THE ANATOLIAN JOURNAL OF CARDIOLOGY

Official journal of the TURKISH SOCIETY OF CARDIOLOGY

The BREATH2 Score as an Independent Predictor of 1-Year Mortality in Patients with Heart Failure with Preserved Ejection Fraction

ABSTRACT

Background: Heart failure with preserved ejection fraction (HFpEF) is a heterogeneous syndrome with substantial early morbidity and mortality. The BREATH2 score was recently developed as an echocardiography-independent screening tool for HFpEF. However, its prognostic significance has not been investigated. This study aimed to evaluate the association between the BREATH2 score and 1-year all-cause mortality in patients with established HFpEF.

Methods: A total of 213 patients with HFpEF were retrospectively analyzed. The primary endpoint was 1-year all-cause mortality. Discriminative performance of the BREATH2, H2FPEF, and HFA-PEFF scores was assessed using receiver operating characteristic analysis. Multiple logistic regression was performed to identify independent predictors of mortality. Kaplan–Meier survival analysis was conducted using a prespecified BREATH2 cut-off (≥6).

Results: During 12-month follow-up, 32 patients (15.0%) died. The BREATH2 score was significantly higher among non-survivors ($P = .001$). Receiver operating characteristic curve analysis demonstrated that BREATH2 had the highest discriminative ability for 1-year mortality (area under the curve [AUC] = 0.683, $P < .001$, 95% CI: 0.616-0.745), outperforming H2FPEF (AUC = 0.554, $P = .324$) and HFA-PEFF (AUC = 0.593, $P < .001$). In multiple analyses adjusting for age, creatinine, and N-terminal pro-B-type natriuretic peptide, BREATH2 remained independently associated with mortality (odds ratio = 1.658 per 1-point increase, $P = .021$, 95% CI: 1.078-2.551). Patients with BREATH2 ≥6 had significantly lower survival compared with those with lower scores (log-rank, $P = .013$).

Conclusion: The BREATH2 score independently predicts 1-year mortality in patients with HFpEF. Beyond its diagnostic role, BREATH2 may serve as a practical early risk stratification tool at initial clinical presentation.

Keywords: BREATH2, heart failure with preserved ejection fraction, mortality, prognostic score, risk stratification

ORIGINAL INVESTIGATION

INTRODUCTION

Heart failure with preserved ejection fraction (HFpEF) accounts for approximately 50% of all heart failure cases worldwide and represents a growing public health burden due to aging populations and increasing comorbidity prevalence.[1-3] Despite therapeutic advances, including sodium–glucose cotransporter-2 inhibitors, mortality and hospitalization rates in HFpEF remain substantial, particularly during the early phase after clinical presentation.[3-5] In contrast to heart failure with reduced ejection fraction, HFpEF is characterized by marked biological and clinical heterogeneity, involving myocardial stiffness, microvascular dysfunction, systemic inflammation, atrial remodeling, and extracardiac comorbidities such as chronic kidney disease, anemia, obesity, and atrial fibrillation.[2,6-8]

This heterogeneity complicates both diagnosis and risk stratification. Over the past decade, structured diagnostic approaches have been developed to improve identification of HFpEF in patients presenting with unexplained dyspnea. The H2FPEF score provides a pragmatic, evidence-based diagnostic framework combining clinical and echocardiographic variables.[9] Similarly, the HFA-PEFF

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Received: May 18, 2026
Accepted: July 24, 2026
Available Online Date: August 25, 2026

Cite this article as: Yalvaç HE, Babayiğit EÇ, Dağhan H. The BREATH2 score as an independent predictor of 1-year mortality in patients with heart failure with preserved ejection fraction. *Anatol J Cardiol.* 2026;XX(X):1-9.

DOI: 10.14744/AnatolJCardiol.2026.6689

algorithm offers a stepwise diagnostic pathway integrating functional testing, imaging, and natriuretic peptide assessment.[10] Although these tools have improved diagnostic standardization, they were not primarily designed for prognostic assessment. Moreover, both approaches require echocardiographic parameters, which may limit rapid application in emergency departments or primary care settings where comprehensive imaging is not immediately available.[9,10]

The recently developed BREATH2 score was introduced as a primary care screening tool for HFpEF that does not rely on echocardiographic variables.[11] Derived from patients undergoing exercise stress echocardiography and validated in external and invasive cohorts, BREATH2 incorporates 7 readily available variables: age ≥65 years, coronary artery disease, atrial fibrillation, elevated natriuretic peptides, anemia, cardiomegaly on chest radiography, and left ventricular high-voltage on electrocardiography.[11] In its original validation, the score demonstrated strong diagnostic discrimination and outperformed the H2FPEF score in identifying HFpEF among symptomatic individuals.[11] These findings positioned BREATH2 as a practical referral tool in primary care settings.

Notably, several components of BREATH2 are independently associated with adverse prognosis in heart failure populations. Elevated natriuretic peptides consistently predict mortality and hospitalization in HFpEF.[12,13] Renal dysfunction is strongly associated with increased mortality, reflecting cardiorenal interaction and systemic congestion.[14,15] Anemia has been linked to impaired exercise capacity and worse outcomes in HFpEF.[16,17] Atrial fibrillation contributes to atrial remodeling, impaired ventricular filling, and increased morbidity and mortality risk.[18,19] Coronary artery disease further amplifies myocardial vulnerability and adverse event risk.[20]

HIGHLIGHTS

- The BREATH2 score independently predicts 1-year all-cause mortality in patients with established heart failure with preserved ejection fraction, extending its role beyond diagnosis to prognostication.
- Each 1-point increase in BREATH2 was associated with a 65.8% increase in the odds of 1-year mortality (odds ratio = 1.658; 95% CI 1.078-2.551; $P = .021$), independent of N-terminal pro-B-type natriuretic peptide and creatinine.
- BREATH2 demonstrated the highest discriminative ability for 1-year mortality (area under the curve [AUC] 0.683), outperforming H2FPEF (AUC = 0.554) and HFA-PEFF (AUC = 0.593).
- Patients with BREATH2 ≥6 showed significantly lower survival over 12 months compared with those with lower scores (log-rank, $P = .013$). As an echocardiography-independent, bedside score, BREATH2 enables rapid risk stratification at initial clinical contact without advanced imaging.

Despite the established prognostic relevance of these individual variables, whether the composite BREATH2 score provides independent prognostic information in HFpEF has not been investigated. Early risk stratification at the time of presentation to the emergency department or outpatient clinic remains a major clinical challenge, and no simple, widely adopted bedside score exists to estimate short-term mortality risk using routinely available data.[2,12,21,22]

Accordingly, the aim of the present study was to evaluate the association between the BREATH2 score and 1-year all-cause mortality in patients with HFpEF. It was hypothesized that, beyond its diagnostic utility, BREATH2 may function as a practical early risk stratification tool in patients presenting to emergency departments or outpatient clinics.

METHODS

Study Design and Ethical Approval

This retrospective observational cohort study was conducted at a tertiary referral center. Consecutive patients diagnosed with HFpEF between January 2023 and December 2023 were screened for eligibility.

The study protocol was approved by the Institutional Ethics Committee (Approval No.: ESH/BAEK 2026/361; Date: May 7, 2026) and conducted in accordance with the principles outlined in the Declaration of Helsinki. Given the retrospective design and use of anonymized data, the requirement for written informed consent was waived by the ethics committee.

Study Population

Heart failure with preserved ejection fraction was defined according to contemporary guideline criteria as the presence of heart failure symptoms and/or signs, left ventricular ejection fraction (LVEF) ≥50%, and objective evidence of structural heart disease or diastolic dysfunction.[6,10,23]

Exclusion criteria were:

- LVEF <50%.
- Significant primary valvular heart disease.
- Hypertrophic or restrictive cardiomyopathy.
- Active malignancy with life expectancy <1 year.
- Incomplete clinical, laboratory, or follow-up data.

After applying these criteria, 213 patients were included in the final analysis. No patients were excluded due to missing baseline or follow-up data.

Data Collection

Baseline demographic, clinical, electrocardiographic, laboratory, and echocardiographic data were extracted from electronic medical records at the time of index evaluation.

Laboratory parameters included hemoglobin, serum creatinine, platelet count, glucose, and N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels. N-terminal pro-B-type natriuretic peptide values were analyzed as continuous variables using raw (non–log-transformed) measurements.

Standard transthoracic echocardiography was performed according to guideline recommendations.[10] The LVEF was calculated using the modified Simpson's biplane method.

Relative wall thickness, transmitral E and A velocities, deceleration time, and left ventricular global longitudinal strain were recorded when available.

Risk Score Assessment

The BREATH2 score was calculated as originally described by Saito et al.[11] The BREATH2 score incorporates 7 readily available, echocardiography-independent clinical variables: elevated natriuretic peptides (B-type natriuretic peptide), cardiomegaly on chest radiography (R), age ≥65 years (E), atrial fibrillation (A), coronary artery disease (T), low hemoglobin/anemia (H), and left ventricular high-voltage on electrocardiography (H). Weighted points range from 0 to 9. The total score was computed at baseline using data obtained at the time of initial clinical evaluation (Figure 1).

The H2FPEF score was calculated according to the methodology described by Reddy et al.[9] The score integrates clinical and echocardiographic parameters, including body mass index, atrial fibrillation, pulmonary artery systolic pressure, age, E/e′ ratio, and use of antihypertensive medications.

The HFA-PEFF score was determined based on the stepwise diagnostic algorithm proposed by the Heart Failure Association of the European Society of Cardiology.[10] Structural, functional, and biomarker domains were evaluated and summed according to established criteria.

All risk scores were calculated at baseline and analyzed as continuous variables.

Follow-Up and Outcome Definition

Patients were followed for a median duration of 12 months. The primary endpoint was all-cause mortality within 1 year from the index date.

Mortality data were obtained from hospital electronic records and, when available, verified through national health registry systems. Time-to-event was calculated from the date of baseline evaluation to the date of death or last clinical contact.

Statistical Analysis

Continuous variables are expressed as mean ± SD or median (interquartile range), as appropriate according to data distribution. Categorical variables are presented as counts and percentages.

Normality was assessed using the Kolmogorov–Smirnov test. Between-group comparisons were performed using the independent samples *t*-test or Mann–Whitney *U*-test for

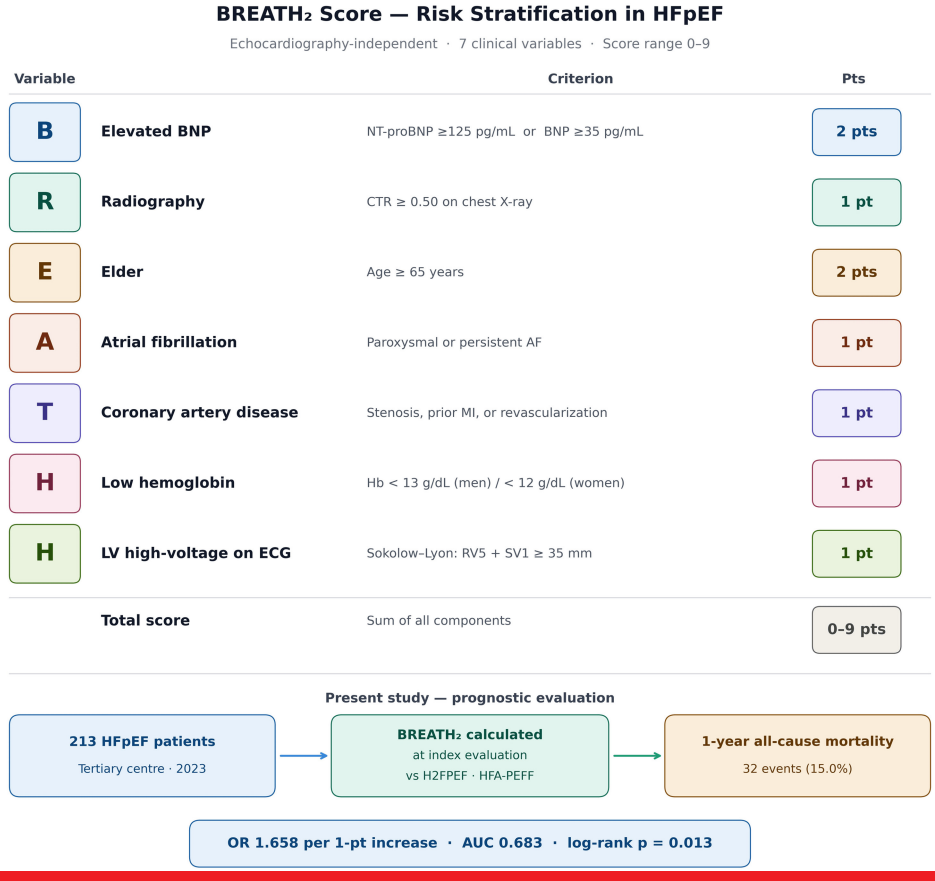

Figure 1. Components of the BREATH2 score and study design. Upper panel: the 7 variables of the BREATH2 score with their weighted point values (range 0-9). Lower panel: study design overview showing baseline BREATH2 score calculation in 213 HFpEF patients and the primary endpoint of 1-year all-cause mortality (32 events, 15.0%). AF, atrial fibrillation; AUC, area under the curve; BNP, B-type natriuretic peptide; CTR, cardiothoracic ratio; ECG, electrocardiography; HFpEF, heart failure with preserved ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; OR, odds ratio.

continuous variables and the chi-square test for categorical variables, as appropriate.

Receiver operating characteristic (ROC) curve analysis was conducted to evaluate the discriminative ability of the BREATH2, H2FPEF, and HFA-PEFF scores for predicting 1-year mortality. Areas under the curve (AUCs) with corresponding 95% CIs were calculated and compared using the DeLong method for correlated ROC curves.

Kaplan–Meier survival curves were generated according to a prespecified BREATH2 cut-off value (≥6), and differences between groups were assessed using the log-rank test.

To identify independent predictors of 1-year mortality, multiple logistic regression analysis was performed using the enter method. Variables with established clinical relevance and/or $P < .10$ in univariable analysis were considered for inclusion. N-terminal pro-B-type natriuretic peptide was entered into the model as a continuous variable per 1000 pg/mL increase. Odds ratios (ORs) with 95% CIs were calculated.

Multicollinearity was assessed using variance inflation factors, and no significant collinearity was observed. Model calibration was evaluated using the Hosmer–Lemeshow goodness-of-fit test.

Given the total number of events (n = 32), the number of covariates included in the final multiple model was restricted to maintain an acceptable events-per-variable ratio and to minimize model overfitting.

A post-hoc power analysis using the Wald test approximation for logistic regression demonstrated that, with a sample size of 213 patients, an observed event rate of 15.0% (n = 32), an OR of 1.658 per 1-point increase in BREATH2 score (SD = 1.69), and a two-sided α of 0.05, the study achieved a statistical power of 99%. The minimum sample size required to detect this effect with 80% power was estimated at 85 patients, indicating that the present cohort provided adequate statistical power for the observed effect size. A two-sided *P*-value < .05 was considered statistically significant.

All statistical analyses were performed using SPSS version 23 (IBM Corp., Armonk, NY, USA) and MedCalc version 23.4.8 (MedCalc Software Ltd., Ostend, Belgium).

RESULTS

Baseline Characteristics

A total of 213 patients with HFpEF were included. During the 12-month follow-up, 32 patients (15.0%) died, and 181 (85.0%) survived.

Non-survivors had significantly lower hemoglobin levels compared with survivors (10.82 ± 1.97 vs. 12.78 ± 2.08 g/dL, $P < .001$). Among risk scores, both BREATH2 and HFA-PEFF were significantly higher in patients who died (6.19 ± 1.55 vs. 5.17 ± 1.67, $P = .002$; and 5.94 ± 0.25 vs. 5.64 ± 0.79, $P = .033$, respectively), whereas H2FPEF scores were similar between groups ($P = .358$).

Echocardiographic assessment demonstrated lower left ventricular ejection fraction (58.77 ± 5.78 vs. 60.86 ± 5.18%, $P = .040$), higher relative wall thickness (0.61 ± 0.21 vs. 0.52 ± 0.14, $P = .004$), lower mitral A-wave velocity (57.29 ± 26.72 vs. 80.45 ± 23.36 cm/s, $P = .001$), and shorter deceleration time (154.84 ± 57.40 vs. 185.84 ± 69.27 ms, $P = .020$) in the mortality group.

Table 1. Baseline Clinical and Echocardiographic Characteristics According to 1-Year Mortality

Variables	Survivors (n = 181)	Non-survivors (n = 32)	*P*
Hemoglobin (g/dL)	12.78 ± 2.08	10.82 ± 1.97	**<.001**
HFA-PEFF score	5.64 ± 0.79	5.94 ± 0.25	.033
H2FPEF score	5.12 ± 2.34	5.53 ± 2.20	.358
BREATH2 score	5.17 ± 1.67	6.19 ± 1.55	**.002**
Interventricular septum thickness (mm)	13.84 ± 3.46	14.56 ± 3.32	.273
Ejection fraction (%)	60.86 ± 5.18	58.77 ± 5.78	.040
Relative wall thickness	0.52 ± 0.14	0.61 ± 0.21	**.004**
Mitral E (cm/s)	82.15 ± 24.72	91.22 ± 22.23	.054
Mitral A (cm/s)	80.45 ± 23.36	57.29 ± 26.72	**.001**
Deceleration time (ms)	185.84 ± 69.27	154.84 ± 57.40	**.020**
Platelet (×10⁹/L)	260.55 ± 91.50	233.74 ± 134.95	.165
Glucose (mg/dL)	132.80 ± 63.72	145.25 ± 67.73	.314
Creatinine (mg/dL)	1.09 ± 0.59	1.71 ± 1.02	**<.001**
NT-proBNP (pg/mL)	2191.9 ± 3843.7	8957.0 ± 10 449.7	**<.001**

NT-proBNP, N-terminal pro-B-type natriuretic peptide. Bold values in Tables 1 and 2 indicate statistically significant results ($P < .05$). Values at borderline significance were intentionally left unbolded.

Laboratory findings showed significantly higher creatinine levels (1.71 ± 1.02 vs. 1.09 ± 0.59 mg/dL, $P < .001$) and markedly elevated NT-proBNP concentrations (8957 ± 10 449 vs. 2192 ± 3844 pg/mL, $P < .001$) among non-survivors (Table 1).

Comparison of Risk Scores

Non-parametric analysis confirmed that BREATH2 scores were significantly higher in non-survivors (Mann–Whitney $U = 1834.5$, $Z = -3.361$, $P = .001$). HFA-PEFF scores were also modestly elevated ($U = 2359.0$, $Z = -2.329$, $P = .020$), whereas H2FPEF scores did not differ significantly between groups ($U = 2586.0$, $Z = -0.972$, $P = .331$) (Table 2).

Receiver Operating Characteristic Curve and Discrimination Analysis

Receiver operating characteristic analysis demonstrated that BREATH2 had the highest discriminative ability for predicting 1-year mortality (AUC = 0.683, $P < .001$, Standard

Table 2. Comparison of Risk Scores According to 1-Year Mortality

Variables	Survivors (n = 181) Mean Rank	Non-survivors (n = 32) Mean Rank	*U*	*P*
BREATH2	101.14	140.17	1834.5	**.001**
HFA-PEFF	104.03	123.78	2359.0	.020
H2FPEF	105.29	116.69	2586.0	.331

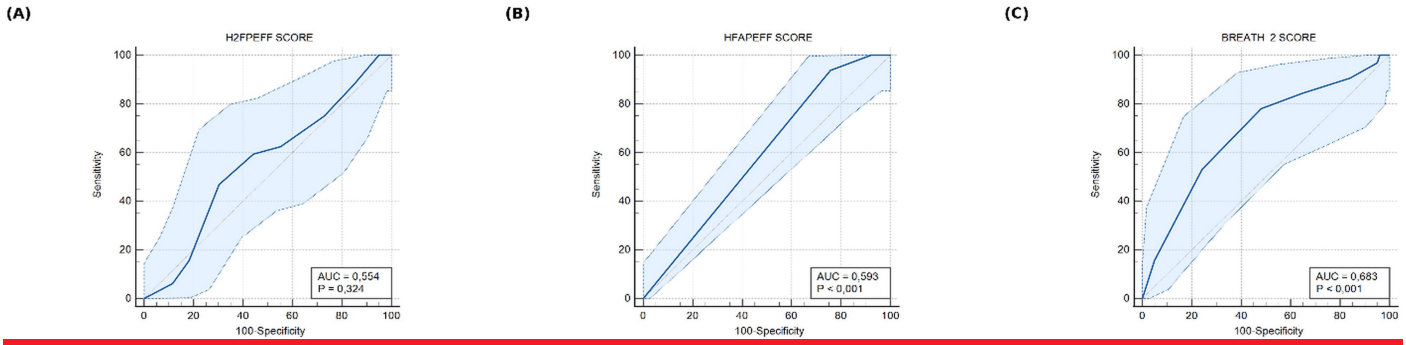

Figure 2. ROC curve analysis of the H2FPEF, HFA-PEFF, and BREATH2 scores for prediction of 1-year all-cause mortality in patients with HFpEF. (A) H2FPEF score (AUC 0.554). (B) HFA-PEFF score (AUC 0.593). (C) BREATH2 score (AUC 0.683). The BREATH2 score demonstrated superior discriminative performance compared with H2FPEF and numerically higher discrimination than HFA-PEFF. AUC, area under the curve; HFpEF, heart failure with preserved ejection fraction; ROC, receiver operating characteristic.

Error = 0.052, 95% CI: 0.616-0.745). HFA-PEFF showed moderate performance (AUC = 0.593, $P < .001$, 95% CI: 0.523-0.659), while H2FPEF demonstrated limited discrimination (AUC = 0.554, $P = .324$, 95% CI: 0.484-0.621) (Figure 2).

DeLong analysis revealed that BREATH2 provided significantly better discrimination than H2FPEF (AUC difference 0.130; 95% CI 0.035-0.224; $P = .007$). The difference between BREATH2 and HFA-PEFF was not statistically significant ($P = .111$). No significant difference was observed between HFA-PEFF and H2FPEF ($P = .528$) (Figure 3).

Kaplan–Meier Survival Analysis

Kaplan–Meier survival analysis demonstrated significantly lower 1-year survival rates in patients with a BREATH2 score ≥6 compared with those with a score <6. The survival curves separated early during follow-up and remained divergent throughout the 12-month period. Log-rank testing confirmed a statistically significant difference between groups (log-rank, $P = .013$) (Figure 4).

Multiple Logistic Regression Analysis

In the multiple logistic regression model including age, creatinine, NT-proBNP (per 1000 pg/mL increase), and BREATH2 score, creatinine remained independently associated with mortality (OR = 1.861, $P = .014$, 95% CI: 1.131-3.061). N-terminal pro-B-type natriuretic peptide was also an independent predictor (OR = 1.354, $P = .004$, 95% CI: 1.145-3.124). Importantly, each 1-point increase in BREATH2 score was associated with a 65% increase in the odds of 1-year mortality (OR = 1.658, $P = .021$, 95% CI: 1.078-2.551). Age was not independently associated with mortality ($P = .752$).

Model calibration was acceptable (Hosmer–Lemeshow $\chi^2 = 3.276$, $P = .513$).

In an exploratory model including anemia, anemia was not independently associated with mortality ($P = .338$), and the association between BREATH2 and mortality was attenuated ($P = .052$), likely reflecting collinearity between related biological variables (Table 3).

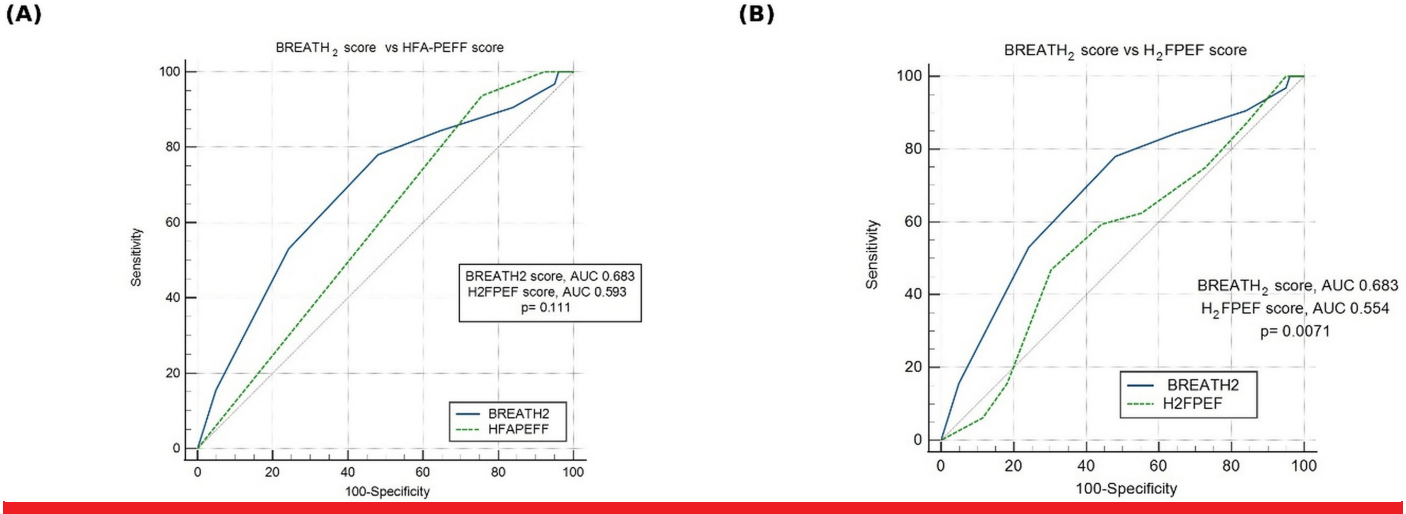

Figure 3. DeLong comparison of ROC curves for prediction of 1-year all-cause mortality in patients with HFpEF. (A) Comparison between BREATH2 and HFA-PEFF scores ($P = .111$). (B) Comparison between BREATH2 and H2FPEF scores ($P = .0071$). BREATH2 demonstrated significantly greater discriminative performance compared with H2FPEF, while no statistically significant difference was observed compared with HFA-PEFF. HFpEF, heart failure with preserved ejection fraction; ROC, receiver operating characteristic.

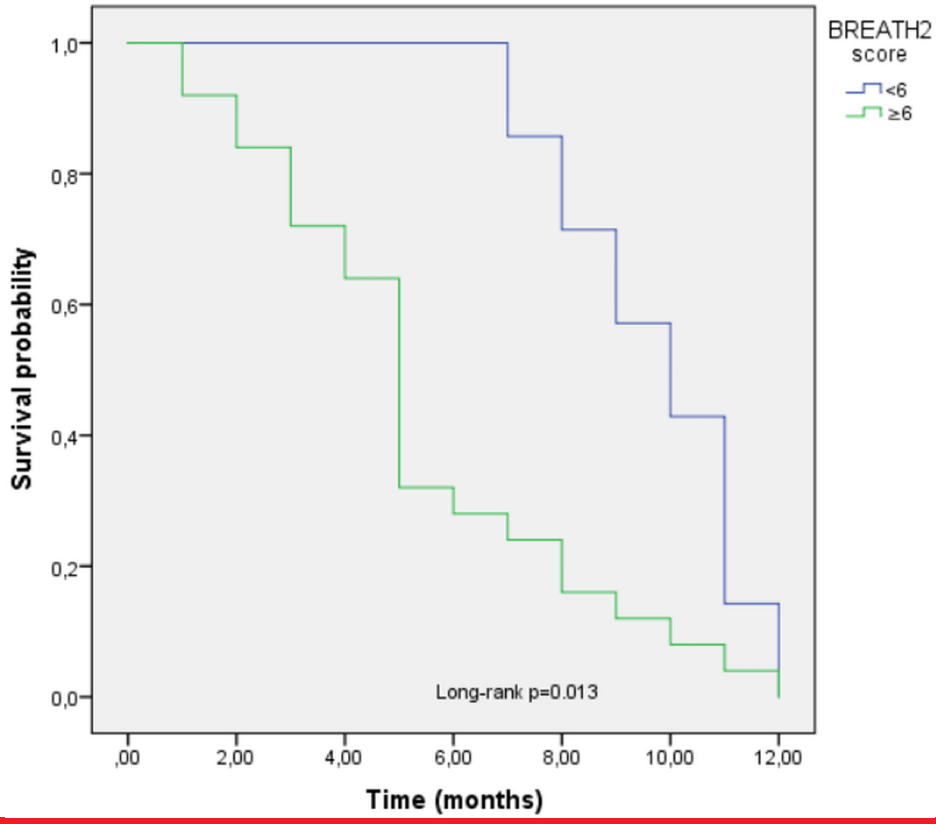

Figure 4. Kaplan–Meier survival curves according to BREATH2 score categories for prediction of 1-year all-cause mortality in patients with HFpEF. Patients with BREATH2 ≥6 demonstrated significantly reduced survival compared with those with BREATH2 <6 (log-rank *P* = .013). HFpEF, heart failure with preserved ejection fraction.

DISCUSSION

Heart failure with preserved ejection fraction remains a diagnostically and prognostically complex syndrome characterized by marked biological heterogeneity.[1-3] Despite therapeutic advances, including Sodium-Glucose Cotransporter-2 (SGLT2) inhibitors, HFpEF carries a 1-year mortality of 20%-29% and a 30-day all-cause readmission rate exceeding 20%, underscoring a persistent and largely unmet need for early risk stratification.[4,5] Individuals with HFpEF have a 5-year survival rate of only 35%-40% after a first hospitalization, yet the tools available to identify patients at highest short-term risk at the point of first clinical contact remain limited. Risk stratification is particularly challenging because many patients present without overt congestion and require advanced imaging or stress testing for definitive characterization.[9,10] While dedicated prognostic models for HFpEF have been proposed in recent years—including the PREDICT-HFpEF model, which achieved a C-statistic of 0.73 for 1-year outcomes using 11 clinical variables derived from the DELIVER trial[24]—these tools rely on complex variable sets and trial-enriched populations that may not reflect unselected clinical practice. The need for simple, echocardiography-independent tools applicable at initial presentation therefore remains.

Table 3. Multivariable Logistic Regression Analysis for 1-Year Mortality

Variables	OR	95% CI	*P*
Creatinine	1.861	1.131-3.061	.014
NT-proBNP (per 1000 pg/mL increase)	1.354	1.145-3.124	.004
BREATH2	1.658	1.078-2.551	.021
Age (years)	0.991	0.935-1.050	.752

NT-proBNP, N-terminal pro-B-type natriuretic peptide; OR, odds ratio.

The BREATH2 score was originally developed by Saito et al[11] as a pragmatic primary care screening tool to identify patients likely to have HFpEF without reliance on echocardiography. In its derivation cohort of 622 patients referred for exercise stress echocardiography, BREATH2 achieved an AUC of 0.84 for HFpEF diagnosis and outperformed the H2FPEF score. External validation in an independent cohort (n = 105) and in patients with invasively confirmed HFpEF via exercise right heart catheterization (n = 79) further confirmed its discriminative ability, yielding AUCs of 0.78 and 0.75, respectively.[11] Despite this strong diagnostic foundation, the prognostic implications of the score had not previously been evaluated.

The present study extends the conceptual framework of the BREATH2 score by demonstrating to the authors' knowledge, for the first time, that it is independently associated with 1-year all-cause mortality in patients with established HFpEF. This finding suggests that the biological domains

captured by the score are not merely diagnostic correlates but reflect pathophysiologic mechanisms that also drive disease progression and mortality.

Heart failure with preserved ejection fraction prognosis is shaped by a complex interplay between myocardial stiffening, atrial dysfunction, systemic inflammation, endothelial dysfunction, and extracardiac comorbidities.[6-8,21] Large community-based studies have consistently shown that non-cardiac comorbidities significantly influence survival in HFpEF populations.[21] The components of BREATH2—age, coronary artery disease, atrial fibrillation, elevated natriuretic peptides, anemia, cardiomegaly, and electrocardiographic left ventricle (LV) high-voltage—represent clinically accessible surrogates of this multidimensional vulnerability, each with established independent prognostic relevance in heart failure.

Elevated natriuretic peptides reflect increased wall stress and hemodynamic burden and are consistently associated with mortality in HFpEF.[12,13] Renal dysfunction embodies the cardiorenal axis and consistently predicts mortality in heart failure populations.[14,15] Anemia contributes to impaired oxygen delivery, neurohormonal activation, and reduced functional reserve and has been associated with worse outcomes in HFpEF.[16,22] Atrial fibrillation is highly prevalent in HFpEF and confers excess mortality risk through impaired ventricular filling and adverse atrial remodeling.[18,19] Coronary artery disease signals advanced myocardial vulnerability and adverse remodeling.[20] Importantly, the original BREATH2 derivation study also demonstrated the strong independent association of elevated natriuretic peptides and anemia with HFpEF presence,[11] reinforcing the biological plausibility of the prognostic findings.

Crucially, the independent association between BREATH2 and mortality persisted after adjustment for creatinine and NT-proBNP, suggesting incremental prognostic information beyond isolated biomarker assessment. In a syndrome characterized by multimorbidity and systemic impairment, composite clinical scores may better capture multidimensional risk than individual laboratory parameters alone.[21]

The Kaplan–Meier analysis further strengthens this interpretation. Patients with BREATH2 ≥6 exhibited early and sustained separation in survival curves over 12 months, indicating that the score identifies individuals at heightened short-term risk. This temporal pattern is particularly relevant for frontline clinical decision-making.

It is also important to contextualize the AUC of 0.683 observed for 1-year mortality prediction. Prognostic discrimination in HFpEF cohorts is inherently limited due to biological heterogeneity and competing non-cardiovascular risks, and AUC values rarely exceed 0.70-0.75 even with dedicated prognostic models.[21] For reference, the HFA-PEFF score demonstrated an AUC of 0.726 for all-cause mortality in a single-center Chinese cohort,[25,26] while a 2024 meta-analysis reported a pooled AUC of only 0.65 for the HFA-PEFF score across all-cause death endpoints.[27] Similarly, among patients hospitalized with HFpEF, both the HFA-PEFF and H2FPEF scores achieved AUCs of 0.63 and 0.58, respectively, for adverse outcome prediction.[28,29] Machine learning-derived models utilizing electronic health record data achieved AUCs of 0.78-0.79 for 1-year mortality but required complex algorithmic infrastructure.[22] In this context, BREATH2 achieving an AUC of 0.683 using only 7 routinely available, echocardiography-free variables is clinically meaningful. A score that can be calculated at the bedside without imaging—and still provides prognostic discrimination comparable to or exceeding established HFpEF-specific scoring systems—has substantial practical value for rapid risk assessment at initial presentation.

The distinction between diagnostic and prognostic performance warrants emphasis, and the pattern observed in the present study has precedent in the literature. The HFA-PEFF score, developed primarily as a diagnostic algorithm, has subsequently demonstrated independent prognostic value for all-cause mortality [Hazard Ratio (HR) = 1.314 per point; $P = .039$][26] and HF rehospitalization when applied to hospitalized HFpEF populations.[28] Similarly, Egashira et al[30] reported that higher HFA-PEFF scores independently predicted cardiovascular events (HR = 1.65 per point; $P < .001$).[13] In contrast, the H2FPEF score has demonstrated more inconsistent prognostic utility across studies; a 2021 meta-analysis found an association with mortality (OR = 1.73; $P < .01$),[16] yet subsequent cohort studies found no independent association with cardiovascular mortality.[15,24] The present data extend this framework by demonstrating that BREATH2, a score that does not require echocardiography and is simpler to apply at first contact, outperforms H2FPEF and achieves prognostic discrimination comparable to HFA-PEFF, while retaining a practical advantage in settings without immediate access to imaging. When a diagnostic score integrates variables that are tightly linked to the pathophysiologic drivers of mortality, prognostic extension becomes not only plausible but clinically applicable.

Several limitations should be acknowledged. This was a single-center, retrospective cohort study, and the relatively limited number of mortality events (n = 32) constrains the number of covariates that could be included in the multiple logistic regression model without risking overfitting. Although a post-hoc power analysis confirmed adequate statistical power for the observed effect size, the moderate AUC underscores that BREATH2 alone is not sufficient for definitive risk stratification and should not replace comprehensive multimodal assessment. The retrospective design also precludes assessment of some potentially important variables such as New York Heart Association (NYHA) functional class at presentation, serial biomarker changes, or detailed comorbidity burden indices. Furthermore, mortality ascertainment relied primarily on hospital electronic records supplemented by national registry data where available, which may undercount deaths occurring outside the healthcare system. The study cohort was drawn from a single tertiary referral center in Türkiye, and generalizability to primary care or community-based settings—where BREATH2 was originally intended to be applied—requires dedicated prospective evaluation. Prospective multicenter validation

in independent HFpEF cohorts, ideally including primary care and emergency department populations, is necessary to confirm the durability and generalizability of the prognostic signal. Furthermore, the long-term mortality burden previously documented in Turkish heart failure populations suggests that findings from this cohort may have broader relevance in similar real-world clinical settings.[31]

In conclusion, the BREATH2 score, initially developed as a primary care screening tool for HFpEF,[11] demonstrates an independent and clinically meaningful association with 1-year mortality in patients with established HFpEF. These findings position BREATH2 not only as a diagnostic facilitator but also as a practical early prognostic instrument at initial clinical contact.

Data Availability: The data supporting this study are available from the corresponding author upon reasonable request.

Ethics Committee Approval: This study was approved by the Ethics Committee of Eskişehir City Hospital (Approval No.: ESH/BAEK 2026/361; Date: 07/05/2026).

Informed Consent: Written informed consent was obtained from all patients who agreed to take part in the study.

Peer-review: Externally peer-reviewed.

Acknowledgments: No external funding was received for this study. The authors used artificial intelligence–assisted tools solely for language editing and grammatical improvement. All scientific content, statistical analyses, interpretations, and final manuscript preparation were performed and approved by the authors.

Author Contributions: Concept – H.E.Y.; Design – H.E.Y.; Supervision – H.E.Y.; Resources – H.E.Y., E.Ç.B.; Materials – H.E.Y., E.Ç.B.; Data Collection and/or Processing – E.Ç.B., H.D.; Analysis and/or Interpretation – H.E.Y., E.Ç.B.; Literature Search – H.E.Y., E.Ç.B.; Writing – H.E.Y.; Critical Review – H.E.Y., E.Ç.B., H.D.

AI-Assisted Technologies Statements: The authors used artificial intelligence–assisted tools (Claude, Anthropic, San Francisco, CA, USA) solely for language editing and grammatical improvement. All scientific content, statistical analyses, interpretations, and final manuscript preparation were performed and approved by the authors.

Declaration of Interests: The authors have no conflicts of interest to declare.

Funding: The authors declare that this study received no financial support.

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