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BRIEF REPORT

Heart Failure in Advanced Chronic Kidney Disease

Overlooked No More

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Heart failure (HF) represents a significant burden of cardiovascular morbidity and mortality in the growing population of patients with chronic kidney disease (CKD).[1] However, HF often remains undiagnosed until late in the disease course, mainly due to the absence of standardized early identification pathways.[2] Accordingly, this study aimed to: 1) determine the prevalence and clinical characterization of HF in outpatients with advanced CKD using the current universal definition; and 2) assess the diagnostic performance of N-terminal pro-B-type natriuretic peptide (NT-proBNP) for HF detection.

What is the clinical question being addressed?
What are the prevalence and clinical characteristics of HF in outpatients with advanced CKD, as defined by the current universal definition of HF, and what is the diagnostic performance of NT-proBNP for identifying HF in this population?

What is the main finding?
A substantial proportion of patients with advanced CKD attending routine nephrology visits are already in Stage B (53.3%) or Stage C (38.6%) HF. A fixed NT-proBNP cut-off of ≥500 pg/mL offers better diagnostic performance for identifying CKD patients with significant cardiac structural or functional abnormalities than more complex age- and eGFR-adjusted thresholds.

METHODS

This prospective, multicenter study enrolled adults (≥18 years of age) with advanced CKD (estimated glomerular filtration rate [eGFR] ≥15 and <45 mL/min/1.73 m^2) from outpatient nephrology clinics at 6 Spanish hospitals between May 2022 and February 2025. Key exclusion criteria included an established diagnosis of HF, left ventricular ejection fraction of ≤50% on any prior echocardiogram, renal replacement therapy (current or planned), or kidney transplantation. The study protocol was approved by

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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ABBREVIATIONS AND ACRONYMS

AUC = area under the curve

CKD = chronic kidney disease

eGFR = estimated glomerular filtration rate

HF = heart failure

NT-proBNP = N-terminal pro-B-type natriuretic peptide

the Institutional Review Board at each site and adhered to the principles of the Declaration of Helsinki. All enrolled patients provided written informed consent.

At baseline, all participants underwent a complete physical examination, vital signs, anthropometric measurements, electrocardiography, a comprehensive transthoracic echocardiogram, lung ultrasound, venous Doppler echography, and specific laboratory assessments, including NT-proBNP and carbohydrate antigen 125.

Patients were categorized by the KDIGO (Kidney Disease Improving Global Outcomes) nomenclature. The prevalence of HF within each KDIGO-defined CKD stage was evaluated according to the revised stages of the HF continuum proposed by the universal definition of HF.[3] For NT-proBNP rule-in cut-point assessment, HF was defined noninvasively as the presence of cardiac structural or functional abnormalities (as determined by left ventricular ejection fraction <50%, left atrial enlargement [left atrial volume >34 mL/m^2], mitral peak E velocity to average annular e' velocity [E/e'] >15, moderate/severe ventricular hypertrophy, or moderate/severe valvular obstructive or regurgitant lesion) associated with HF symptoms/signs attributable to these abnormalities or objective evidence of congestion by imaging. Objective evidence of congestion included: 1) elevated echocardiographic filling pressures (≥2 of left atrial volume >34 mL/m^2; E/e' >14; or peak tricuspid regurgitation velocity >2.8 m/s); 2) pleural effusion and/or ≥3 B-lines in at least 1 zone by 8-zone lung ultrasound; 3) dilated inferior vena cava (≥21 mm); 4) abnormal hepatic vein Doppler; 5) abnormal portal vein Doppler (pulsatility index >30%); 6) discontinuous intrarenal vein Doppler; or 7) elevated carbohydrate antigen 125 (≥35 U/mL).

NT-proBNP was analyzed using logistic regression on a continuous scale and at various fixed thresholds to identify the optimal rule-in value balancing specificity and sensitivity. Operating characteristics were assessed across key subgroups: eGFR (<30 vs 30-44 mL/min/1.73 m^2), age (<75 vs ≥75 years), atrial fibrillation (yes vs no), and body mass index (<30 vs ≥30 kg/m^2) using DeLong's method. Additionally, we applied the age- and eGFR-corrected rule-in cutoffs for outpatient settings as recently proposed by the HFA (Heart Failure Association) of the European Society of Cardiology.[4] Statistical analyses were conducted using Stata 18.5 (StataCorp) or R version 4.4.2 (R Project for Statistical Computing). A value of $P < 0.05$ was considered statistically significant.

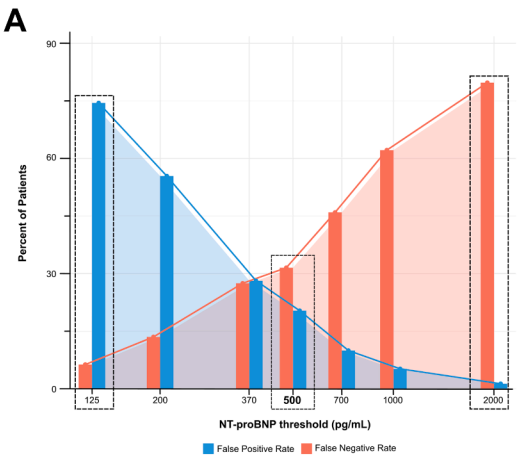
RESULTS

A total of 453 CKD participants were included. The median age was 75 years (Q1-Q3: 67-80 years), 31.1% were women, and 54.5% (n = 247) had a history of diabetes mellitus. A total of 231 patients (51%) were receiving sodium-glucose cotransporter 2 inhibitors at baseline. The median eGFR was 27 mL/min/1.73 m^2 (Q1-Q3: 22-35 mL/min/1.73 m^2), with 60% (n = 272) in CKD stage G4 (eGFR <30 mL/min/1.73 m^2). The median urine albumin-creatinine ratio was 215 mg/g (Q1-Q3: 42-591 mg/g); 37.1% (n = 167) had microalbuminuria, and 42.4% (n = 191) had macroalbuminuria. Among the overall population, the distribution of CKD KDIGO stages was as follows: G3bA1, 40 (8.8%); G3bA2, 73 (16.1%); G3bA3, 68 (15.0%); G4A1, 52 (11.5%); G4A2, 94 (20.8%); and G4A3, 126 (27.8%). The prevalence of HF stages A, B, and C was 41 (9.1%), 237 (53.3%), and 175 (38.6%), respectively. Stage B HF, based on echocardiographic criteria alone (excluding NT-proBNP), was present in 37.3% (169/453) of patients.

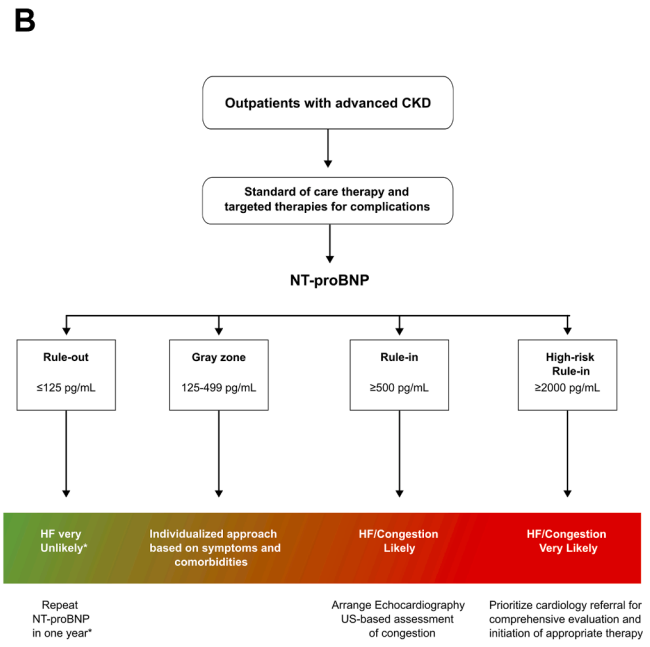
The median NT-proBNP in the overall cohort was 369 pg/mL (Q1-Q3: 178-891 pg/mL), with higher plasma concentrations in patients meeting the noninvasive HF definition (760 pg/mL; Q1-Q3: 325-1,619 pg/mL vs 228 pg/mL; Q1-Q3: 119-406 pg/mL; $P < 0.001$). An NT-proBNP level of ≥500 pg/mL offered balanced diagnostic performance, with 69% sensitivity (95% CI: 62%-75%) and 80% specificity (95% CI: 74%-85%), resulting in a PPV of 76% (95% CI: 70%-82%) and an area under the curve (AUC) of 0.741 (95% CI: 0.700-0.781; $P < 0.001$) (**Figure 1A**). Overall, 199 participants (44%) met this threshold, and its diagnostic performance remained consistent across all subgroups (eGFR, age, atrial fibrillation, body mass index), with no statistically significant differences in AUC (DeLong $P > 0.05$). A total of 195 patients (43%) met the HFA age- and eGFR-adjusted rule-in threshold, yielding 64% sensitivity (95% CI: 57%-70%), 77% specificity (95% CI: 71%-82%), and an AUC of 0.705 (95% CI: 0.663-0.747; $P < 0.001$). The fixed NT-proBNP cutoff of ≥500 pg/mL significantly increased the AUC by 0.036 (from 0.705 to 0.741; DeLong $P = 0.027$) and produced a net reclassification index of 0.071 (95% CI: 0.011-0.133) compared with the HFA-adjusted thresholds.

The HFA NT-proBNP high-risk rule-in threshold of ≥2,000 pg/mL exhibited 99% specificity (95% CI: 96%-100%), with a positive likelihood ratio (LR+) of 15.6 (95% CI: 4.92-49.5) (**Figure 1A**). Among the 48 (10.6%) participants meeting this threshold, 35 patients (73%) had objective evidence of congestion by ultrasound. At the other extreme, 73 patients (16.6%)

FIGURE 1 **Diagnostic Performance of NT-proBNP Thresholds and Proposed Clinical Algorithm in Advanced Chronic Kidney Disease**



	Rule-out <125 pg/mL (n=73)	Rule-in ≥500 pg/mL (n=199)	High-risk Rule-in ≥2000 pg/mL (n=48)
Sensitivity	94% (95% CI: 90-97)	69% (95% CI: 62-75)	20% (95% CI: 15-26)
Specificity	26% (95% CI: 20-32)	80% (95% CI: 74-85)	99% (95% CI: 96-100)
PPV	55% (95% CI: 50-60)	76% (95% CI: 70-82)	94% (95% CI: 83-99)
NPV	81% (95% CI: 70-90)	72% (95% CI: 67-79)	56% (95% CI: 51-61)
LR+	1.26 (95% CI: 1.16-1.37)	3.37 (95% CI: 2.57-4.41)	15.6 (95% CI: 4.92-49.5)
LR-	0.25 (95% CI: 0.14-0.43)	0.40 (95% CI: 0.32-0.49)	0.81 (95% CI: 0.75-0.86)
Accuracy	59% (95% CI: 54-64)	74% (95% CI: 70-78)	60% (95% CI: 56-65)



(A) False positive (FP) and false negative (FN) rates of rule-out and rule-in cutoffs. The blue bars depict the FP rate calculated as FP / (FP + TN), meaning the proportion of patients without adjudicated HF who would be incorrectly classified as positive. The red bars depict the FN rate calculated as FN / (FN + TP), meaning the proportion of patients with adjudicated HF who would be missed. Shaded areas join the tops of successive bars to emphasize the trend of rising FN rate and falling FP rate as the cutoff increases. The sensitivity, specificity, PPV, NPV, LR+, LR−, and accuracy are presented for the rule-out and rule-in thresholds (dashed boxes). (B) Proposed algorithm for the use of NT-proBNP for the diagnosis of HF in outpatients with advanced CKD. *In the absence of compelling clinical signs/symptoms. CKD = chronic kidney disease; HF = heart failure; LR+ = positive likelihood ratio; LR− = negative likelihood ratio; NPV = negative predictive value; NT-proBNP = N-terminal pro-B-type natriuretic peptide; PPV = positive predictive value; TN = true negative; TP = true positive.

had NT-proBNP plasma levels below the HFA-recommended rule-out threshold of 125 pg/mL, demonstrating high diagnostic performance for HF exclusion (94% sensitivity; 95% CI: 90%-97%; and negative likelihood ratio [LR−] of 0.25; 95% CI: 0.14-0.43) (Figure 1A).

DISCUSSION

Our results underscore that a substantial proportion of patients with advanced CKD attending routine nephrology visits have already entered the HF continuum, warranting proactive identification. Therefore, nephrologists should maintain a high index of suspicion for HF because recognizing these patients promptly and initiating interventions to prevent the progression to more advanced HF stages may favorably impact patient outcomes. Our data indicate that a fixed NT-proBNP cutoff of ≥500 pg/mL provides slightly better diagnostic performance for identifying patients with significant cardiac structural/functional abnormalities (associated with HF signs/symptoms or objective congestion) than more complex age- and eGFR-adjusted thresholds.

Interestingly, a similar rule-in NT-proBNP decision threshold was recently derived and validated in ambulatory patients with heart failure with preserved ejection fraction (HFpEF) and chronic exertional dyspnea, using gold-standard diagnostic criteria.[5] Based on our results, we propose integrating structured HF assessment and NT-proBNP-based screening into routine nephrology care (Figure 1B): 1) an NT-proBNP <125 pg/mL is indicative of a low likelihood of significant structural or functional cardiac abnormalities, potentially prompting routine surveillance in the absence of compelling clinical signs/symptoms; 2) a fixed NT-proBNP cutoff of ≥500 pg/mL increases the likelihood of structural and/or functional cardiac abnormalities or the presence of congestion, warranting further diagnostic work-up (ie, echocardiography and ultrasound-based

congestion assessment); and 3) markedly elevated NT-proBNP levels (≥2,000 pg/mL), though less prevalent (10.6% in our cohort), represent a high-risk subgroup given their strong association with objective evidence of congestion and the high specificity (99%) of this threshold. Consequently, these patients may warrant prompt cardiology referral for comprehensive evaluation and initiation of appropriate therapy. However, it is crucial to emphasize that this proposed cutoff strategy serves as an aid to clinical decision-making and should always be integrated with a comprehensive patient assessment, including pretest probability and comorbidities.

STUDY LIMITATIONS. First, our study included only patients with advanced CKD, with a low prevalence of severe obesity, and in whom HFpEF was the predominant HF phenotype. Therefore, our findings are most applicable to this specific population. Second, because the adjudication of HF relied solely on noninvasive assessments rather than invasive hemodynamic confirmation, our evaluation of NT-proBNP performance could be subject to circular bias, particularly when assessing its ability to exclude HF. Finally, the absence of external validation limits the robustness and generalizability of our findings. Consequently, the proposed thresholds require further confirmation before widespread clinical application.

CONCLUSIONS

Recognizing that most advanced CKD patients are already in stage B or C HF and implementing NT-proBNP-guided algorithms in nephrology clinics could improve HF underdiagnosis in CKD, lead to timelier therapy, and potentially mitigate the excessive HF morbidity and mortality observed in this vulnerable population.

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