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Neutrophil Percentage-to-Albumin Ratio as a Novel Predictor of Diuretic Resistance and Mortality in Patients with Heart Failure with Preserved Ejection Fraction

ABSTRACT

Background: Heart failure with preserved ejection fraction (HFpEF) is increasingly recognized as a systemic inflammatory and metabolic disorder. Diuretic resistance remains a major therapeutic challenge in this population. The neutrophil percentage-to-albumin ratio (NPAR), a novel marker of systemic inflammation, may serve as a predictor of diuretic resistance and adverse outcomes in HFpEF.

Methods: This retrospective cohort study included 1487 HFpEF patients treated between January 2017 and August 2022. Patients were divided into 2 groups: those with and without diuretic resistance. Clinical, laboratory, and echocardiographic parameters were compared between groups. Receiver-operating characteristic (ROC) analysis, logistic regression, and Kaplan–Meier survival analyses were used to determine predictive and prognostic factors.

Results: Patients with diuretic resistance exhibited significantly higher NPAR values, H_2FPEF scores, NT-proBNP levels, and echocardiographic indices of diastolic dysfunction. ROC analysis identified an NPAR cut-off of 13.98 for predicting diuretic resistance (AUC = 0.892, 95% CI: 0.741-0.993, $P < .01$). Multiple Cox's proportional hazard regression analysis revealed that NPAR, hs-C-reactive protein, sodium, NT-proBNP, left atrial volume index, and E/e′ were independent predictors of diuretic resistance. Kaplan–Meier analysis demonstrated increased mid-term mortality in patients with NPAR > 13.98 (log-rank $P < .001$). Elevated NPAR independently predicted mortality in the diuretic-resistant HFpEF subgroup (OR = 1.95, 95% CI: 1.80-2.22, $P < .001$).

Conclusion: NPAR is a simple and accessible inflammatory biomarker that independently predicts diuretic resistance and mortality in HFpEF. The findings underscore the role of systemic inflammation in HFpEF pathophysiology and highlight NPAR as a potential tool for early risk stratification and therapeutic decision-making.

Keywords: Diuretic resistance, heart failure with preserved ejection fraction, neutrophil-to-albumin ratio, systemic inflammation

ORIGINAL INVESTIGATION

INTRODUCTION

Heart failure (HF) is a common clinical syndrome with rising prevalence, particularly in older adults.[1] In contemporary cohorts, heart failure with preserved ejection fraction (HFpEF) constitutes a substantial proportion of HF presentations[2] and is diagnosed according to current European Society of Cardiology (ESC) criteria.[3]

Congestion is the leading cause of hospitalization in acute decompensated HF, and diuretics remain the cornerstone of symptomatic relief.[4] However, epidemiological studies indicate that diuretic resistance develops in approximately 20-35% of HF patients.[5] Although HFpEF has historically been considered to have a better prognosis than HFrEF, most observational studies suggest that this difference is not significant.[6]

Beyond hemodynamic impairment, HFpEF is increasingly viewed as a systemic inflammatory state in which comorbidity-driven microvascular endothelial inflammation contributes to myocardial dysfunction and progression of

Sefa Erdi Ömür
Kayıhan Karaman
Çağrı Zorlu
Gülşen Genç Tapar

Department of Cardiology, Tokat Gaziosmanpaşa University, Tokat, Türkiye

Corresponding author:
Sefa Erdi Ömür
✉ sefaerdi61@gmail.com

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symptoms. In line with this concept, readily available hemogram-derived inflammatory indices—such as neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio—have been proposed as practical markers of subclinical inflammation and have shown prognostic value in HF.[7,8]

More recently, the neutrophil percentage-to-albumin ratio (NPAR) has emerged as a simple composite biomarker integrating an inflammatory component and a negative acute-phase reactant and has been associated with adverse outcomes across cardiovascular conditions.[9-12] However, data regarding the value of NPAR for identifying diuretic resistance and related prognosis specifically in HFpEF are limited. Therefore, this study was designed to investigate the relationship between systemic inflammation and diuretic resistance in HFpEF using NPAR as an inflammatory marker.

METHODS

A total of 1927 HFpEF patients receiving regular HF maintenance treatment in the cardiology department of the local cardiology hospital between January 2017 and August 2022 were included in the study. A total of 440 patients were excluded from the study due to missing data (Flowchart, Supplementary Material). This was a single-center retrospective cohort study conducted in the cardiology department of a tertiary referral cardiology hospital. The study complies with the principles outlined in the Declaration of Helsinki. No funding was received for the study from any institution or organization. The study was approved by the Ethics Committee of the local university hospital (25-MOBAEK-144, Date: 22.04.2025). The study did not receive financial support (no funding) from any institution or organization. Artificial intelligence–supported technologies [such as Large Language Models (LLM), chatbots, or image generators] were not used in the production of the study.

HIGHLIGHTS

- The neutrophil percentage-to-albumin ratio (NPAR) was significantly higher in heart failure with preserved ejection fraction (HFpEF) patients with diuretic resistance, indicating a strong link between systemic inflammation and poor diuretic response.
- The NPAR ≥13.98 predicted diuretic resistance with 86% sensitivity and 85% specificity (AUC = 0.892, $P < .01$), demonstrating its potential as a reliable clinical marker.
- Elevated NPAR levels were independently associated with increased all-cause mortality in HFpEF, even after adjustment for NT-proBNP, hs-CRP, and echocardiographic parameters.
- Multiple Cox's proportional hazard regression analysis confirmed that NPAR remained an independent predictor of mid-term mortality (HR = 1.62, $P < .001$, 95% CI = 1.31-1.94).
- The NPAR may serve as a simple, inexpensive, and accessible biomarker for identifying high-risk HFpEF patients and guiding early management strategies.

Patients were included in the study by searching the local hospital system database. Data were determined from institutional electronic health records, including laboratory results (serum sodium, creatinine/estimated glomerular filtration rate (eGFR), spot urine sodium), medication administration records (loop diuretic dose increases, metolazone use, IV inotropes), and inpatient clinical documentation. For each potentially eligible case, the diagnosis of HFpEF was confirmed by reviewing echocardiography reports and relevant clinical data. Patients with missing baseline variables were excluded as shown in the study flowchart. The inclusion period corresponded to the entire database search interval (January 2017-August 2022). The authors included consecutive adult patients hospitalized for worsening HF (index hospitalization) who met diagnostic criteria for HFpEF (LVEF ≥50%) according to contemporary ESC (3). Outpatient clinic visits were not used as an index event; outpatient data were considered only for baseline history and for routine post-discharge follow-up documentation when available. Patients with HFpEF were classified into diuretic-resistant and non–diuretic-resistant groups based on predefined criteria, and all-cause mortality was assessed retrospectively from existing records. Diuretic resistance was defined as the presence of one or more (≥1) of the following during the index hospitalization: hyponatremia, requirement to increase the daily furosemide-equivalent dose to >160 mg/day and/or add metolazone, spot urine sodium <50 to 70 mmol/L measured after diuretic administration (when available), worsening renal function (creatinine increase ≥0.3 mg/dL within 48-72 h or ≥25% from baseline), and need for IV inotropic therapy.[13,14]

Acute infection or sepsis, pulmonary embolism, severe valve disease (moderate mitral stenosis and all other severe valve diseases and prosthetic valve disease), malignancy, coagulation disorder, patients under 18 years of age, acute or chronic stroke, storage diseases (glycogen, lipid, lysosomal, etc.), acute kidney disease, mechanical valve, end-stage renal disease, severe anemia, patients with recent acute coronary syndrome (first 6 months) were excluded from the study.

Laboratory and Demographic Examination

All blood samples were obtained from peripheral venous blood after patients were hospitalized with worsening HF. Lipid panel, fasting plasma glucose, creatine kinase myocardial band (CK-MB), troponin-I, NT-proBNP (ng/mL), hs-C-reactive protein (CRP), and other routine parameters were obtained from the blood samples. Complete blood count (CBC) was evaluated with an automatic blood cell counter (Coulter LH 780 Hematology Analyzer, Beckman Coulter Corp, Hileh, Florida, USA). Patients with fasting plasma glucose level >125 mg/dL, HbA1c level >6.5%, or using antidiabetic drugs (oral/insulin) were considered as diabetes mellitus (DM) patients. Patients with low-density lipoprotein cholesterol (LDL-C) level above 100 mg/dL or using antilipidemic drugs were considered as hyperlipidemia (HL) patients. Use of antihypertensive drugs or systolic and diastolic blood pressures above 140-90 mm Hg were considered as hypertension (HT). Patients who had smoked for the last 6 months were considered as smokers.

Echocardiographic Evaluation

Echocardiographic evaluations were performed in the ECHO unit of the center with the Vivid S5 ECHO device (General Electric, Milwaukee, WI, USA) using a 2.5-3.5 MHz transducer in the left decubitus position for all participants. All Doppler ECHO and Tissue Doppler Imaging (TDI) ECHO measurements were performed during normal breathing. Data obtained with 2-dimensional, color Doppler, continuous wave (CW)/pulsed wave (PW) Doppler ECHO were examined and recorded by 3 experienced echocardiographers who were unaware of the participants. The left ventricular ejection fractions (LVEF) of all participants were calculated using the modified Simpson's method.

From the parasternal long axis view; left atrium (LA), left ventricular end diastolic diameter (LVDD), left ventricular end systolic diameter (LVSD), left ventricular posterior wall thickness (LVPWT), interventricular septum in diastole (IVSD) measurements were performed. LA volume was measured by planimetrically drawing the left atrium borders from standard apical 2- and 4-chamber views at the end of systole. Left atrium (LA) volume was divided by body surface area to obtain left atrial volume index (LAVI). Estimated systolic pulmonary artery pressure (sPAP) was calculated based on the tricuspid regurgitation pressure gradient calculated from the peak tricuspid regurgitation flow velocity using the Bernoulli equation. Transmitral early diastolic flow velocity (E) was measured in the apical 4-chamber view by pulsed-wave Doppler with the sample volume placed at the tips of the mitral leaflets. Early diastolic mitral annular velocity (e′) was assessed using TDI in the apical 4-chamber view, positioning the sample volume at the septal or lateral mitral annulus. The E/e′ ratio was calculated as an estimate of left ventricular filling pressure.

Follow-Up

Patients were followed for a mean duration of 8.3 ± 2.1 months. Two investigators abstracted baseline characteristics and in-hospital endpoints from electronic records using a standardized data collection form. Follow-up duration was calculated from the date of index admission/discharge. Post-discharge information at approximately 1, 3, 6, and 12 months was ascertained retrospectively from documentation available in the electronic medical record, including routine outpatient clinic visits and telephone contacts performed as part of standard clinical care. Mortality status and dates were obtained from institutional records (and linked registries when available). No study-driven follow-up contact was performed. All clinical endpoints were independently adjudicated in a blinded manner by 2 members of the event adjudication committee.

Statistical Analysis

The data obtained from the study were evaluated with SPSS 25.0 (SPSS, Inc., Chicago, IL, USA) program. For statistical significance, $P \leq .05$ was taken as the test. Normality of continuous variables was assessed using the Kolmogorov–Smirnov test. Continuous variables with normal distribution were summarized as mean ± standard deviation and compared with *t*-test. Those without normal distribution were presented as median (interquartile range) and compared with Mann-Whitney U-test. Categorical variables were presented as frequency (percentage) and compared using χ^2 test and Fisher's exact tests. The best cut-off values of NPAR were calculated using the ROC curve analysis. The best cut-off value obtained from the ROC curve of NPAR was taken as the cut-off value for categorizing NPAR values as high and low. Univariate logistic regression analysis was performed to determine the predictors of mortality in HFpEF patients with diuretic resistance. Variables that were significant in the univariate logistic regression analysis ($P < .05$) were included in the Multiple Cox's regression analysis. The results of the logistic analysis were presented as Odds Ratio (OR) and 95% CI. Kaplan-Meier survival curve was used to examine the difference in event-free survival rates between the groups and statistical significance was determined using the log-rank test. The proportional hazards assumption was assessed using Schoenfeld residuals and was not violated. A Multiple Cox's proportional hazard regression analysis was performed to assess the independent prognostic significance of the NPAR on mid-term mortality. Time to event was defined from the index admission date until death or last follow-up, and survivors were censored at last contact. A modeling system was constructed for this purpose. The modeling was constructed in 3 separate hierarchical steps to allow parsimonious adjustment for potential confounders. Model 1 included demographic variables (age and sex). Model 2 further adjusted for major prognostic comorbidities and laboratory parameters, including HT, DM, estimated glomerular filtration rate (eGFR), serum sodium, serum albumin, and atrial fibrillation. Model 3, the fully adjusted model, included cardiac and inflammatory markers (NT-proBNP, hs-CRP, LAVI, E/e′ ratio, sPAP, H_2FPEF score, and diuretic resistance status). NPAR was analyzed both as a continuous variable and as a dichotomous variable using the receiver operating characteristic (ROC)-derived cutoff of 13.98. Hazard ratios (HR) and 95% cCI were calculated. Nonlinear associations between NPAR and mortality risk were further explored using restricted cubic spline analysis. A 2-sided $P < .05$ was considered statistically significant.

RESULTS

During the study period (January 2017-August 2022), 1927 HFpEF patients were screened. After excluding 440 patients due to missing data, 1487 patients constituted the final study cohort. Among these, 248 patients met the definition of diuretic resistance, whereas 1239 did not. Basic demographic, clinical, and laboratory characteristics, echocardiographic results, and medications used by the patients included in the study are detailed in Table 1. H_2FPEF score and NPAR were found to be statistically higher in the diuretic resistant group. Routine blood tests; neutrophil percentage, ALT, AST, hs-CRP, troponin, NT-proBNP; echocardiographic parameters; sPAP, LVDD, LA, LAVI, LVPWT, IVSD, E/e′, and medication; carbonic anhydrase inhibitors use were found to be significantly higher in the diuretic resistant group compared to the other group. Albumin, sodium level, and LVEF were significantly higher in the non-diuretic resistant group compared to the other group.

Table 1. Baseline Demographic, Clinical, Laboratory, and Echocardiographic Characteristics of HFpEF Patients According to Diuretic Resistance Status

Variables	Diuretic Resistant (n = 248)	No Diuretic Resistant (n = 1239)	*P*
Age (mean ± SD)	62.34 ± 11.30	61.91 ± 10.87	.552
Gender (female, n%)	144 (58.06)	720 (58.11)	.794
BMI (mean ± SD)	33.25 ± 4.80	31.29±3.44	.053
DM n (%)	63 (25.40)	312 (25.18)	.530
HT n (%)	148 (59.67)	743 (59.96)	.188
HL n (%)	61 (24.5)	310 (25.02)	.804
COPD n (%)	37 (14.9)	165 (13.31)	.637
AF n (%)	122 (49.19)	609 (49.15)	.997
Current Smoker n (%)	38 (15.32)	186 (15.01)	.883
Previous myocardial infarction n (%)	92 (37.09)	459 (37.04)	.795
H_2FPEF score	7.01 ± 0.88	6.05 ± 0.91	.035
NPAR	16.83 ± 2.08	14.92 ± 2.13	< .001
Hematological results			
Creatinine (mg/dL)	1.35 ± 0.71	1.33 ± 0.69	.559
eGFR (mL/dk/1.73 m^2)	58.41 ± 12.47	59.18 ± 12.09	.473
Hemoglobin (g/dL)	10.30 ± 1.33	10.82 ± 1.20	.704
Hematocrit value	35.52 ± 9.57	35.79 ± 8.93	.507
Platelet (X10^3/μL)	258.36 ± 12.33	259.51 ± 11.34	.768
Neutrophil percentage (%)	68.66 ± 10.52	55.41 ± 10.79	< .001
TSH (ng/dL)	2.13 ± 0.51	2.09 ± 0.48	.617
T4 (ng/dL)	1.55 ± 0.21	1.59 ± 0.32	.580
Albumin (g/dL)	2.10 ± 0.92	4.33 ± 0.91	< .001
Total cholesterol (mg/dL)	219.17 ± 32.17	222.89 ± 30.71	.594
LDL cholesterol(mg/dL)	122.31 ± 20.12	125.03 ± 19.94	.761
ALT (U/L)	62.31 ± 10.71	55.13 ± 9.83	< .001
AST (U/L)	51.39 ± 9.71	45.12 ± 8.09	< .001
Sodium (mmol/L)	128.31 ± 13.70	134.88 ± 12.73	< .001
Potassium(mmol/L)	4.92 ± 1.37	4.53 ± 1.06	.052
Magnesium (mg/dL)	2.14 ± 0.78	2.11 ± 0.66	.329
hs-CRP (mg/L)	35.57 ± 12.70	28.32 ± 10.34	< .001
Troponin (ng/mL)	62.72 ± 13.61	42.52 ± 11.13	< .001
NT-proBNP (ng/mL)	2471 ± 357.46	1539 ± 210.41	< .001
Echocardiographic findings			
LVEF (%)	53.14 ± 2.17	55.22 ± 3.41	.031
LVDD (mm)	51.26 ± 2.36	50.51 ± 2.29	.018
LVSD (mm)	36.47 ± 3.28	35.51 ± 2.79	.059
LA size (mm)	5.29 ± 1.06	4.52 ± 0.41	< .001
LAVI (ml/m^2)	48.91 ± 2.13	46.81 ± 1.85	< .001
LVPWT (mm)	12.21 ± 1.31	11.13 ± 0.84	.029
IVSD (mm)	13.09 ± 1.11	11.29 ± 0.79	.017
E/e'	14.52 ± 1.37	13.05 ± 1.28	.022
sPAP (mm Hg)	45.21 ± 3.70	42.32 ± 2.89	< .001
Medication			
ACE, ARB n (%)	138 (55.64)	682 (55.04)	.664
B blocker n (%)	152 (61.29)	756 (61.01)	.537
Furosemid n (%)	232 (93.54)	1155 (93.22)	.834
Spironolactone/eplerenone n (%)	103 (41.53)	508 (41.00)	.758
Thiazides n (%)	130 (52.41)	645 (52.05)	.349

(*Continued*)

Table 1. Baseline Demographic, Clinical, Laboratory, and Echocardiographic Characteristics of HFpEF Patients According to Diuretic Resistance Status (*Continued*)

Variables	Diuretic Resistant (n = 248)	No Diuretic Resistant (n = 1239)	*P*
Thiazide-like agents n (%)	28 (11.29)	138 (11.13)	.618
Carbonic anhydrase inhibitors n (%)	155 (62.50)	21 (1.69)	< .001
SGLT2 inhibitors n (%)	54 (21.77)	262 (21.14)	.553
Anticoagulant n (%)	126 (50.80)	622 (50.20)	.827
Digoksin n (%)	49 (19.75)	237 (19.12)	.223
ASA n (%)	40 (16.80)	201 (16.22)	.307
Ultrafiltration therapy, n (%)	148 (59.67)	39 (3.14)	< .001
IV inotropic therapy, n (%)	152 (61.29)	35 (2.82)	< .001

Values are presented as mean ± SD for continuous variables and n (%) for categorical variables. Percentages are column percentages.
ACE, angiotensin-converting enzyme; ALT, alanine aminotransferase; ARB, angiotensin receptor blockers; ASA, acetylsalicylic acid; AST, aspartate aminotransferase; BMI, body mass index; BUN, blood urea nitrogen; CRP, C-reactive protein; dL, deciliter; dk, minute; DM, diabetes mellitus; g, gram; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; HL, hyperlipidemia; HPL, hyperlipidemia; HT, hypertension; IVSD, interventricular septal diameter; LA, left atrium; LAVI, left atrial volume index; LDL, low-density lipoprotein; LVDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; LVPWT, left ventricular posterior wall thickness; LVSD, left ventricular end-systolic diameter; m, meter; mg, milligram; mmol, millimole; mm, millimeter; mm Hg, millimeters of mercury; mL, milliliter; µL, microliter; NPAR, neutrophil percentage-to-albumin ratio; NT-proBNP, N-terminal pro–B-type natriuretic peptide; SD, standard deviation; SGLT2, sodium-glucose cotransporter-2; TSH, thyroid-stimulating hormone; U, unit; WBC, white blood cell count.

In ROC analysis, the cut-off value of NPAR score for diuretic resistance in HFpEF was determined as 13.98 with 86% sensitivity and 85% specificity (AUC = 0.892, 95% CI = 0.741–0.993, $P < .01$) (Figure 1). Multiple Cox's regression analysis revealed that H_2FPEF score, LA size, LAVI, E/e', Sodium, hs-CRP, NT-proBNP, and NPAR were independent potential predictors of HFpEF diuretic resistance (Table 2).

Kaplan–Meier cumulative survival curves showed that the risk of mortality was increased in patients with HEpEF and NPAR > 13.98 compared to patients with NPAR < 13.98 (log-rank test: $P < .001$) (Figure 2). Multiple Cox's proportional hazard regression analysis for NPAR levels associated with mid-term mortality is presented in Table 3. NPAR was found to be an independent predictor of mid-term mortality in HFpEF patients with diuretic resistance [Odds ratio (OR) = 1.952, $P < .001$, 95% CI: 1.803-2.224].

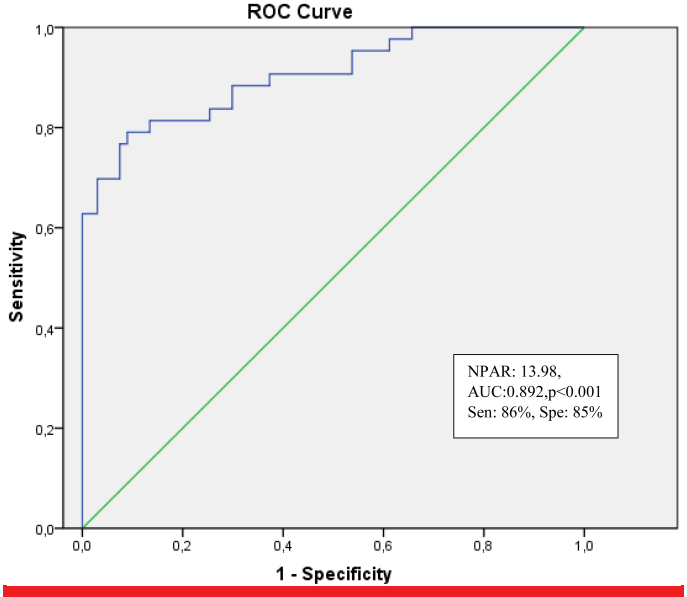

Figure 1. ROC curve of NPAR in predicting diuretic resistance in patients with HF

Multiple Cox's regression analysis was conducted to determine the independent predictors of all-cause mortality in patients with HFpEF (Table 4). In univariate analysis, higher NPAR levels were significantly associated with increased risk of mortality (HR = 1.93, $P < .001$, 95% CI: 1.68-2.20). After adjusting for demographic and clinical parameters in Model 2, the association remained robust (HR = 1.71, $P < .001$, 95% CI: 1.45-2.01). In the fully adjusted Model 3, which incorporated echocardiographic and laboratory parameters, NPAR persisted as an independent predictor of mortality (HR = 1.62, $P < .001$, 95% CI: 1.31-1.94). Among other variables, higher NT-proBNP, elevated hs-CRP, increased LAVI, higher E/e' ratio, and presence of diuretic resistance were also significantly associated with increased mortality. Conversely, higher serum sodium and albumin levels were found to be protective factors. This Figure 3 demonstrates the adjusted hazard ratios and 95% confidence intervals for the variables included in the Multiple Cox's proportional hazard regression analysis model.

Among the 248 patients classified as diuretic-resistant, the frequency of each component criterion is summarized in Table 5. The most common components were hyponatremia (Na <135 mmol/L; 92/248, 37.1%) and loop diuretic escalation to >160 mg/day furosemide-equivalent (71/248, 28.6%), whereas post-diuretic spot urine sodium was available in 120 patients.

DISCUSSION

In this study, it was aimed to demonstrate the association between diuretic-resistance and systemic inflammation in patients with HFpEF using NPAR. NPAR was found to be significantly higher in the group with diuretic-resistance. The findings suggest that the risk of developing diuretic-resistance increases in parallel with rising NPAR levels. Therefore, the authors conclude that heightened systemic

Table 2. Univariate and Multiple Cox Regression to Identify Independent Predictors in Heart Failure Patients

Variables	Univariate Analysis OR (95% CI)	*P*	Multiple Analysis OR (95% CI)	*P*
H_2FPEF score	1.128 (1.012-1.259)	.030	1.104 (1.018-1.231)	.021
LVEF (%)	0.879 (0.759-0.987)	.034	0.861 (0.751-0.963)	.041
LVDD (mm)	1.089 (1.012-1.178)	.024	1.057 (1.009-1.132)	.038
LA size (mm)	1.351 (1.141-1.451)	< .001	1.228 (1.097-1.341)	.026
LAVI (mL/m^2)	1.293 (1.112-1.412)	< .001	1.182 (1.045-1.263)	.029
E/e′	1.187 (1.092-1.341)	.018	1.123 (1.044-1.219)	.036
sPAP (mm Hg)	1.271 (1.149-1.418)	< .001	1.134 (1.052-1.301)	.020
Sodium (mmol/L)	1.257 (1.097-1.340)	< .001	1.127 (1.043-1.249)	.018
hs-CRP (mg/L)	1.371 (1.207-1.501)	< .001	1.201 (1.081-1.327)	.042
NT-proBNP (ng/mL)	1.288 (1.121-1.396)	< .001	1.158 (1.043-1.271)	.025
NPAR	2.544 (1.982-3.216)	< .001	2.236 (1.812-2.962)	< .001
ALT (U/L)	1.021 (0.971-1.064)	.338	1.015 (0.956-1.078)	.462
AST (U/L)	1.028 (0.982-1.071)	.212	1.019 (0.962-1.082)	.295
Troponin (L)	1.094 (0.918-1.281)	.286	1.068 (0.911-1.245)	.341
IVSD (mm)	1.048 (0.974-1.123)	.214	1.029 (0.948-1.117)	.311
LVPWT (mm)	1.052 (0.991-1.141)	.072	1.036 (0.961-1.124)	.198
Hemoglobin (g/dL)	0.973 (0.927-1.018)	.216	0.982 (0.931-1.027)	.283
Age (years)	1.014 (0.994-1.036)	.164	1.008 (0.981-1.032)	.372

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CI, confidence interval; CRP, C-reactive protein; IVSD, interventricular septal diameter; LA, left atrial; LAVI, left atrial volume index; LVDD, left ventricular diastolic diameter; LVEF, left ventricular ejection fraction; LVPWT, left ventricular posterior wall thickness; NPAR, neutrophil percentage-to-albumin ratio; OR, odds ratio; sPAP, systolic pulmonary artery pressure.

inflammation may pave the way for the development of diuretic-resistance.

Beyond its relationship with diuretic resistance, the extended analysis revealed that elevated NPAR independently predicted all-cause mortality in patients with HFpEF. Multiple Cox's proportional hazard regression analysis modeling demonstrated that NPAR remained a strong and independent prognostic factor even after adjusting for age, comorbidities, NT-proBNP, hs-CRP, echocardiographic parameters (LAVI, E/e′, sPAP), and diuretic resistance status. This indicates that the systemic inflammatory burden quantified by NPAR not only contributes to treatment resistance but also carries mid-term prognostic significance. Importantly, NPAR values above the identified cut-off (13.98) were associated with almost a 2-fold increase in mortality risk, underscoring its clinical relevance in the risk stratification of HFpEF.

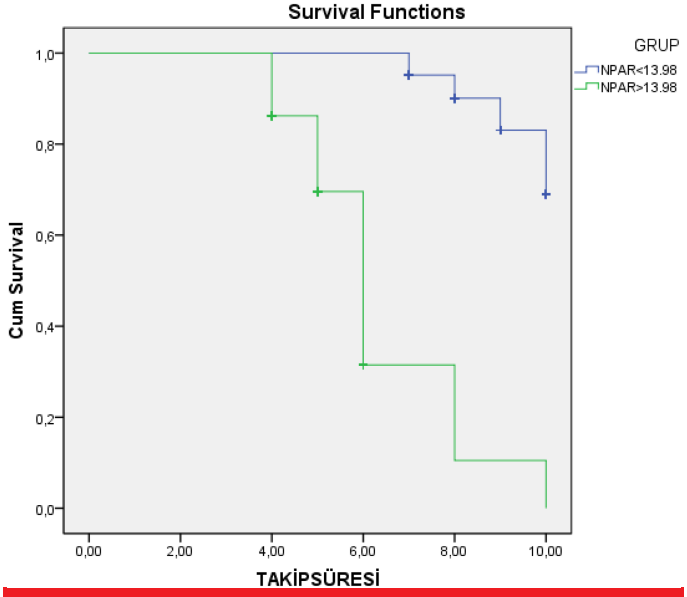

Figure 2. Kaplan–Meier survival curve analysis showing the association between NAPR and mortality in patients with diuretic resistance

HFpEF accounts for more than half of all HF cases in individuals aged over 65 years.[15] Comorbid conditions such as advanced age, HT, DM, obesity, and atrial fibrillation contribute to the pathophysiology of HFpEF by promoting low-grade systemic inflammation.[16,17] Consequently, HFpEF is now regarded not only as a disease characterized by diastolic dysfunction but also as a multisystem syndrome underpinned by inflammation.[17]

Systemic inflammation plays an increasingly recognized role in the pathophysiology of both HFrEF and HFpEF. Neutrophils, one of the key cellular markers of inflammation,

Table 3. Hazard Ratios Based on Cox Regression Models to Estimate the Effects of NPAR, NT-proBNP, E/e′, and LA Size on Mid-Term Mortality in Patients with HFpEF and Diuretic Resistance

Variables	Hazard Ratio (95% CI)	*P*
NPAR	1.952 (1.403-2.224)	< .001
NT-proBNP	1.213 (1.052-1.552)	.008
E/e′	1.139 (0.893-1.213)	.117
LA size (mm)	1.104 (0.937-1.217)	.204

NPAR, neutrophil percentage-to-albumin ratio; NT-proBNP, N-terminal pro–B-type natriuretic peptide; LA, left atrium.

Table 4. Multiple Cox Proportional Hazards Models for All-Cause Mortality

Variables	Model 1 HR (95% CI)	*P*	Model 2 HR (95% CI)	*P*	Model 3 HR (95% CI)	*P*
NPAR (per 1 unit)	1.93 (1.68-2.20)	< .001	1.71 (1.45-2.01)	< .001	1.62 (1.31-1.94)	< .001
Age (per year)	1.03 (1.01-1.06)	.004	1.02 (1.00-1.04)	.021	1.01 (0.99-1.03)	.162
Male sex	1.12 (0.82-1.54)	.459	1.07 (0.79-1.47)	.639	1.09 (0.78-1.52)	.612
Hypertension	—	—	1.18 (0.87-1.59)	.283	1.11 (0.80-1.54)	.537
Diabetes mellitus	—	—	1.34 (1.02-1.78)	.039	1.29 (0.97-1.73)	.081
Sodium (per 1 mmol/L)	—	—	0.96 (0.94-0.98)	.001	0.97 (0.95-0.99)	.004
Albumin (per 1 g/dL)	—	—	0.81 (0.69-0.95)	.009	0.84 (0.72-0.98)	.026
NT-proBNP (per 100 ng/mL)	—	—	—	—	1.12 (1.04-1.21)	.002
hs-CRP (per mg/L)	—	—	—	—	1.05 (1.02—-1.09)	.003
LAVI (per mL/m^2)	—	—	—	—	1.03 (1.01-1.05)	.018
E/e′ ratio (per unit)	—	—	—	—	1.04 (1.01-1.07)	.012
sPAP (per mm Hg)	—	—	—	—	1.02 (1.00-1.04)	.046
H_2FPEF score	—	—	—	—	1.09 (1.02-1.16)	.008
Diuretic resistance	—	—	—	—	1.78 (1.21-2.61)	.004

CI, Confidence interval; CRP, C-reactive protein; E/e′, mitral inflow to annular velocity ratio; HR, Hazard ratio; LAVI, Left atrial volume index; sPAP, systolic pulmonary artery pressure.

are associated with coronary artery disease, HF, and stroke. They contribute to myocardial injury through proteolytic enzymes such as elastase and myeloperoxidase.[18-20] Neutrophil activation promotes the release of proinflammatory cytokines including CRP, TNF-α, IL-1, and IL-6, leading to impaired cardiac function and increased cardiovascular mortality.[21,22]

Our results support this mechanistic link, demonstrating that higher hs-CRP and NT-proBNP levels, alongside elevated NPAR, were significant predictors of mortality. This finding aligns with previous evidence that inflammatory and neurohormonal activation synergistically contribute to disease progression and poor outcomes in HFpEF. The inclusion of echocardiographic parameters such as LAVI and E/e′ in the model further confirms that both structural and inflammatory factors interact to influence mid-term prognosis.

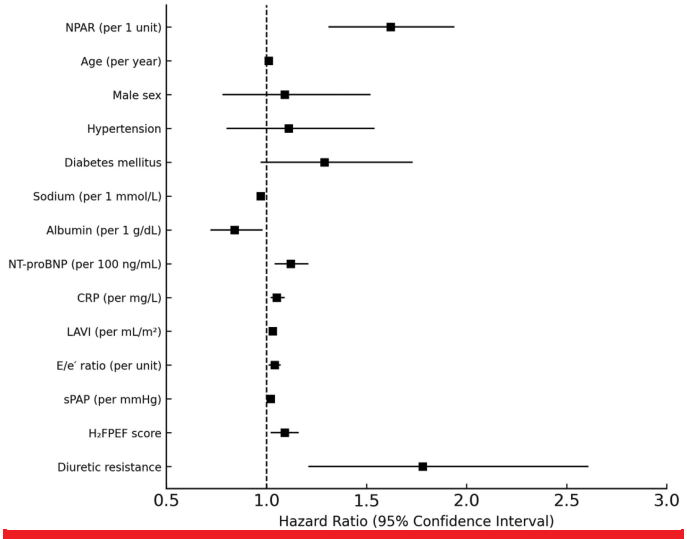

Figure 3. Forest plot of adjusted hazard ratios (HR) and 95% CI for all-cause mortality in HFpEF patients

Diuretic-resistance in HFrEF is a multifactorial process that often reflects disease progression. Previous studies have shown that a high diuretic requirement due to diuretic-resistance is associated with increased mortality and sudden death in HFrEF patients.[23,24] Impaired renal perfusion, secondary to reduced cardiac output and elevated central venous pressure, diminishes the pressure gradient across the kidneys and limits natriuresis. Additionally, activation of the renin—angiotensin—aldosterone system (RAAS) and the sympathetic nervous system enhances sodium reabsorption in the distal tubules, reducing diuretic efficacy and necessitating dose escalation.[25-27] Although diuretic resistance has been extensively described in HFrEF, it is also highly relevant in HFpEF, where congestion-driven admissions are common and impaired natriuresis may be observed despite high-dose loop diuretics, particularly in patients with concomitant chronic kidney disease. Contemporary reports indicate that resistance to high-dose loop diuretics can be frequent in hospitalized HFpEF populations, underscoring the need for practical markers that capture treatment non-response early during decongestion.[28]

While many causes can explain diuretic resistance in HFrEF patients, it has been reported that comorbid conditions play a role in HFpEF patients.[25] In obesity and metabolic syndrome, adipokines released from adipose tissue trigger proinflammatory cytokine production, while hypertension brings about vascular inflammation and decreased nitric oxide bioavailability. In diabetes, advanced glycation end products initiate vascular and myocardial inflammatory processes.[16,17] For these reasons, HFpEF has recently begun to be considered a systemic inflammatory and metabolic syndrome.[29]

Many studies have shown an increased proinflammatory state in patients with HFpEF.[17] Some inflammatory markers have been suggested to have predictive and prognostic value for HF. Pro-inflammatory cytokines such as TNF-α, IL-1, and IL-6 released from inflammatory cells activate inflammatory

Table 5. Components of the Diuretic-Resistance Definition Among Patients Classified as Diuretic-Resistant (n = 248)

Component Criterion (Index Hospitalization)	Data Source (Retrospective Ascertainment)	n / 248	%
Hyponatremia (Na <135 mmol/L)	Lab (serum sodium)	92 / 248	37.1
Loop diuretic escalation (>160 mg/day furosemide)	Medication orders + MAR	71 / 248	28.6
Additional metolazone use	Medication orders + MAR	54 / 248	21.8
Low post-diuretic spot urine sodium (<50 to 70 mmol/L)*	Lab (spot urine sodium after diuretic)	33 / 120	27.5
Worsening renal function (Cr ↑ ≥0.3 mg/dL within 48-72 hour)	Serial creatinine/eGFR	65 / 248	26.2
Need for IV inotropic therapy	MAR/ICU-ward orders	18 / 248	7.3

*Due to the retrospective cohort study design, spot urine sodium was not available in all patients; percentages for this component were calculated among patients with available measurements (n = 120).
Diuretic resistance was defined as the presence of ≥1 component criterion.
eGFR, estimated glomerular filtration rate; ICU, intensive care unit; MAR, Medication Administration Record.

signaling pathways in both cardiomyocytes and endothelium. This process leads to cellular apoptosis, fibrosis, and ventricular remodeling.[18,21] Progressive inflammatory activation results in ventricular diastolic dysfunction and contributes to the progression of HFpEF. Thus, in HFpEF, inflammation plays a central role in the disease's underlying pathophysiology and diuretic resistance by causing endothelial dysfunction.[29]

Proinflammatory cytokines (TNF-α, IL-1, IL-6) can impair renal microcirculation, reducing glomerular filtration, increasing vascular permeability, and triggering distal tubular sodium reabsorption. These processes weaken the natriuretic response and contribute to diuretic resistance.[30] Inflammation also triggers neurohormonal activation, leading to increased RAAS and sympathetic system activity, causing renal vasoconstriction and sodium retention. Therefore, inflammation can be considered an essential pathophysiological link that exacerbates diuretic resistance in HFpEF.[25,27] From a clinical standpoint, early assessment of natriuretic response using urinary sodium has emerged as a pragmatic approach to detect inadequate diuretic response, and low post-diuretic urinary sodium has been associated with poorer decongestion and more intensive diuretic regimens in acute HF. These observations align with the concept that inflammation and endothelial dysfunction—central features of HFpEF—may impair renal microcirculation and sodium handling, thereby contributing to diuretic resistance and worse outcomes.[31] Taken together, recent evidence supporting an inflammatory/oxidative HFpEF phenotype suggests that systemic oxidative stress may also contribute to impaired natriuretic response and predispose to diuretic resistance; accordingly, antioxidant protection and signaling homeostasis have been reported to be altered in HFpEF, supporting the biological plausibility of the findings.[32]

Serum albumin (SA) has anti-inflammatory and antioxidant activity.[26] SA inhibits the release of proinflammatory cytokines by regulating signaling systems between inflammatory cells, such as neutrophils. Studies have shown that low serum albumin levels are independently associated with both short- and long-term mortality in patients with acute coronary syndrome and myocardial infarction.[30,33,34]

The neutrophil-to-albumin ratio has recently been defined as a new biomarker reflecting systemic inflammatory load.[27] The neutrophil percentage indicates acute inflammatory response and immune activation, while serum albumin level is a negative acute phase reactant reflecting inflammation.[30,33] Combining these 2 parameters more strongly represents the severity of inflammatory processes.[27,33] Elevated NPAR indicates predominant inflammatory activity and insufficient albumin reserves, thus signifying a worsened prognosis. Clinical studies have shown that high NPAR levels are closely associated with the prognosis of HF, coronary artery disease, atrial fibrillation, severe sepsis, and acute kidney injury.

In this context, the findings extend the existing evidence and confirm that NPAR not only reflects systemic inflammation but also independently predicts both diuretic resistance and mortality risk in HFpEF, consistent with previous data.[35] Therefore, NPAR may serve as a simple, inexpensive, and accessible marker to assess systemic inflammation and identify high-risk HFpEF patients in clinical practice.

Clinical implementation of NPAR may aid in early identification of patients at high risk of poor outcomes, facilitating timely optimization of therapy and closer follow-up. Future large-scale prospective studies are warranted to validate NPAR as a prognostic biomarker and to explore whether interventions targeting systemic inflammation can improve outcomes in this patient population.

Study Limitations

This study has several limitations that should be acknowledged.

First, it was a single-center and retrospective study, which may limit the generalizability of the findings. Second, although the authors adjusted for multiple confounding variables, residual confounding cannot be fully excluded. Third, inflammatory markers such as interleukin-6, TNF-α, and other cytokines were not routinely measured, which may have limited the assessment of the complete inflammatory profile. Fourth, the mean follow-up duration was relatively short (8.3 ± 2.1 months), which may limit the assessment of true long-term outcomes and could lead to underestimation of late events. Therefore, the prognostic value of NPAR should be interpreted as reflecting mid-term risk and requires confirmation in multicenter studies with longer follow-up. Finally, the study design does not allow for establishing a causal relationship between elevated NPAR and adverse outcomes. Future multicenter, prospective studies with longer follow-up and a broader inflammatory marker panel are required to confirm these results.

CONCLUSION

In conclusion, elevated NPAR levels were significantly associated with both diuretic resistance and increased all-cause mortality in patients with HFpEF.

NPAR reflects the combined effect of systemic inflammation and nutritional status, providing an accessible and inexpensive biomarker for risk stratification.

The findings indicate that NPAR can serve as a valuable tool for identifying high-risk HFpEF patients and guiding early management strategies.

Further large-scale studies are needed to confirm its prognostic value and to explore potential therapeutic approaches targeting inflammation in this population.

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Ethics Committee Approval: This study was approved by the Tokat Gaziosmanpaşa University Faculty of Medicine, Non-Interventional Scientific Research Ethics Committee (Approval No.: 25-MOBAEK-144; Date: April 22, 2025).

Informed Consent: Since the study was conducted retrospectively, informed consent was not obtained from the patients. Information was received from the ethics committee of the hospital due to the current situation.

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SUPPLEMENTARY MATERIAL

Initial screening (January 2017 – August 2022)

HFpEF patients identified from institutional database: n = 1927

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Exclusion criteria applied

Missing clinical or echocardiographic data (n = 440)

Acute infection, sepsis, or malignancy

Severe valvular disease or prosthetic valve

Acute coronary syndrome (<6 months)

End-stage renal disease, severe anemia, age < 18 years

↓

Eligible HFpEF patients included in final analysis

n = 1487

↓

Grouping according to diuretic resistance

Diuretic-resistant group: n = 248

Non–diuretic-resistant group: n = 1239

↓

Statistical analyses performed

ROC curve → NPAR cut-off (13.98) for diuretic resistance prediction

Logistic regression → Independent predictors of diuretic resistance

Cox regression → Predictors of all-cause mortality

Kaplan–Meier survival analysis → Mortality according to NPAR level

↓

Main outcomes

Elevated NPAR (>13.98) predicted both diuretic resistance and higher mortality risk in HFpEF patients.