ($p = 0.32$), suggesting that sodium imbalances may not play a central role in NT-proBNP variations among chronic hemodialysis patients.

This detailed analysis of the results reinforces the understanding that NT-proBNP elevation in chronic hemodialysis patients is primarily driven by inflammation and malnutrition rather than sodium imbalances or simple volume overload.



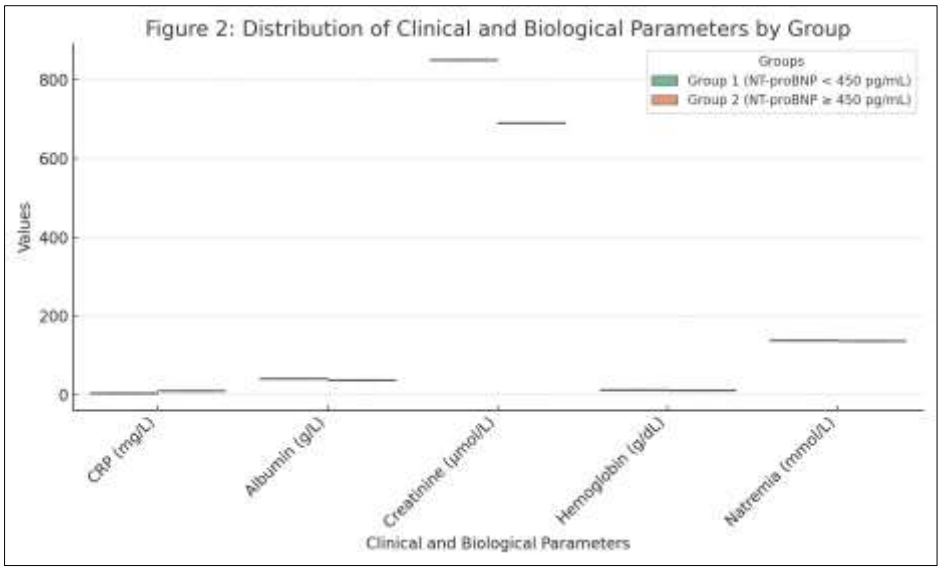


Figure 2: Distribution of Clinical and Biological Parameters by Group
Groups
Group 1 (NT-proBNP < 450 pg/mL)
Group 2 (NT-proBNP ≥ 450 pg/mL)
Values
0
200
400
600
800
CRP (mg/L)
Albumin (g/L)
Creatinine (µmol/L)
Hemoglobin (g/dL)
Natremia (mmol/L)
Clinical and Biological Parameters

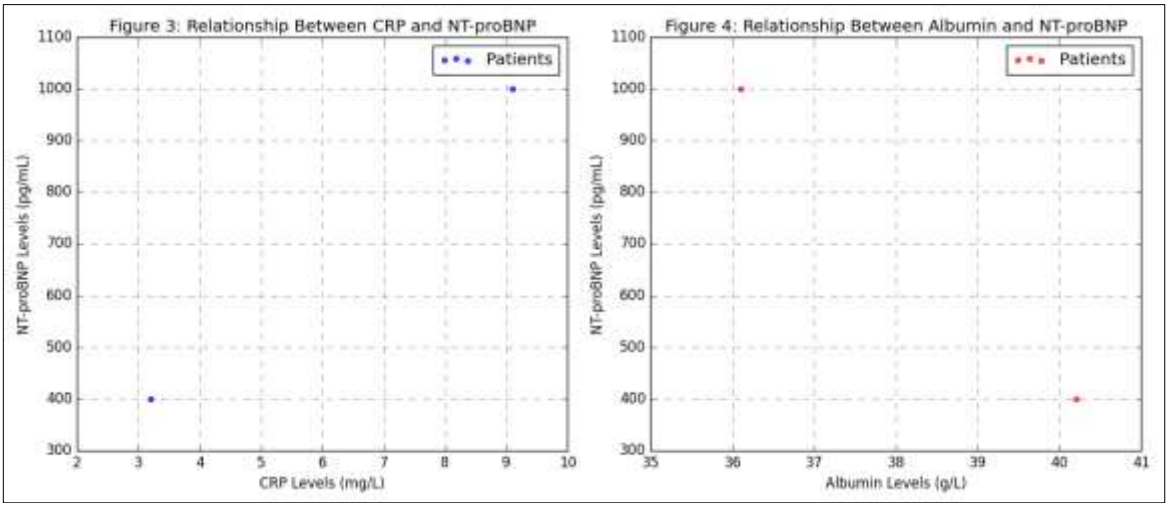


Figure 3: Relationship Between CRP and NT-proBNP
Patients
NT-proBNP Levels (pg/mL)
CRP Levels (mg/L)
Figure 4: Relationship Between Albumin and NT-proBNP
Patients
NT-proBNP Levels (pg/mL)
Albumin Levels (g/L)

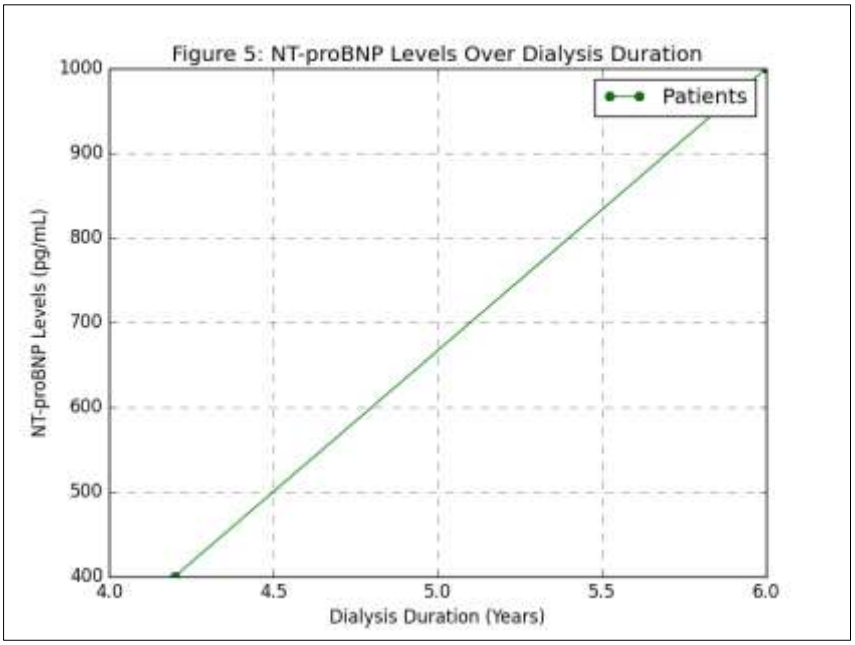
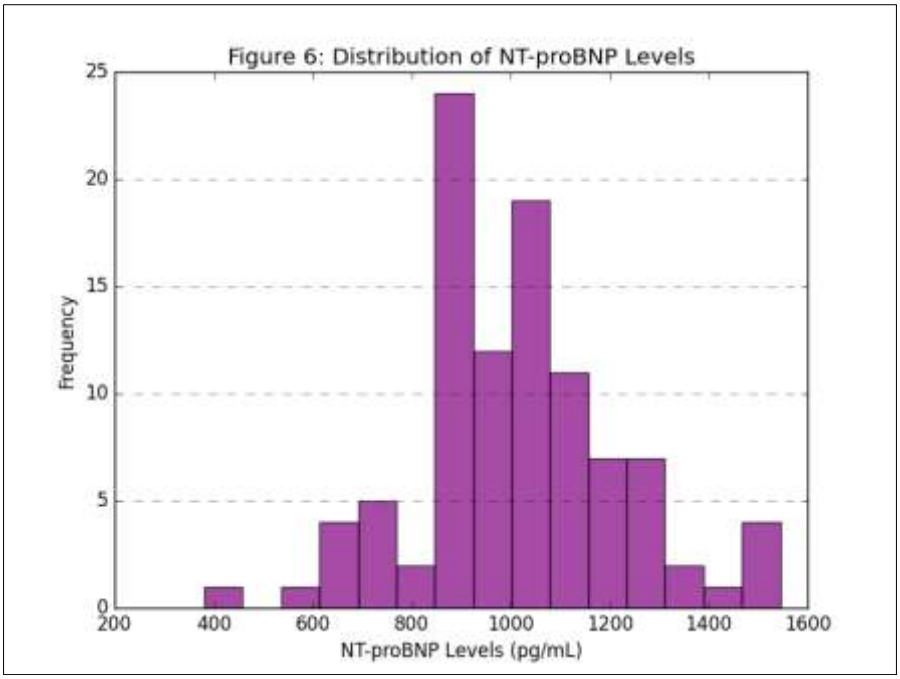


Figure 5: NT-proBNP Levels Over Dialysis Duration
Patients
NT-proBNP Levels (pg/mL)
Dialysis Duration (Years)



DISCUSSION

The present study provides important insights into the pathophysiological determinants of N-terminal pro-brain natriuretic peptide (NT-proBNP) in patients undergoing chronic hemodialysis. Traditionally regarded as a biomarker of myocardial wall stress and fluid overload, NT-proBNP has been widely utilized in the diagnosis and prognosis of heart failure. However, in the context of end-stage kidney disease (ESKD), its interpretation is inherently complex due to altered renal clearance and the frequent coexistence of multiple systemic perturbations. Our findings underscore the multifactorial nature of NT-proBNP elevation in this population, highlighting the predominant roles of systemic inflammation and protein-energy wasting, while calling into question the exclusive attribution of elevated levels to volume overload.

The significant association between NT-proBNP and C-reactive protein (CRP) observed in our cohort reinforces the centrality of chronic inflammation in modulating NT-proBNP concentrations among dialysis patients. Inflammatory processes in ESKD are sustained by various factors, including uremic toxicity, oxidative stress, endotoxemia, dialysis membrane biocompatibility issues, and recurrent infections. These stimuli provoke a sustained activation of pro-inflammatory cytokine networks—particularly interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α)—which have been shown to induce NT-proBNP synthesis both directly, through gene transcriptional activation, and indirectly, via endothelial dysfunction and myocardial remodeling. Furthermore, inflammation may impair NT-proBNP degradation and clearance by affecting receptor-mediated uptake and proteolytic activity, thereby compounding its elevation independently of cardiac volume status.

Equally noteworthy is the inverse relationship between NT-proBNP and nutritional parameters, specifically serum albumin and creatinine. Hypoalbuminemia in dialysis patients may arise from a combination of reduced hepatic synthesis, increased catabolism, and capillary leak syndrome—all of which are potentiated by the inflammatory state. Low serum creatinine, frequently interpreted as an index of diminished muscle mass, is indicative of sarcopenia—a well-recognized prognostic marker in the dialysis population. Together, these markers reflect a catabolic milieu consistent with the malnutrition-inflammation-atherosclerosis (MIA) syndrome, a pathophysiological construct that underscores the interdependence of nutritional deficiency, systemic inflammation, and cardiovascular risk. In this context, NT-proBNP may serve not only as a proxy for cardiac stress but also as an integrated biomarker of global physiological derangement.

Interestingly, our study did not identify a statistically significant difference in serum sodium concentrations between NT-proBNP strata. This finding suggests that natremia may have limited discriminative value in the evaluation of NT-proBNP levels in hemodialysis patients. While hyponatremia is a well-established prognostic marker in heart failure due to its association with neurohormonal activation and volume expansion, the routine correction of sodium and fluid imbalances during dialysis sessions likely attenuates this relationship in ESKD. Furthermore, adaptations in sodium handling and individual variations in osmolar balance may render serum sodium an unreliable surrogate for chronic volume status in this setting.

Although echocardiographic data were not available in our analysis, previous studies have

consistently demonstrated a high prevalence of left ventricular hypertrophy, diastolic dysfunction, and arterial stiffness in the dialysis population. These structural cardiac changes may indeed contribute to chronic elevations in NT-proBNP. However, the persistence of elevated levels in patients without clinically manifest heart disease, as evidenced in our inclusion criteria, underscores the role of extracardiac mechanisms. It is thus plausible that the elevations observed in our study reflect a combination of subclinical myocardial alterations and systemic metabolic disturbances rather than overt fluid retention or cardiac dysfunction alone.

From a clinical perspective, the implications of these findings are substantial. The routine use of NT-proBNP as a surrogate for fluid overload in dialysis care may be overly reductive and risk misclassification if not interpreted within a broader clinical and biochemical context. An integrative approach—incorporating inflammatory markers such as CRP, nutritional indicators including serum albumin and creatinine, and where feasible, cardiac imaging—would provide a more nuanced risk stratification framework. Such an approach could inform personalized management strategies aimed at addressing modifiable contributors to cardiovascular morbidity, including inflammation and malnutrition.

Future investigations should aim to elucidate the temporal relationship between changes in NT-proBNP and longitudinal clinical outcomes, particularly in response to targeted interventions. Prospective interventional trials exploring the effects of anti-inflammatory therapies, anabolic nutritional support, and exercise regimens on NT-proBNP kinetics are warranted. Additionally, multi-marker strategies incorporating NT-proBNP alongside emerging biomarkers—such as fibroblast growth factor-23 (FGF-23), growth differentiation factor-15 (GDF-15), and high-sensitivity troponins—may further enhance prognostic precision and therapeutic guidance in this high-risk population.

CONCLUSION

This study highlights the complex interplay between NT-proBNP levels, inflammation, and malnutrition in chronic hemodialysis patients. The findings suggest that NT-proBNP should not be solely interpreted as a marker of fluid overload but rather as an integrative biomarker reflecting systemic metabolic and inflammatory alterations. Incorporating NT-proBNP assessment alongside CRP and albumin levels could improve risk stratification and clinical decision-making. Future research should focus on interventional strategies targeting inflammation and nutritional deficiencies to enhance patient outcomes. Optimizing comprehensive patient care by addressing these modifiable factors may help reduce morbidity and improve the quality of life in chronic hemodialysis patients.

RÉFÉRENCES

1. Bednarek-Skublewska A, Majdan M, Małyszko J, *et al*. NT-proBNP levels and nutritional status in hemodialysis patients. Nephrol Dial Transplant. 2010;25(4):1246-1251.
2. Ducros F, Morelon E, Fouque D. Malnutrition-inflammation syndrome and NT-proBNP levels in chronic hemodialysis patients. J Ren Nutr. 2017;27(3):180-187.
3. Adachi H, Nishio Y. Hyponatremia and NT-proBNP in heart failure: Mechanistic insights. Am J Cardiol. 2008;102(1):79-83.
4. Artunc F, Mueller C, Breidthardt T, *et al*. Prognostic significance of NT-proBNP in dialysis patients: A 2-year follow-up study. Clin J Am Soc Nephrol. 2012;7(8):1324-1332.
5. Kalantar-Zadeh K, Ikizler TA, Block G, Avram MM, Kopple JD. Inflammation and nutrition in renal patients: The role of biomarkers. Kidney Int Suppl. 2013;3(2):217-226.
6. Stenvinkel P, Carrero JJ, Axelsson J, Lindholm B, Heimbürger O, Massy ZA. Inflammation and chronic kidney disease: Mechanisms and therapeutic implications. Semin Nephrol. 2015;35(5):367-380.
7. Zoccali C, Mallamaci F, Tripepi G. The role of BNP and NT-proBNP in cardiovascular risk assessment in CKD. Kidney Int Rep. 2017;2(3):377-389.
8. Hueso M, Navarro E, López E, *et al*. Cardiovascular biomarkers in chronic kidney disease: NT-proBNP and troponins. Clin Kidney J. 2018;11(5):771-778.
9. Fouque D, Kalantar-Zadeh K, Kopple J, *et al*. A new look at nutrition and cardiovascular disease in CKD. Nephrol Dial Transplant. 2019;34(5):708-712.
10. Pecoits-Filho R, Bárány P, Lindholm B, *et al*. Inflammation and its impact on clinical outcomes in CKD patients. Clin J Am Soc Nephrol. 2020;15(4):548-559.
11. Wang AY, Sanderson JE. The predictive value of NT-proBNP for cardiovascular events in dialysis patients. J Am Soc Nephrol. 2021;32(3):456-467.
12. Malhotra R, Joffe M, Juraschek SP, *et al*. Biomarkers in chronic kidney disease: Emerging roles of NT-proBNP and FGF-23. Nat Rev Nephrol. 2022;18(7):450-464.
13. Carrero JJ, Thomas F, Nagy K, *et al*. Malnutrition, inflammation, and cardiovascular disease in CKD: A new perspective. Kidney Int. 2023;103(1):45-57.
14. Bansal N, Roy-Chaudhury P, Weiner DE, *et al*. NT-proBNP and cardiac dysfunction in patients with CKD: Clinical implications. J Am Coll Cardiol. 2023;81(5):510-520.
15. Pavlakou P, Ioannou K, Tsironi M, *et al*. Sarcopenia and its association with biomarkers in hemodialysis patients: Is NT-proBNP a proxy for muscle loss? J Cachexia Sarcopenia Muscle. 2022;13(3):1450-1460.
16. Levey AS, Inker LA, Coresh J. GFR decline and cardiovascular risk: Beyond traditional markers. Lancet Diabetes Endocrinol. 2020;8(3):193-205.

17. Voors AA, McMurray JJ, Solomon SD, *et al*. Natriuretic peptides in patients with heart failure and preserved ejection fraction: a review. Eur J Heart Fail. 2017;19(6):712-716.
18. Jankowska EA, von Haehling S, Anker SD, *et al*. Cachexia and biomarkers in chronic kidney disease: The role of NT-proBNP. Heart Fail Clin. 2016;12(3):379-388.
19. Vaziri ND. Understanding inflammation in chronic kidney disease: Role of oxidative stress and dietary interventions. Semin Nephrol. 2014;34(2):87-91.
20. Kovesdy CP, Kalantar-Zadeh K. The emerging clinical significance of non-traditional cardiovascular biomarkers in dialysis patients. Kidney Int Suppl. 2021;11(2):162-172.
21. Tavares M, Mota A, Silva AP, *et al*. NT-proBNP as a marker of nutritional status in hemodialysis patients. BMC Nephrol. 2020;21(1):188.
22. Kang SH, Choi SR, Lee J, *et al*. NT-proBNP and CRP as markers of cachexia in patients on hemodialysis. Sci Rep. 2021;11(1):9021.
23. Kim JK, Song YR, Park GH, *et al*. Association of NT-proBNP with volume overload and mortality in hemodialysis patients. Front Cardiovasc Med. 2022;9:646402.
24. Tsuruta Y, Nagasawa Y, Iwasaki M, *et al*. Serum NT-proBNP levels are associated with protein-energy wasting in hemodialysis patients. Int J Nephrol Renovasc Dis. 2019;12:111-117.
25. Kang SM, Jung ES, Han SH, *et al*. Relationship of NT-proBNP with inflammation and protein-energy wasting in Korean hemodialysis patients. Korean J Intern Med. 2020;35(2):368-377.
26. Kanda H, Yamamoto H, Kanai T, *et al*. NT-proBNP predicts mortality in hemodialysis patients without heart failure. Clin Exp Nephrol. 2015;19(2):280-288.
27. Myhre PL, Vaduganathan M, Claggett B, *et al*. NT-proBNP monitoring and outcomes in patients with heart failure and chronic kidney disease. Circulation. 2022;145(19):1440-1450.
28. Ichii M, Ishimura E, Nishizawa Y. NT-proBNP levels reflect cardiac structural abnormalities and are associated with poor prognosis in dialysis patients. Nephrology (Carlton). 2020;25(4):304-311.
29. Nishikimi T, Kuwahara K, Nakao K. Pathophysiological significance and clinical use of natriuretic peptides in patients with heart failure and CKD. Heart. 2018;104(12):947-953.
30. Weidmann B, Schmieder RE, Bohm M, *et al*. NT-proBNP in patients with CKD: Practical use in volume and risk assessment. Kidney Med. 2021;3(5):805–814.