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ORIGINAL RESEARCH

HEART FAILURE AND CARDIOMYOPATHIES

# A Machine Learning-Derived Score to Effectively Identify Heart Failure With Preserved Ejection Fraction

Kevin C. Bermea, MD,[a] Jana P. Lovell, MD,[a] Allison G. Hays, MD,[a] Erin Goerlich, MD,[a] Soumya Vungarala, MBBS,[a] Vivek Jani,[a] Sanjiv J. Shah, MD,[b] Kavita Sharma, MD,[a] Luigi Adamo, MD PhD[a]

## ABSTRACT

**BACKGROUND** The diagnosis of heart failure with preserved ejection fraction (HFpEF) in the clinical setting remains challenging, especially in patients with obesity.

**OBJECTIVES** This study aimed to identify novel predictors of HFpEF well suited for patients with obesity.

**METHODS** We performed a retrospective analysis of a well-characterized cohort of patients with obesity with HFpEF (n = 404; mean body mass index [BMI] 36.6 kg/m$^2$) and controls (n = 67). We used the machine learning algorithm Gradient Boosting Machine to analyze the association of various parameters with the diagnosis of HFpEF and subsequently created a multivariate logistic model for the diagnosis.

**RESULTS** Gradient Boosting Machine identified BMI, estimated glomerular filtration rate, left ventricular mass index, and left atrial to left ventricular volume ratio as the strongest predictors of HFpEF. These variables were used to build a model that identified HFpEF with a sensitivity of 0.83, a specificity of 0.82, and an area under the curve (AUC) of 0.88. Internal validation of the model with optimism-adjusted AUC showed an AUC of 0.87. Within the studied cohort, the novel score outperformed the H2FPEF score (AUC: 0.88 vs 0.74; $P < 0.001$).

**CONCLUSIONS** In a HFpEF cohort with obesity, BMI, estimated glomerular filtration rate, left ventricular mass index, and left atrial to left ventricular volume ratio most correlated with the identification of HFpEF, and a score based on these variables (HFpEF-JH score) outperformed the currently used H2PEF score. Further validation of this novel score is warranted, as it may facilitate improved diagnostic accuracy of HFpEF, particularly in patients with obesity. (JACC Adv 2024;3:101040)


Heart failure with preserved ejection fraction (HFpEF) is a clinical syndrome characterized by signs and symptoms of heart failure in the context of a preserved left ventricular ejection fraction (LVEF).[1] Both the incidence and prevalence of HFpEF continue to rise with significant associated morbidity and mortality.[2] However, the diagnosis of HFpEF in the clinical setting remains challenging,

From the [a]Division of Cardiology, Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA; and the [b]Division of Cardiology, Department of Medicine, Northwestern University Feinberg School of Medicine, Chicago, Illinois, USA.

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**ABBREVIATIONS AND ACRONYMS**

**AUC** = area under the curve

**BMI** = body mass index

**E/e'** = early mitral inflow velocity-mitral annulus velocity ratio

**eGFR** = estimated glomerular filtration rate

**GBM** = Gradient Boosting Machine

**HFpEF** = heart failure with preserved ejection fraction

**JH** = Johns Hopkins

**LA** = left atrial

**LA/LVr** = left atrial to left volumes ratio

**LV** = left ventricle

**LVEF** = left ventricular ejection fraction

**LVMi** = left ventricular mass index

**ROC** = receiver operating characteristic

especially in the significant proportion of HFpEF patients who are obese.[3]

Scoring algorithms have been developed to help rule in or out the diagnosis of HFpEF in the clinical setting.[2] These include the H2FPEF and the HFA-PEFF scores. The H2FPEF score utilizes clinical and echocardiographic variables,[4] while the HFA-PEFF score utilizes biomarkers and echocardiographic parameters.[5-7] Both scores have good specificity but limited sensitivity, as many patients fall in the intermediate scoring range.[2] Further diagnostic testing (eg, diastolic stress testing with exercise echocardiography or invasive exercise hemodynamic testing) is recommended for patients with scores within the intermediate range. These specialized forms of testing are not widely available, leaving a potentially large proportion of HFpEF undiagnosed or misdiagnosed.[2]

Given the limitations of these scoring systems, we applied machine learning techniques to analyze a contemporary, well-characterized cohort of obese patients with HFpEF, and controls, with the ultimate goal of identifying novel predictors of HFpEF well suited for obese patients.

## METHODS

**PATIENT SELECTION.** We performed a retrospective analysis of previously characterized patients with HFpEF, merging 2 cohorts of HFpEF patients with elevated body mass index (BMI).[8,9] The first cohort was created by gathering data at Northwestern University and Johns Hopkins University HFpEF Clinic between 2016 and 2019 as part of a prospective American Heart Association-funded study. This cohort was composed of 113 HFpEF and 44 control patients. The second cohort included 363 patients retrospectively enrolled in the Johns Hopkins Hospital HFpEF registry between 2014 and 2022, and 28 controls (together referred to as the JHU cohort). Both cohorts have been previously published.[8,9] In both cohorts, the diagnosis of HFpEF was based on the Framingham criteria for heart failure[10] and at least 2 of the following: 1) structural heart disease as evidenced by left ventricular (LV) hypertrophy or left atrial enlargement; 2) N terminal pro-brain natriuretic peptide ≥100 pg/mL; or 3) elevated pulmonary capillary wedge pressure on hemodynamic assessment (≥15 mm Hg at rest or ≥25 mm Hg with exercise). Exclusion criteria included history of any prior echocardiogram with LVEF <40%, infiltrative or restrictive cardiomyopathy, hypertrophic cardiomyopathy, active myocarditis, constrictive pericarditis, congenital heart disease, isolated pulmonary arterial HTN, clinically significant valvular regurgitation or stenosis, systolic blood pressure <100 mm Hg, current use of intravenous inotropic medication or need for mechanical circulatory support, and current pregnancy or breastfeeding. The control group for both cohorts consisted of carefully screened patients who did not present with any symptoms of heart failure or cardiovascular disease and who had no detectable abnormalities on echocardiography that would suggest underlying cardiac pathology, such as valvular disease, hypertrophic cardiomyopathy, or other structural abnormalities.

**PATIENT DATA.** Clinical variables were gathered in the context of dedicated study protocols. The echocardiographic assessment was performed in accordance with the American Society of Echocardiography guidelines.[11] For the purpose of this study, the biological sex of participants was ascertained by self-report, with individuals indicating their sex as either male or female based on their biological attributes.

**STATISTICAL ANALYSIS.** Clinical characteristics were compared between HFpEF and control groups using a *t*-test and chi-square, as appropriate. As an initial evaluation, we ran Gradient Boosting Machine (GBM) algorithm[12] to explore the variables that were most associated with a diagnosis of HFpEF. GBM is a machine learning algorithm that iteratively investigates the association between variables of interest and produces a ranking of their association.[12] Variables with more than 50% missing values were excluded from the GBM analysis (Supplemental Table 1). We analyzed associations of HFpEF diagnosis with the following clinical variables, echocardiography parameters, and laboratory values: age, sex, ethnicity, race, number of antihypertensive medications, history of myocardial infarction, atrial fibrillation, diabetes, BMI, LVEF, interventricular septum diastolic thickness, LV mass index (LVMi), left atrial to LV volume ratio (LA/LVr), LV volume, estimated glomerular filtration rate (eGFR) measured by the Chronic Kidney Disease Epidemiology Collaboration creatinine equation, presence of concomitant conditions such as hypertension, diabetes, and hyperlipidemia. The initial GBM analysis was

generated with 1,000 trees, an interaction depth of 3, a shrinkage rate of 0.01, and 5-fold cross-validation. Data preprocessing involved standardization of continuous variables (centering and scaling) and imputation of missing values using k-nearest neighbors, with k = 2.

The variables with the highest relative contribution to the HFpEF phenotype as assessed by GBM were used to build a multivariate logistic regression model. Before proceeding, a correlation matrix was made to assess if the variables meet the criteria for a multivariate logistic regression model, the correlation was calculated using Pearson's correlation. In addition, to minimize the overfitting, patients with missing values in such variables in the original data were excluded.

Using the predictors from the logistic model, an empirical receiver operating characteristic (ROC) curve was generated, and the maximum Youden index was calculated based on the true positive rate and the false positive rate across various cutoff values. In addition, optimism-adjusted area under the curve (AUC) was calculated with 1,000 bootstraps resamples[13] to validate the findings. Finally, a comparison of the performance of the score developed and the H2FPEF score was made with a DeLong test. Data analysis was completed with R (version 4.1.1), and the ROC curves were generated using the ROCit and pROC. The overall structure of our study is summarized in Figure 1.

Finally, to gain further insight into the clinical value of the tool generated, we sought to compare the performance of the new score to the performance of an established HFpEF clinical score. The H2FPEF score was recently shown to outperform another established score (HFA-PEFF) in terms of diagnostic ability,[4,7] and therefore, we selected it as our benchmark. This comparison utilized the DeLong test, applied to the entire cohort as well as specific subsets of obese (BMI >30 kg/m$^2$) and nonobese (BMI <30 kg/m$^2$) patients.

The study complies with the Declaration of Helsinki. The study was approved by the Johns Hopkins Medicine and Northwestern Institutional Review Boards.

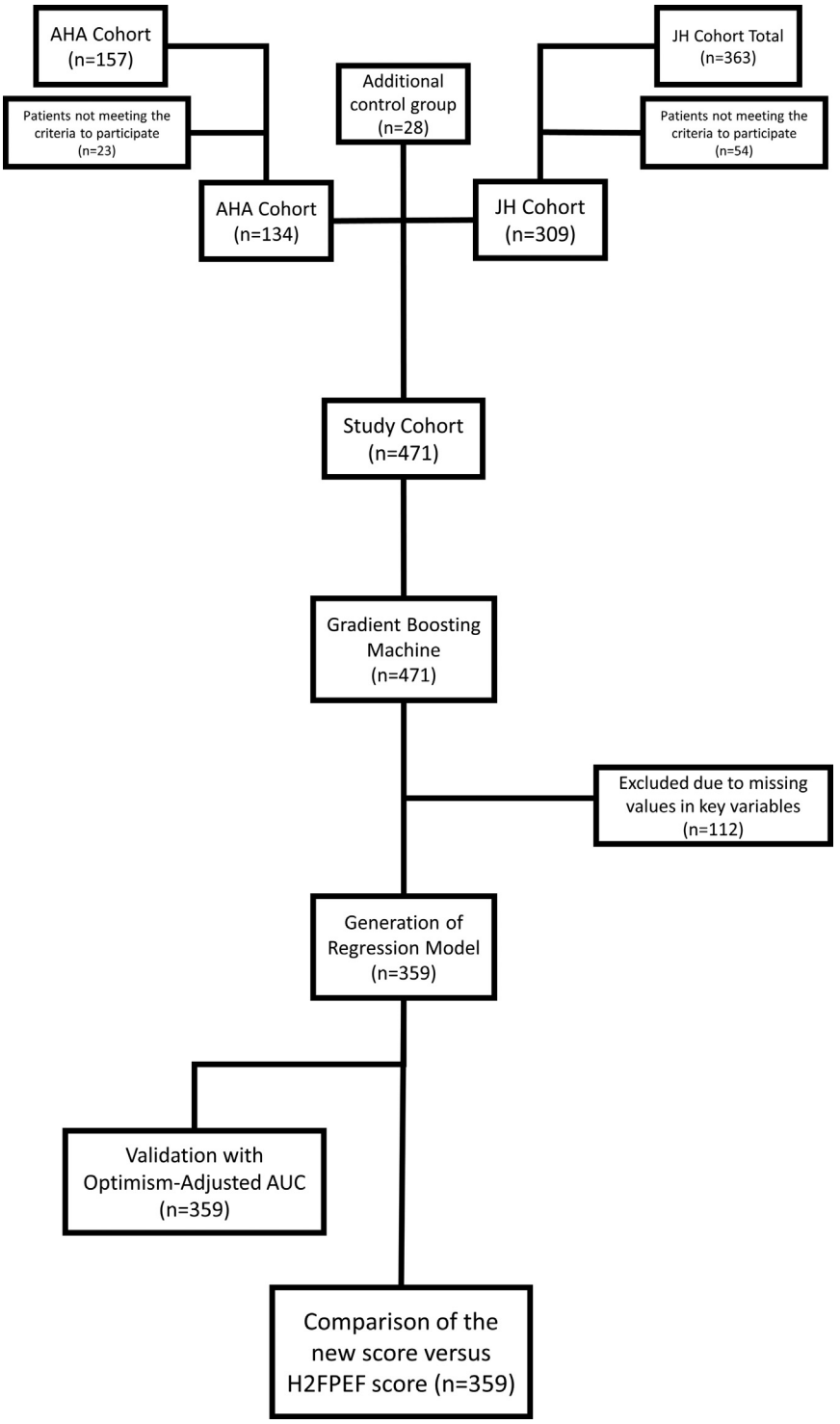
## RESULTS

**CLINICAL CHARACTERISTICS OF THE STUDY SAMPLE.** The demographics of the patients from our study cohort are reported in Table 1. Overall, HFpEF patients and controls had similar characteristics in terms of age and sex. The median age in the HFpEF cohort was 66.6 years and the median age in the controls was 62.8 years ($P = 0.29$). Sixty-five percent of HFpEF patients and 48% of controls were female ($P = 0.11$). As compared to controls, individuals with HFpEF had a higher prevalence of hypertension (94% vs 58%; $P < 0.01$), atrial fibrillation (31% vs 14%; $P = 0.01$), and diabetes (49% vs 17%; $P < 0.01$), as well as higher BMI (mean 36.6 vs 26.9 kg/m$^2$; $P < 0.01$) and higher body surface area (mean 2.1 vs 1.9 m$^2$; $P < 0.01$). On echocardiography, HFpEF patients had increased interventricular septum (mean 1.2 vs 1.08 cm; $P < 0.01$), higher LA/LVr (mean 0.72 vs 0.61; $P < 0.01$), and higher LA volume (mean 61.5 vs 55 ml; $P < 0.01$). Additionally, compared to control patients, HFpEF patients had worse renal function (higher creatinine: mean 1.2 vs 0.9 mg/dL; $P = 0.02$; lower eGFR: mean 56 vs 75 mL/min/1.73 m$^2$; $P < 0.01$) Table 1.

**DERIVATION OF A NOVEL CLINICAL PREDICTION TOOL TO PREDICT HFpEF BASED ON BMI, GFR, LVMi, AND LA/LVr.** GBM analysis highlighted BMI, eGFR, LVMi, and LA/LVr as the top variables predictive of HFpEF. The relative contribution of these variables was 22.96% for BMI, 17.05% for LVMi, 16.03% for eGFR, and 15.16% for LA/LVr (Figure 2, Table 2). Based on these results, we built a multivariable logistic regression model to quantify the relationship between these variables and HFpEF. Patients with missing values in these 4 variables were excluded leaving a cohort of 359 patients (Figure 1, Table 3). BMI showed the strongest association with HFpEF ($P$ = 9.26E-09; z-value 5.74), followed by eGFR ($P$ = 6.49E-06; z-value = −4.5), LVMi ($P$ = 2.61E-05; z-value = −4.2), and LA/LVr ($P$ = 0.002; z-value = 3.09), Table 4 shows the correlation matrix of these 4 variables. We used the regression model to define a clinical prediction rule (ie score) to predict the presence of HFpEF based on the values of these 4 variables. The formula for this novel score, named HFpEF-JH score, is reported in Figure 3A.

The ROC curve showed an AUC of 0.88 (Figure 3B). The optimal cutoff for the model was determined as the maximum value of the empirical true positive rate-false positive rate for each fitted value as the cutoff. The optimal value was found to be 0.83. Using this cutoff, we calculated the sensitivity and specificity of the model for the diagnosis of HFpEF as 0.83 and 0.82, respectively (Figure 3B). The calculated optimism-adjusted AUC with 1,000 resamples was 0.87 (Figure 3C). A sensitivity analysis in the subset of patients with elevated pulmonary capillary wedge pressure (≥15 resting and ≥25 with physical activity) also showed a sensitivity of 0.83 which suggests that the score had the same performance in patients in

**FIGURE 1 Consort Diagram for the Identification of Novel Clinical Predictors of HFpEF in Obese Patients and Definition of Novel Clinical Prediction Rule to Detect HFpEF**




Two different cohorts of HFpEF patients were merged into a single study cohort. Since the JH HFpEF cohort does not include controls, this cohort was integrated with data from 28 control patients gathered at johns hopkins hospital. Potential predictors of HFpEF were then explored using gradient boosting machine (GBM). Next, the variables identified with GBM were used to generate a logistic regression model to detect HFpEF. To reduce bias, before this step patients missing values in key variables previously associated with HFpEF were removed, leaving a cohort of 359 patients for analysis via multiparametric regression. The performance of this model was validated internally by optimism-adjusted AUC, and finally, the performance of the new score was compared with that of the H2FPEF Score. AUC = area under the curve; HFpEF = heart failure with preserved ejection fraction.

which the diagnosis of HFpEF was confirmed by invasive hemodynamics.

**THE HFpEF-JH SCORE OUTPERFORMS THE H2FPEF SCORE.** We decided to compare the performance of the HFpEF-JH score to that of the H2FPEF score. As shown in Figure 4A, in our study cohort, the H2FPEF score had a sensitivity of 0.19, a specificity of 0.98, with a positive predictive value of 0.98 at the cutoff of 6, with an AUC of 0.74 for the diagnosis of HFpEF. In contrast, HFpEF-JH score had a sensitivity of 0.83, and specificity of 0.82, with a positive predictive value of 0.96 at the 0.83 cutoff (Figure 4B). The unidirectional DeLong's test showed a *P* value of 8.136e-06, indicating a statistically significant difference between the 2 scores. When focusing on obese (BMI >30 kg/m$^2$; 227 HFpEF patients and 21 controls) vs nonobese (BMI <30 kg/m$^2$; 75 HFpEF patients and 36 controls) patients, the HFpEF-JH score had better discriminatory power than the H2FPEF score in obese patients (DeLong's test in patient with BMI >30 kg/m$^2$; $P < 0.001$) but not in nonobese patients (DeLong's test in patient with BMI <30 kg/m$^2$, $P = 0.118$). Figure 4C shows that overall the H2FPEF score performed well in terms of ruling out HFpEF in controls. However, it demonstrated low sensitivity in identifying HFpEF, with a large proportion of patients with HFpEF having an intermediate score using the HF2PEF scoring method. Figure 4D shows that the HFpEF-JH score had very high sensitivity and good specificity.

## DISCUSSION

We studied a large cohort of well-characterized, mostly obese HFpEF patients and controls. Using a machine learning algorithm, we identified BMI, eGFR, LVMi, and LA/LVr as the clinical and echocardiographic variables with the strongest association with HFpEF in obese patients. Through multivariable logistic regression, we developed a novel score (HFpEF-JH score) using these 4 clinical variables to identify patients with HFpEF with a sensitivity of 0.83 and a specificity of 0.82. This score outperformed the H2FPEF score, especially in patients with BMI>30 kg/m$^2$ (Central Illustration).

The gold standard diagnosis of HFpEF is made by invasive exercise hemodynamic testing. This is not always practical in the clinical setting as hemodynamic testing, particularly with exercise, is generally available only in specialized centers. Diastolic stress testing with exercise echocardiography can also help make the diagnosis, but it, too, is not widely available. Therefore, in routine clinical practice, HFpEF

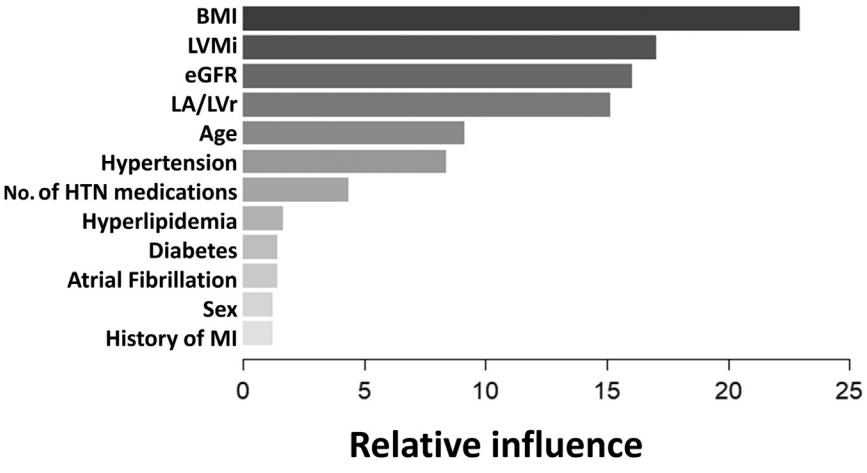
**TABLE 1 Clinical and Demographic Characteristics of Patients in the Study Cohort**

| | Control (n = 67) | HFpEF (n = 404) | *P* Value |
|---|---|---|---|
| Demographics | | | |
| Age, y | 62.82 (56.83-71.71) | 66.60 (57.98-73.00) | 0.147[a] |
| Female (%) | 32 (48) | 261 (65) | 0.012[b] |
| Ethnicity (%) | | | |
| Non-Hispanic/Latino | 62 (94) | 398 (99) | 0.03[b] |
| Race (%) | | | |
| Asian | 6 (10) | 4 (<1) | |
| Black or African American | 18 (29) | 103 (50) | |
| White | 38 (60) | 187 (47) | |
| Other | 6 (10) | 4 (<1) | <0.001[b] |
| Body composition | | | |
| Height, m | 1.70 (1.58-1.78) | 1.65 (1.58-1.73) | 0.152[c] |
| Weight, kg | 78.70 (63.28-94.40) | 102.6 (84.18-121.65) | <0.001[c] |
| BMI, kg/m$^2$ | 26.99 (23.65-31.72) | 36.6 (29.8-44.1) | <0.001[a] |
| BSA, m$^2$ | 1.89 (1.69-2.10) | 2.14 (1.93-2.33) | <0.001[c] |
| Comorbidities (%) | | | |
| Hypertension | 38 (58) | 377 (94) | <0.001[b] |
| Hyperlipidemia | 29 (44) | 238 (59) | 0.03[b] |
| History of MI | 10 (15) | 28 (7) | 0.045[b] |
| Atrial fibrillation | 9 (14) | 123 (31) | 0.006[b] |
| Diabetes | 11 (17) | 198 (49) | <0.001[b] |
| Number of HTN meds (%) | | | |
| 0-1 | 52 (78) | 195 (48) | |
| 2-3 | 14 (21) | 206 (51) | |
| >4 | 1 (1) | 3 (1) | <0.001[b] |
| Echocardiography | | | |
| LV ejection fraction, % | 62.29 (57.38-65.72) | 65 (60-70) | <0.001[c] |
| LVEDD, cm | 4.43 (4-4.86) | 4.56 (4.15-5) | 0.114[c] |
| IVS, diastolic thickness, cm | 1.08 (0.96-1.2) | 1.2 (1-1.4) | 0.002[a] |
| LVPW, diastolic thickness, cm | 0.97 (0.9-1.08) | 1.09 (0.93-1.21) | <0.001[a] |
| LVM, g | 186.5 (150.63-310) | 190.38 (150.13-231.43) | 0.32[c] |
| LVMi, g/m$^2$ | 99.9 (76.33-152.75) | 88.5 (71.3-109.3) | 0.306[a] |
| E/A | 1 (0.8-1.29) | 1 (0.77-1.4) | <0.001[a] |
| E/e' | 10.37 (7.12-12.98) | 13.17 (9.7-17.03) | 0.720[a] |
| LA/LVr | 0.61 (0.5-0.73) | 0.72 (0.54-0.95) | 0.002[a] |
| LA volume, ml | 55 (44-67.75) | 61.5 (47-77.88) | 0.002[c] |
| LV volume, ml | 91 (74-107.75) | 82 (67-102) | 0.371[c] |
| Laboratory studies | | | |
| BUN, mg/dL | 17 (13-22.5) | 23 (16-31) | <0.001[a] |
| Creatinine, mg/dL | 0.9 (0.72-1.1) | 1.2 (0.97-1.62) | <0.001[a] |
| eGFR, mL/min/1.73 m$^2$ | 75 (61-93) | 56 (39-71) | <0.001[c] |
| Troponin I, ng/mL | 0.01 (0-0.06) | 0 (0-0.04) | 0.012[a] |
| Ferritin, ng/mL | 173.15 (56.15-554.75) | 94 (49.5-203) | 0.053[a] |
| TIBC, μg/dL | 240 (195.25-317.25) | 318.5 (279-366.5) | 0.005[c] |
| Hemoglobin, g/dL | 12.1 (9.25-13.8) | 12.3 (11-13.3) | 0.306[a] |
| Scores | | | |
| H2FPEF score | 2 (1-4) | 4 (3-5) | <0.001[c] |
| HFpEF-JH score | 0.6 (0.39-0.78) | 0.94 (0.87-0.98) | <0.001[c] |

Values are median (IQR: 0.25-0.75) or n (%). *P* values reported are based on Wilcoxon[a] for non-normal distributed continuous variables, chi-square for categorical variables[b], and t-test[c] for normal continuous variables.

BMI = body mass index; BSA = body surface area; BUN = blood urea nitrogen; E/A = early and late mitral inflow velocities during diastole; E/e' = early mitral inflow velocity-mitral annulus velocity ratio; eGFR = estimated glomerular filtration rate; HTN = hypertension; IVS = interventricular septum; LA = left atrial; LA/LVr = left atrial to left volumes ratio; LV = left ventricle; LVEDD = left ventricular end diastolic diameter; LVM = left ventricular mass; LVMi = left ventricular mass index; LVPW = left ventricular posterior wall; MI = myocardial infraction; TIBC = total iron binding capacity.

**FIGURE 2** Barplot of the Association of Different Variables With HFpEF Diagnosis As Determined by the Multinomial Gradient Boosting Machine Model




The gradient boosting machine model was trained with 1,000 trees, an interaction depth of 3, a shrinkage rate of 0.01, and 5-fold cross-validation. The barplot shows the relative influence of the top 12 predictor variables in the model, with the most important variable at the top. Body mass index (BMI), left ventricular mass indexed (LVMi), estimated glomerular filtration rate (eGFR), and left atrial to left ventricular ratio (LA/LVr) were identified as the 4 top correlates of HFpEF. HTN = hypertension; MI = myocardial infraction; other abbreviations as in Figure 1.

remains mostly a diagnosis that involves the use of signs and symptoms of HF, natriuretic peptides, and resting echocardiography which can lead to underdiagnosis or misdiagnosis. Current expert consensus guidelines suggest using existing clinical prediction tools (H2FPEF or HFA-PEFF) to help identify HFpEF patients.[2,14] However, these scores have significant limitations. First, both scores rely on Doppler echocardiographic parameters, which can be difficult to measure properly in a large proportion of HFpEF patients, particularly those with obesity, and echocardiography is an imperfect tool for the estimation of elevated LV filling pressures.[15] In addition, both scores are based on univariate predictors, and therefore, the presence of a variable does not affect the "weight" of the other variables. This artificially simplifies the complexity of the HFpEF syndrome.[16] Our HFpEF-JH score was derived from a cohort of HFpEF patients with especially high BMI. It was derived via machine learning to account for the interaction between variables, and it was intentionally designed to use routinely measured continuous variables. This produced a score that relies on variables that can be easily assessed with basic laboratory testing, a physical exam, and a standard echocardiographic assessment and yet is arguably better poised to capture the complexity of HFpEF, given our use of multivariable modeling in score development as opposed to simply adding together univariate predictors.

**TABLE 2** Relative Contribution of Variables in a Gradient Boosting Machine Model for Predicting HFpEF Diagnosis

| | Relative Influence |
|---|---|
| Body mass index | 22.96 |
| LV mass index | 17.05 |
| eGFR | 16.03 |
| LA/LVr | 15.16 |
| Age | 9.14 |
| Hypertension | 8.38 |
| Number of HTN medications | 4.35 |
| Hyperlipidemia | 1.66 |
| Diabetes | 1.43 |
| Atrial fibrillation/flutter | 1.40 |
| Sex | 1.24 |
| History of MI | 1.21 |

The relative contribution is expressed in base 100. The top 4 variables were selected and included in the logistic regression model.
Abbreviations as in Table 1.

In our machine learning analysis that led to the development of the HFpEF-JH score, higher BMI showed the strongest association with HFpEF. This is in line with the findings of several prior studies,[17,18] and BMI is incorporated in the HF2PEF score.[5] In addition, our study revealed a strong association between HFpEF and higher LVMi, which is a key

component of the HFA-PEFF score.[6] Interestingly, we also found that lower eGFR and higher LA/LVr had a strong association with HFpEF, stronger than many other variables classically associated with HFpEF such as E/e′ or atrial fibrillation.[9] The association between low eGFR and risk of HFpEF is not surprising in light of prior data indicating a correlation between eGFR and abnormalities in indices of cardiac mechanics. In a prospective analysis of patients with early-stage chronic kidney disease (mean serum creatinine 1.43 mg/dL), low eGFR was associated with alterations in echocardiographic strain parameters.[19] In a similar population, eGFR was found to be inversely correlated with LA volume index, pulmonary artery systolic pressure, and E/e′ ratio.[20] In patients with HFpEF, lower eGFR correlated with lower global longitudinal strain as well as a higher risk of cardiovascular hospitalization or death.[21] Furthermore, there is evidence of an association between CKD and new-onset HFpEF independent of echocardiographic parameters.[22] The specific association between increased LA/LVr and HFpEF that we describe has not been reported before but is also not unexpected. In fact, Melenovsky et al[23] reported previously that LA enlargement is characteristic of HFpEF patients, not only as compared to controls but also as compared to patients with hypertension without HFpEF. Moreover, alterations in the LA/LVr have been shown to correlate with alterations in the LA to LV hemodynamic relationship.[24,25] HFpEF is often characterized by abnormal LA function, which results in the inability of the LA to fill and empty properly, leading to underfilling of the LV. The result is progressive LA enlargement and progressive LV size reduction, leading to an increased LA/LVr.

Interestingly, in our study, age, number of antihypertensive medications, history of atrial fibrillation or pulmonary hypertension, and E/e' were not among the strongest predictors of HFpEF, despite the fact that all of these variables are used in the H2FPEF score. This likely reflects the fact that GBM identified BMI, eGFR, LVMi, and LA/LVr as variables that together have a stronger association with HFpEF and, after adjusting for BMI, eGFR, LVMi, and LA/LVr, the correlation between the variables included in the H2FPEF score and HFpEF was greatly diminished. Age is incorporated into eGFR, the number of antihypertensive medications is likely related to LVMi, and LA/LVr incorporates atrial fibrillation and E/e′ ratio (patients with atrial fibrillation and elevated E/e′ ratio would be expected to have higher LA/LVr and

**TABLE 3 Clinical and Demographic Characteristics of Patients in the Regression Model Cohort**

| | Control (n = 57) | HFpEF (n = 302) | *P* Value |
|---|---|---|---|
| Demographics | | | |
| Age, y | 62.82 (57.76-72) | 65.7 (57.98-72.08) | 0.291[a] |
| Female (%) | 31 (54) | 202 (66) | 0.11[b] |
| Ethnicity (%) | | | |
| Non-Hispanic/Latino | 52 (93) | 300 (99) | 0.011[b] |
| Race (%) | | | |
| Asian | 5 (9) | 2 (<1) | |
| Black or African American | 18 (34) | 160 (53) | |
| White | 29 (55) | 137 (45) | |
| Other | 1 (2) | 3 (1) | <0.001[b] |
| Body composition | | | |
| Height, m | 1.68 (1.58-1.77) | 1.65 (1.57-1.76) | 0.303[a] |
| Weight, kg | 76.2 (61.68-93.89) | 103.53 (83.91-121.53) | <0.001[a] |
| BMI, kg/m$^2$ | 26.53 (23.07-32) | 36.62 (29.95-43.65) | <0.001[c] |
| BSA, m$^2$ | 1.88 (1.64-2.09) | 2.13 (1.91-2.33) | <0.001[a] |
| Comorbidities (%) | | | |
| Hypertension | 34 (60) | 284 (94) | <0.001[b] |
| Hyperlipidemia | 25 (44) | 175 (58) | 0.073[b] |
| History of MI | 8 (14) | 23 (8) | 0.19[b] |
| Atrial fibrillation | 8 (14) | 91 (30) | 0.019[b] |
| Diabetes | 9 (16) | 146 (48) | <0.001[b] |
| Number of HTN meds (%) | | | |
| 0-1 | 46 (81) | 145 (48) | |
| 2-3 | 10 (17) | 156 (51) | |
| >4 | 1 (2) | 3 (1) | <0.001[a] |
| Echocardiography | | | |
| LV ejection fraction, % | 62.5 (57.5-66.44) | 65 (60-69.41) | 0.003[a] |
| LVEDD, cm | 4.4 (4-4.87) | 4.5 (4.14-4.98) | 0.138[a] |
| IVS, diastolic thickness, cm | 1.06 (0.94-1.2) | 1.2 (1-1.38) | <0.001[c] |
| LVPW, diastolic thickness, cm | 0.97 (0.9-1.08) | 1.09 (0.93-1.2) | <0.001[a] |
| LVM, g | 203 (150.72-315) | 193.5 (151.74-229.93) | 0.122[c] |
| LVMi, g/m$^2$ | 105.3 (80.21-158) | 89.3 (72.19-110.3) | <0.001[c] |
| E/A | 1 (0.8-1.29) | 1 (0.77-1.4) | 0.795[c] |
| E/e' | 10.37 (7.12-12.98) | 13.17 (9.7-17.03) | <0.001[c] |
| LA/LVr | 0.61 (0.49-0.74) | 0.72 (0.54-0.95) | 0.003[c] |
| LA volume, ml | 52 (42-72.5) | 62 (48-79) | <0.001[a] |
| LV volume, ml | 84.5 (74-106) | 83.75 (67-102.88) | 0.955[a] |
| Laboratory studies | | | |
| BUN, mg/dL | 17 (13-23) | 23 (16-30) | <0.001[c] |
| Creatinine, mg/dL | 0.9 (0.71-1.1) | 1.2 (1-1.6) | <0.001[c] |
| eGFR, mL/min/1.73 m$^2$ | 76 (62-94) | 56 (39-71) | <0.001[a] |
| Troponin I, ng/mL | 0.01 (0-0.07) | 0 (0-0.04) | 0.024[c] |
| Ferritin, ng/mL | 163.6 (53.9-571.5) | 97 (47.5-201) | 0.071[c] |
| TIBC, μg/dL | 235 (191.5-317.5) | 316.5 (275.75-355) | 0.009[a] |
| Hemoglobin, g/dL | 11.9 (8.85-13.6) | 12.2 (11.0-13.2) | 0.148[c] |
| Scores | | | |
| H2FPEF score | 2 (1-3) | 4 (3-5) | <0.001[a] |
| HFpEF-JH score | 0.6 (0.39-0.78) | 0.94 (0.87-0.98) | <0.001[a] |

Values are median (IQR: 0.25-0.75) or n (%). *P* values reported are based on a t-test[a] for normal continuous variables, chi-square for categorical variables[b], and Wilcoxon[c] for non-normal distributed continuous variables.
Abbreviations as in Table 1.

**TABLE 4 Correlation Matrix of the Variables Used for the Multivariate Logistic Regression Model**

| | eGFR | LA/LVr | LVMi | BMI |
|---|---|---|---|---|
| eGFR | 1.00 | −0.1305 | −0.1337 | 0.01901 |
| LA/LVr | −0.1305 | 1.00 | −0.0429 | −0.1091 |
| LVMi | −0.1337 | −0.0429 | 1.00 | −0.1802 |
| BMI | 0.01901 | −0.1091 | −0.1802 | 1.00 |

The values in the matrix represent Pearson's correlation coefficient of each interaction.

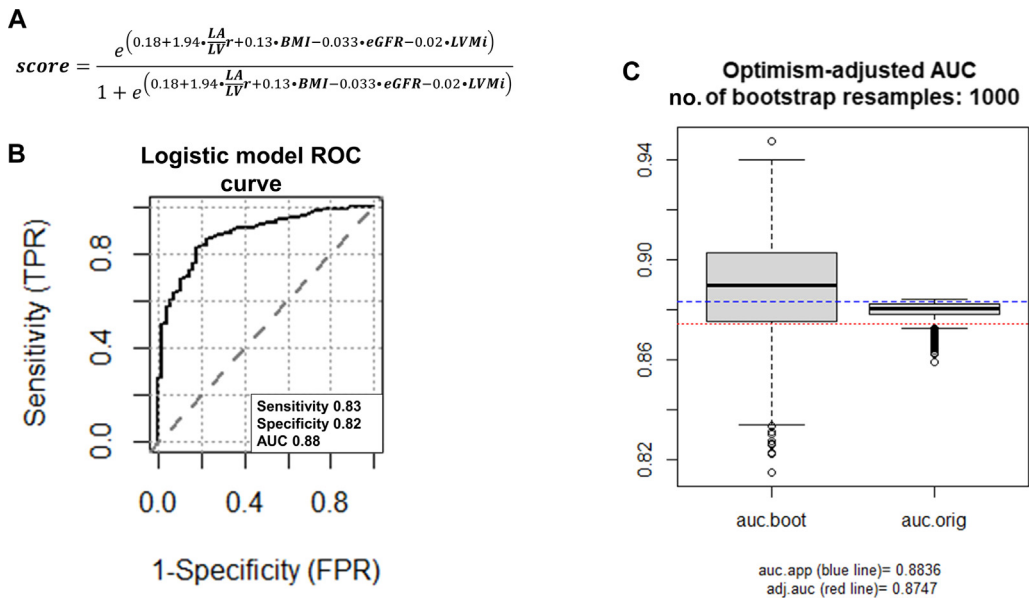
Abbreviations as in Table 1.

the LA/LVr is likely also a better reflector of the chronic burden of atrial fibrillation and increased LV filling pressures than a binary history of atrial fibrillation variable or a single time point measurement of E/e′). Lastly, natriuretic peptides, which are included in the HFA-PEFF score and often used for the diagnosis of HFpEF, also did not make it into the final score, but this too is not surprising given the insensitivity of natriuretic peptide as a diagnostic test for HFpEF in obese patients and the high prevalence of natriuretic peptide deficiency in HFpEF patients.[26]

It bears emphasis that our new score outperformed the H2FPEF score in patients with BMI>30 kg/m$^2$ but not in patients with BMI <30 kg/m$^2$. This likely reflects the fact that the median BMI of HFpEF patients in our study cohort (36.6) was higher than in the study cohort used to derive the H2FPEF score (33.0), and it suggests that the new score might be especially valuable in identifying HFpEF in obese patients.

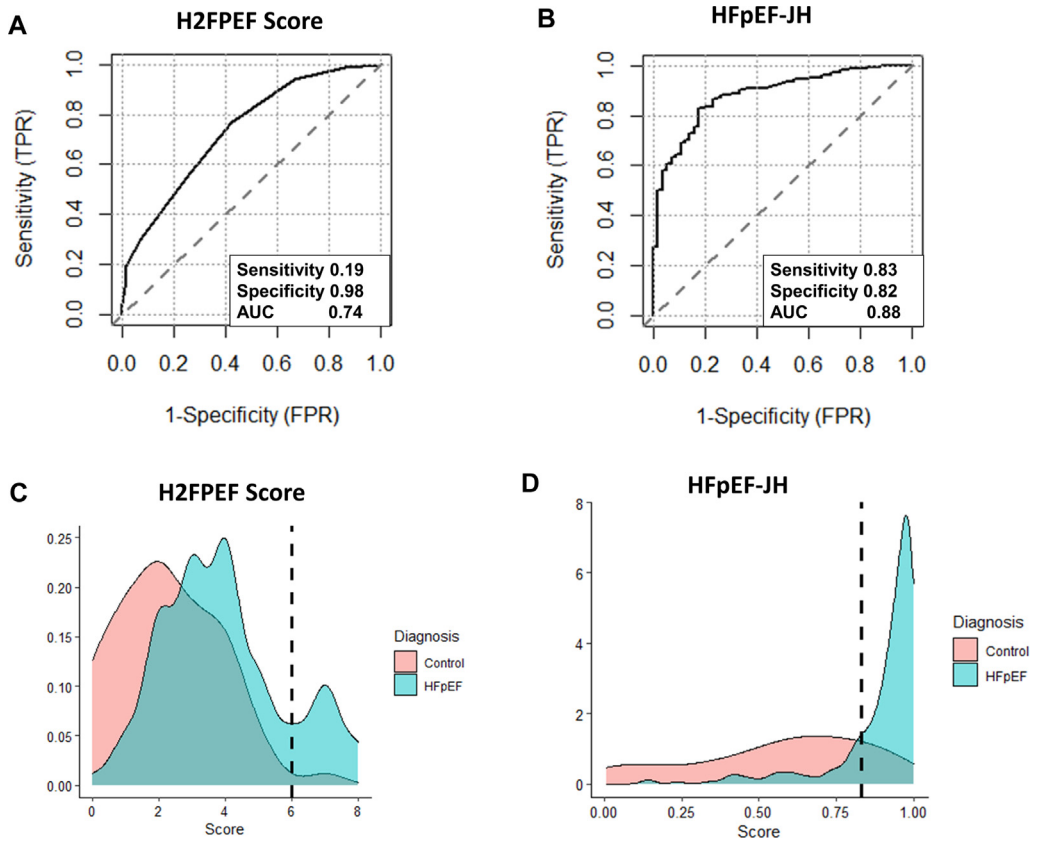
**STUDY LIMITATIONS.** Our study has several strengths, including the size and level of characterization of the cohort analyzed (including data on patients from 2 institutions), the inclusion of patients with high BMI, the identification of novel predictors of HFpEF, and the fact that we produced a score that, in the studied

**FIGURE 3 Multivariable Logistic Regression Model Built With the Top 4 Variables Identified via GBM**




(A) Formula of the regression model defined using the 4 variables selected based on the GBM output. (B) ROC curve of the logistic regression model in the studied cohort. The plot displays the sensitivity and specificity of the model at a cutoff of 0.83. (C) Optimism-adjusted AUC for the new score (HFpEF-JH). The box plot on the left represents an estimation of the performance by calculating the AUC from each bootstrap resample; the box plot on the right represents the AUC obtained from each model generated, tested in the original data subset where the model was generated. The analysis was done with 1,000 bootstrap resamples and the adjusted AUC was 0.87 versus 0.88 from the original model. The red line represents the adjusted AUC and the blue line is the AUC from the original model. FPR = false positive rateother; GBM = Gradient Boosting Machine; TPR = true positive rate; other abbreviations as in Figure 1.

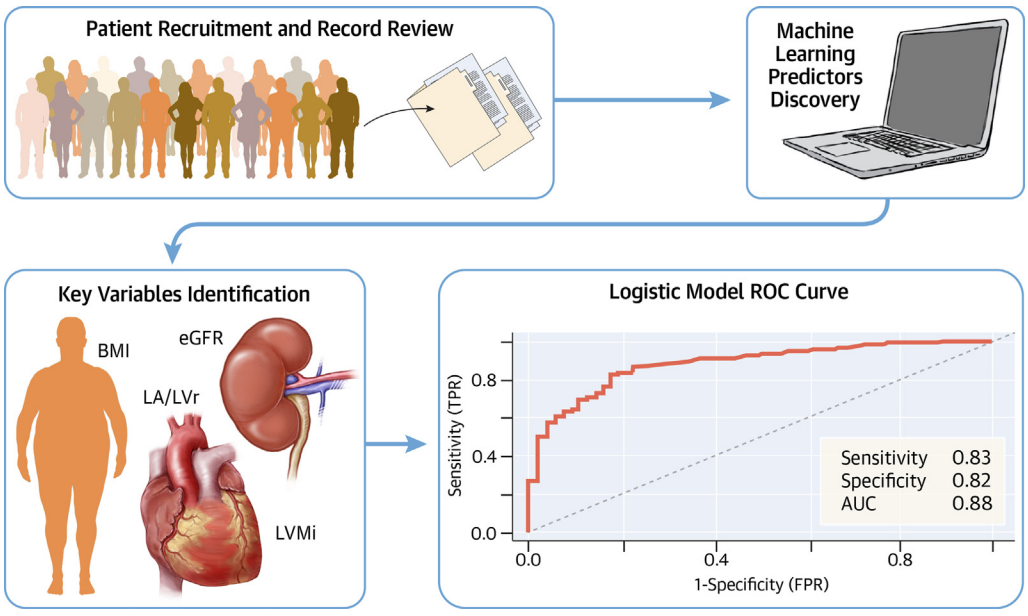
**FIGURE 4** Comparison of the H2FPEF Score and HFpEF-JH Score




A and B show the ROC curves of the H2FPEF and the HFpEF-JH scores in the regression cohort, respectively. The sensitivity, specificity, and AUC of the model at a cutoff of 6 (for the H2FPEF Score) and 0.83 (for the HFpEF-JH Score) are displayed. C and D show the density plots showing the distribution of HFpEF Patients and controls assessed with the H2FPEF score and HFpEF-JH score, respectively. The dashed lines on the density plots indicate the cutoff value of each score, 6 for the H2FPEF score and 0.83 for the HFpEF-JH score. A significant proportion of the HFpEF patients' H2FPEF score is distributed below the cutoff value of 6, mostly in the 3 to 6 range, while most of them score above the cutoff value (0.83) With the HFpEF-JH. Abbreviations as in **Figures 1 and 3**.

cohort, outperforms the current leading clinical prediction rule to detect HFpEF. However, our study is not without limitations. Firstly, while our data were validated internally using the bootstrap method, our findings were not validated in an independent cohort and, therefore, should be viewed as preliminary, given the need for external validation to be able to determine the utility of a diagnostic test. Although the HFpEF-JH score outperformed the H2FPEF score in our study, such a result could be expected since the HFpEF-JH score was derived in our study sample. Second, the study used previously collected data from prospective cohort studies, and therefore, candidate variables for the final score were limited to those available in the data sets used for score derivation. In the clinical setting, scores for the diagnosis of HFpEF are typically used when clinicians are unsure about the diagnosis, not in asymptomatic patients. Since the controls used to develop our score were asymptomatic patients, it is unclear how the score will perform in a real-life clinical scenario when the diagnosis of HFpEF is suspected due to the presence of symptoms or other clinical, laboratory, or imaging findings Finally, our controls had a median BMI of 26.99, considerably lower than the HFpEF patients included in the study.

**CENTRAL ILLUSTRATION** **Development of a Novel Score to Diagnose HFpEF in the Clinical Setting**




**Bermea KC, et al. JACC Adv. 2024;3(7):101040.**

1) A diverse cohort of well-characterized obese HFpEF patients and controls was created merging 2 existing cohorts of HFpEF patients. 2) The cohort was analyzed via machine learning to identify predictors of HFpEF diagnosis. 3) eGFR, BMI, LVMi, and LA/LV ratio emerged as the variables with the strongest association with the HFpEF diagnosis. 4) These variables were used to generate a regression model, and 5) the regression model was used to generate the HFpEF-JH Score, a novel score to help diagnose HFpEF in the clinical setting. BMI = body mass index; eGFR = estimated glomerular filtration rate; LA/LVr = left atrial to left volumes ratio; LVMi = left ventricular mass index; other abbreviation as in Figure 1.

## CONCLUSIONS

We identified BMI, eGFR, LVMi, and LA/LVr as the strongest predictors of HFpEF in an obese HFpEF cohort, and we used these variables to develop a novel score to detect HFpEF. The HFpEF-JH score is based on variables easily measurable with a standard echocardiogram, basic laboratory testing, and a physical exam. We provide an online form to calculate this score on any patient of interest with suspected HFpEF. This score points to novel and previously unappreciated predictors of HFpEF and, in our study cohort, identified HFpEF with higher sensitivity and overall discriminatory power than the leading score currently used to explore a potential diagnosis of HFpEF. The HFpEF-JH score (used in addition, or alternative to existing clinical decision tools) warrants external validation as the score could help improve diagnostic accuracy in the identification of HFpEF, particularly in obese patients, and especially when gold standard hemodynamic testing is not readily available.

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**ADDRESS FOR CORRESPONDENCE:** Dr Luigi Adamo, Division of Cardiology, Johns Hopkins University School of Medicine, 720 Rutland Avenue - Ross Research Building 809, Baltimore, Maryland 21205, USA. E-mail: ladamo2@jhmi.edu. X handle: @luigiadamomdphd OR Dr Kavita Sharma, Advanced Heart Failure & Transplant Cardiology, Johns Hopkins University Heart Failure with Preserved Ejection Fraction Program, The Johns Hopkins Hospital, 600 N. Wolfe Street - Carnegie 568C, Baltimore, Maryland, 21287, USA. E-mail: ksharma8@jhmi.edu. X handle: @KSharmaMD.

## PERSPECTIVES

**COMPETENCY IN MEDICAL KNOWLEDGE:** HFpEF is a debilitating condition and its diagnosis remains challenging. Using machine learning, we found that BMI, eGFR, LVMi, and LA/LVr are strongly associated with HFpEF. While the LA/LVr is not commonly reported, it can be easily calculated by having the LA and LV volumes which are usually part of the echocardiography report. We built a new score to identify HFpEF that incorporates these variables and outperformed existing scores for the diagnosis of HFpEF, especially in obese patients. This new score, named HFpEF-JH, could significantly facilitate the detection of HFpEF in the clinical setting. However, further validation of our findings in independent cohorts is needed before widespread use of this new score in the clinical setting.

**TRANSLATIONAL OUTLOOK:** The identification of BMI, eGFR, LVMi, and LA/LVr as the variables with the strongest association with HFpEF points to these parameters as promising clinical tools to detect and possibly monitor HFpEF patients. The HFpEF-JH score built using these variables could become a useful tool to screen patients for inclusion in clinical trials.

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**KEY WORDS** chronic kidney disease, HFpEF diagnosis, left atrial enlargement, left ventricular hypertrophy, obesity

**APPENDIX** For a supplemental table, please see the online version of this paper.