Echocardiographic Estimate of Pulmonary Capillary Wedge Pressure Improves Outcome Prediction in Heart Failure Patients With Reduced and Mildly Reduced Ejection Fraction

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Background: An echocardiographic algorithm to estimate pulmonary capillary wedge pressure (ePCWP) and pulmonary vascular resistance (ePVR) has been recently validated versus right heart catheterization.

Objective: To assess the prognostic significance of these measures in heart failure (HF) patients with reduced and mildly reduced ejection fraction.

Methods: Consecutive outpatients with HF and left ventricular ejection fraction (LVEF) <50% undergoing echocardiography were selected and followed up for the composite end point of all-cause death or HF hospitalization.

Results: Out of 2,214 patients (71 ± 12 years, 76% males, LVEF 35% ± 9%), ePCWP (16 ± 6 mm Hg) was elevated (>15 mm Hg) in 52% of cases and ePVR (1.7 ± 0.7 Wood units) was elevated (>2 Wood units) in 25% of cases. Patients with increased ePCWP were older and had a higher New York Heart Association class, more pronounced cardiac remodeling, systolic/diastolic dysfunction, and neurohormonal activation, particularly when ePVR was also elevated ($P < .001$). Over a median follow-up of 33 (17-48) months, both measures stratified patients for the risk of the primary end point (log-rank 151 for ePCWP and 60 for ePVR; $P < .001$). At adjusted regression analysis, ePCWP (hazard ratio for 1 mm Hg increase 1.03 [95% CI, 1.01-1.04]; $P < .001$) but not ePVR ($P = .07$) predicted the primary end point, even in patients with atrial fibrillation ($P = .019$), outperforming current diastolic dysfunction grading ($P < .001$) and both E/e' and left atrial volume index ($P < .001$). The addition of ePCWP to a multivariable prognostic model improved the accuracy of risk prediction ($P < .001$).

Conclusion: The echocardiographic estimates of PCWP retained clinical and prognostic significance in a large contemporary cohort of patients with chronic HF and LVEF <50%. (J Am Soc Echocardiogr 2025;■:■-■.)

Keywords: Pulmonary capillary wedge pressure, Filling pressures, Echocardiography, Diastolic function, Chronic heart failure

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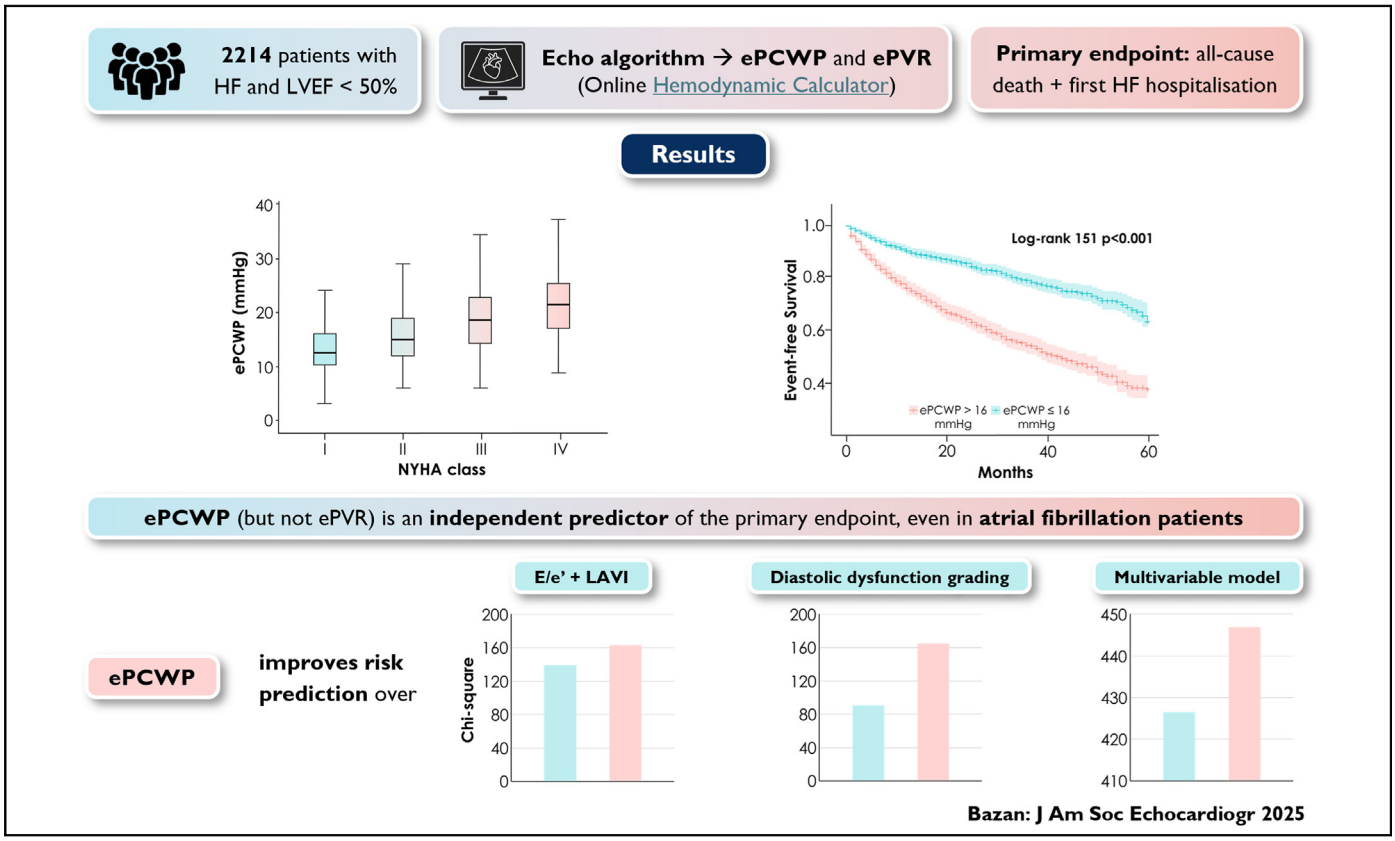

Central Illustration A quantitative echocardiographic algorithm to estimate PCWP retains clinical and prognostic significance in HF patients with LVEF <50%, even in patients with AF, outperforming both E/e' and LAVi and current diastolic dysfunction grading and improving the accuracy of risk prediction of a multivariable prognostic model.

Abbreviations

AF = Atrial fibrillation

CO = Cardiac output

COPD = Chronic obstructive pulmonary disease

eGFR = Estimated glomerular filtration rate

ePCWP = Estimated pulmonary capillary wedge pressure

ePVR = Estimated pulmonary vascular resistance

HF = Heart failure

HFmrEF = Heart failure with mildly reduced ejection fraction

HFpEF = Heart failure with preserved ejection fraction

HFrEF = Heart failure with reduced ejection fraction

HR = Hazard ratio

INTRODUCTION

Heart failure (HF) has been traditionally defined as the inability of the heart to match perfusion to systemic requests without increasing left ventricular (LV) filling pressures.[1] In the chronic setting, this results in a maladaptive response led by the activation of neurohormonal systems, with adverse remodeling, HF symptoms and signs, poor quality of life, and increased risk of hospitalization and cardiac death.[2]

Elevated LV filling pressures, at rest or during exercise, are landmark findings in HF patients and correlate to clinical severity.[3,4] Accordingly, the invasive measure of cardiopulmonary hemodynamics through right heart catheterization (RHC) has been associated with the risk of hospitalization and death in HF patients.[5-7]

While RHC remains the gold standard technique for assessing cardiopulmonary hemodynamics, its invasive nature and restricted accessibility pose challenges for large-scale population studies.[1,8] Echocardiography has therefore been proposed as a noninvasive, reliable, and cost-effective tool to estimate LV filling pressure and pulmonary and systemic hemodynamics in the clinical practice to improve HF management.[9] Accordingly, a multiparametric algorithm to estimate LV filling pressure has been proposed by the latest international guidelines.[10-14] However, the relatively high rate of indeterminate cases,[15] the qualitative output (elevated vs normal LV filling pressure), and the impossibility of applying this algorithm in specific subpopulations (e.g., patients with atrial fibrillation [AFI) are the major limitations of that algorithm.[16] Furthermore, the additional formula necessary to estimate pulmonary vascular resistance (PVR)[17] has been shown to lack accuracy in patients with elevated pulmonary capillary wedge pressure (PCWP).[18]

To address these limitations, a novel algorithm has been recently developed and validated in 795 patients undergoing RHC with the clinical suspicion of pulmonary hypertension, showing optimal accuracy in estimating PCWP (area under the curve = 0.97, 92% sensitivity, 93% specificity; $P < .001$) and PVR (area under the curve = 0.96, 89% sensitivity, 92% specificity; $P < .001$).[19] Notably, the precision of the model was also retained in patients with chronic HF ($n = 335$), including those with HF with either reduced ejection fraction (HFrEF, $n = 166$), mildly reduced ejection fraction (HFmrEF, $n = 31$), and preserved ejection fraction (HFpEF, $n = 138$), as well as in patients with AF ($n = 205$).[19]

ICD = Implantable cardioverter-defibrillator

IVCd = Inferior vena cava diameter

LAVi = Left atrial volume indexed

LV = Left ventricular

LVAD = Left ventricular assist device

LVEF = Left ventricular ejection fraction

mPAP = Mean pulmonary artery pressure

NT-proBNP = N-terminal fragment of pro-B-type natriuretic peptide concentration

NYHA = New York Heart Association

PCWP = Pulmonary capillary wedge pressure

PVR = Pulmonary vascular resistance

RAP = Right atrial pressure

RHC = Right heart catheterization

RVFAC = Right ventricular fractional area change

SCD = Sudden cardiac death

sPAP = Systolic pulmonary artery pressure

SV = Stroke volume

TAPSE = Tricuspid annular plane systolic excursion

WU = Wood unit

Therefore, the aim of this study was to assess the clinical and prognostic significance of the echocardiographic estimates of PCWP (ePCWP) and PVR (ePVR) in a large contemporary cohort of HF patients.

METHODS

Subjects and Study Design

For this study, clinical data and the index echocardiography exam performed at our center of prospectively enrolled consecutive patients with systolic HF (LV ejection fraction [LVEF] <50%), including those with either HFrEF (LVEF ≤40%) or HFmrEF (LVEF 41%-49%), referred to our center between January 2012 and April 2021, were retrospectively analyzed. To avoid potential misclassification due to the evolving definition of this syndrome and to mitigate the impact of specific etiologies and their treatments on cardiopulmonary hemodynamics,[20] patients with HFpEF (LVEF ≥50%) were not included in this study. Diastolic function assessment in specific cardiomyopathies presents complex and distinct characteristics, as highlighted in studies on hypertrophic cardiomyopathy, amyloidosis, and valvular heart disease[10,21]; these conditions require a dedicated investigation, considering both their pathophysiological features and the impact of disease-specific medical and interventional therapies.

Only outpatients not on parenteral diuretic therapy or pharmacological/mechanical hemodynamic support at enrollment were included.

All patients underwent a comprehensive two-dimensional echocardiogram (performed by either expert cardiologists or certified sonographers, under the supervision of an expert cardiologist) and a clinical and biohumoral evaluation, including the measurement of estimated glomerular filtration rate (eGFR; calculated through the CKD-EPI formula) and plasma N-terminal fragment of pro-B-type natriuretic peptide (NT-proBNP) concentration (ECLIA monoclonal method, Roche Diagnostics). The presence of AF at the time of echocardiography was recorded.

The study protocol was approved by the local institutional review board. Since all data were collected for clinical purposes and no invasive procedures were performed, no specific written consent form was necessary for this study. All patients provided consent for the use of their anonymized data for research purposes.

Transthoracic Echocardiography

A standard two-dimensional echocardiography (Philips iE33 or EPIQ7) was performed in all patients.[22-24] Each recorded clip consisted of ≥3 or ≥5 cycles in patients with sinus rhythm or AF, respectively. Chamber dimensions were indexed for body surface area (calculated using the Du Bois formula), while LVEF and indexed left atrium volume (LAVi) were estimated using Simpson's biplane method.[24] Stroke volume (SV) was calculated by multiplying the LV outflow tract velocity-time integral and its estimated cross-sectional area.[25] Cardiac output (CO) was obtained by the product of SV and heart rate, and cardiac index as the ratio of CO to body surface area. The average E/e' ratio for each patient was calculated using both lateral and medial E/e' values. Diastolic function was assessed using the multiparametric approach proposed by the latest international guidelines.[10,11]

Right atrial pressure (RAP) was evaluated semiquantitatively by assessing the maximum inferior vena cava diameter (IVCd) and its collapsibility.[22,26] Systolic pulmonary artery pressure (sPAP) was derived by the sum of RAP and the systolic pressure gradient, obtained from peak tricuspid regurgitation velocity using the simplified Bernoulli's equation.[10,11] Diastolic pulmonary artery pressure was estimated by adding RAP to the end-diastole pressure gradient of pulmonary regurgitation. Mean pulmonary artery pressure (mPAP) was estimated as $(\text{sPAP} + 2 \times \text{dPAP}) \div 3$.[27] Right ventricular systolic function was assessed as tricuspid annular plane systolic excursion (TAPSE), right ventricular S' wave, and right ventricular fractional area change (RVFAC).[26]

As detailed in Chubuchny *et al.*,[19] ePCWP was calculated as $(43 - 0.1 \times \text{TRV} - 0.5 \times \text{LVEF} + 1.0 \times \text{RVFAC} + 0.3 \times \text{LAVi} + 0.7 \times E/e' + 0.9 \times \text{IVCd}) \times \text{mPAP} \div 100$, and ePVR as $(\text{mPAP} - \text{PCWP}) \div \text{CO}$. While the formula includes IVCd, IVC collapsibility is also essential, as it is required for RAP estimation.

In case of missing variables, validated simplified equations were used (Supplemental Table 1).[19] These formulas were incorporated in an automated reporting system, allowing a quick and consistent evaluation of ePCWP and ePVR values without delay. A dedicated online platform has also been developed, intended solely for educational and research purposes, enabling automated calculation of ePCWP and ePVR values using the proposed formulas (Hemodynamic Calculator).

Follow-Up

Investigators blinded to clinical, biohumoral, and echocardiography data assessed patient outcomes by evaluation of electronic medical records or telephone interviews with patients, their relatives, or general practitioners. Follow-up was conducted until April 2023, and the primary end point was a composite of all-cause death and first HF-related hospitalization (intended as the first hospitalization for decompensated HF). Separate secondary end points were all-cause death, first HF-related hospitalization, cardiac death (intended as death secondary to HF progression, myocardial infarction, or sudden cardiac death [SCD]) or LV assist device (LVAD) implantation/heart transplantation, and the combination of SCD and appropriate implantable cardioverter-defibrillator (ICD) shock (intended as a shock occurring during sustained ventricular tachycardia or ventricular fibrillation).

HIGHLIGHTS

- Elevated LV filling pressures correlate to clinical severity and outcomes in HF.
- An echocardiographic algorithm to estimate PCWP and PVR has been recently validated.
- ePCWP predicted all-cause death and HF hospitalization in HFrEF and HFmrEF patients.
- ePCWP retained its prognostic efficacy even in patients with AF.
- ePCWP outperformed current diastolic dysfunction grading in risk prediction.

Statistical Analysis

Statistical analysis was conducted using SPSS software (ver. 25.0, 2017, IBM Statistics) and R software (ver., 2023, R Core Team), and a 2-tailed P value $\leq .05$ was considered statistically significant.

The study population was divided into subgroups according to the cutoffs of PCWP (15 mm Hg) and PVR (2 Wood units [WU]) proposed by the European guidelines on pulmonary hypertension.[8] Subgroups were compared regarding all baseline, clinical, biohumoral, and echocardiographic parameters. Continuous variables were reported as mean ± SD if normally distributed or median (interquartile range) for skewed distributions and compared using the unpaired Student's t test or the Mann-Whitney U test, as appropriate. Categorical variables were expressed as numbers (percentage) and compared using the χ^2 test. Comparisons among multiple groups were conducted via the one-way analysis of variance test or the Kruskal-Wallis test, as appropriate, with Bonferroni's correction for post hoc comparisons. When necessary, the Spearman correlation coefficient was assessed.

The relation between the linear changes in ePCWP and ePVR and the risk of the primary end point was modeled through the penalized-spline smoothing method,[28] while the optimal prognostic cutoffs were identified through the maximally selected log-rank statistics.[29,30] Kaplan-Meier curves and log-rank test were used to assess the risk of events according to these cutoffs.

Univariable and multivariable predictors of the primary end point (after logarithmic transformation in case of skewed variables) were identified through the Cox regression model. Only predictors with a univariable $P \leq .1$ were included into the final multivariable model. In the case of a significant number of missing values, the series mean imputation method was implemented to increase statistical power, as detailed in the Supplemental Material. The model assumptions (notably the proportionality of risks) were confirmed for all the metrics under investigation. To avoid collinearity issues, only variables with a Spearman correlation coefficient <0.6 were included in the multivariable model.

The Brier score was calculated at various time points to evaluate the predictive accuracy of the multivariable model, both before and after the inclusion of ePCWP.

The likelihood ratio test was performed, calculating and graphically reporting the change in global χ^2 values, to assess the improvement in risk prediction by adding ePCWP to a multivariable model, including the other independent outcome predictors, and to compare the accuracy in risk prediction of ePCWP versus diastolic dysfunction grading.

RESULTS

Out of 5,022 outpatients undergoing a first echocardiography in the study period, 2,808 (56%) were excluded because their LVEF was ≥50%. As a result, the final study cohort was composed of 2,214 patients (ages 71 ± 12 years, 76% men, 49% ischemic etiology). Among these, 714 (32%) reported a history of AF, while 302 (14%) patients had chronic obstructive pulmonary disease (COPD) and 594 (27%) were diabetic. Most patients received guideline-recommended medical and device therapies and were classified according to the New York Heart Association (NYHA) functional class I (19%), II (50%), III (23%), and IV (8%; Table 1).

As per entry criteria, LVEF was impaired (mean LVEF, 35% ± 9%; 63% HFrEF) and left chambers were dilated (LV end-diastolic volume index, 95 ± 28 mL/m^2; LAVi, 44 ± 15 mL/m^2). Forward LV output (SV index, 48 ± 11 mL/m^2) and right ventricular systolic function (TAPSE, 19 ± 5 mm) were generally preserved, while diastolic function was altered (E/e', 14 ± 8). The mean ePCWP and ePVR were 16 ± 6 mm Hg and 1.7 ± 0.7 WU (Table 1). Because of missing values (RVFAC in 497 cases, tricuspid regurgitation velocity in 32 cases, IVCd in 25 patients, LAVi in 12 patients), ePCWP and ePVR were estimated through simplified formulas in 539 (24%) cases (Supplemental Table 1).[19]

Clinical Correlates of PCWP and PVR

Patients with ePCWP >15 mm Hg ($n = 1151$, 52%) were older, had more comorbidities (all $P < .05$), received more antineurohormonal therapies and diuretics, and were more frequently implanted with devices (all $P < .001$; Table 1). The ePCWP was consistently associated with NYHA class ($P < .001$, Figure 1) and NT-proBNP levels ($R = 0.52$, $P < .001$; Supplemental Figure 1). Patients with elevated ePCWP had more advanced cardiac remodeling, lower SV index, and worse LV diastolic function (all $P < .001$). In accordance with the inclusion of those metrics in the algorithm, they also had worse LVEF, worse right ventricular systolic function, and higher pulmonary artery pressures (all $P < .001$).

Similar differences, although less pronounced, were found when patients were stratified according to ePVR, as detailed in Supplemental Table 2.

As reported in Figure 2, ePCWP showed a strong association with diastolic dysfunction grading.[10] Nonetheless, by using the current diastolic dysfunction grading, diastolic function was indeterminate or impossible to be categorized in 723 (33%) patients, with mean ePCWP values of 19 ± 6 mm Hg.[10]

Survival Analysis

Over a median follow-up of 33-months (17-48 months), 519 (23%) patients died. Of these, 255 patients died due to cardiac causes (206 HF progression, 31 SCD, 18 acute coronary syndrome) and 187 due to noncardiac causes. In 77 patients the cause of death could not be ascertained; in these cases, patients were censored at the time of death for the primary end point and for cardiac death. During the study, 351 (16%) patients were hospitalized at least once for HF decompensation, while 99 appropriate ICD shocks were reported. Five patients underwent LVAD implantation, and 3 patients received heart transplantation.

The optimal cutoffs of ePCWP and ePVR to predict the risk of the primary end point were 16 mm Hg and 2 WU, respectively

Table 1 Characteristics of the study population according to echo-derived ePCWP values

Variables	All patients *n* = 2214	ePCWP ≤15 mm Hg (*n* = 1063, 48%)	ePCWP >15 mm Hg (*n* = 1151, 52%)	*P*
Clinical features				
Age, years	71 ± 12	68 ± 13	73 ± 11	**<.001**
Sex, male	1,691 (76)	828 (78)	863 (75)	.11
BMI, kg/m^2	27 ± 5	26 ± 5	27 ± 5	**.011**
Ischemic etiology	1,079 (49)	519 (49)	560 (48)	.94
NYHA III-IV	677 (31)	187 (18)	490 (43)	**<.001**
AF	714 (32)	162 (15)	552 (48)	**<.001**
Hypertension	1,086 (49)	516 (49)	570 (50)	.71
Diabetes	594 (27)	244 (23)	350 (30)	**<.001**
COPD	302 (14)	113 (11)	189 (16)	**<.001**
Biohumoral data				
Hb, g/dL	13.0 ± 1.8	13.3 ± 1.7	12.8 ± 1.9	**<.001**
eGFR, mL/min/1.73 m^2	66 ± 25	73 ± 24	60 ± 25	**<.001**
NT-proBNP, ng/L	1,789 (668-4,551)	739 (303-1,789)	3,169 (1,428-7,167)	**<.001**
Treatment				
Beta-blockers	1,945 (88)	932 (88)	1,013 (88)	.33
ACEi/ARB	1,507 (70)	788 (74)	719 (63)	**<.001**
ARNI	212 (10)	79 (7.4)	113 (12)	**.001**
MRA	1,381 (64)	619 (58)	762 (66)	**<.001**
Furosemide	1,437 (66)	518 (49)	919 (80)	**<.001**
ICD	675 (30)	279 (26)	396 (34)	**<.001**
CRT	520 (24)	191 (18)	392 (29)	**<.001**
Echo variables				
LVEDVi, mL/m^2	95 ± 28	90 ± 24	99 ± 31	**<.001**
LAVi, mL/m^2	44 ± 15	36 ± 10	50 ± 16	**<.001**
LVEF, %	35 ± 9	39 ± 7	32 ± 9	**<.001**
SVi, mL/m^2	48 ± 11	51 ± 10	45 ± 11	**<.001**
Mean E/e'	14 ± 8	10 ± 4	18 ± 9	**<0.001**
ePCWP, mm Hg	16 ± 6	11 ± 2	21 ± 5	**<.001**
ePVR, WU	1.7 ± 0.7	1.5 ± 0.5	1.9 ± 0.8	**<.001**
sPAP, mm Hg	40 (33-48)	34 (30-38)	47 (41-55)	**<.001**
mPAP, mm Hg	23 (19-29)	19 (17-21)	29 (25-34)	**<.001**
TAPSE, mm	19 ± 5	20 ± 5	17 ± 5	**<.001**
RVFAC, %	38 ± 8	40 ± 7	37 ± 9	**<.001**
IVCd, mm	18 ± 5	16 ± 3	21 ± 5	**<.001**
Diastolic dysfunction grade 2-3	720 (33)	208 (20)	512 (52)	**<.001**
Moderate to severe MR	429 (19)	40 (4)	389 (34)	**<.001**
Moderate to severe TR	222 (10)	13 (1)	209 (18)	**<.001**

ACEi, Angiotensin converting-enzyme inhibitors; *ARB*, angiotensin receptor blockers; *ARNI*, angiotensin receptor-neprilysin inhibitors; *BMI*, body mass index; *CRT*, cardiac resynchronization therapy; *Hb*, hemoglobin; *LVEDVi*, LV end-diastolic volume index; *MR*, mitral regurgitation; *MRA*, mineralocorticoid receptor antagonists; *SVi*, SV index; *TR*, tricuspid regurgitation.
Values are mean ± SD, median (interquartile interval), or *n* (%).
Bold type indicates statistical significance.

(Supplemental Figure 2). Patients with ePCWP >16 mm Hg had a higher risk of the primary end point (hazard ratio [HR] = 2.57 [95% CI, 2.22-2.98]; $P < .001$) and of all-cause death (HR = 2.25 [95% CI, 1.89-2.71]; $P < .001$), first HF-related hospitalization (HR = 2.76 [95% CI, 2.20-3.45]; $P < .001$), and cardiac death or LV assist device (LVAD) implantation/heart transplantation (HR = 3.52 [95% CI, 2.63-4.72]; $P < .001$), but not of SCD or appropriate ICD shock ($P = .258$; Figure 3). The prognostic significance of ePCWP was maintained independently of LVEF (with a discriminatory power that diminished as LVEF decreased; Supplemental

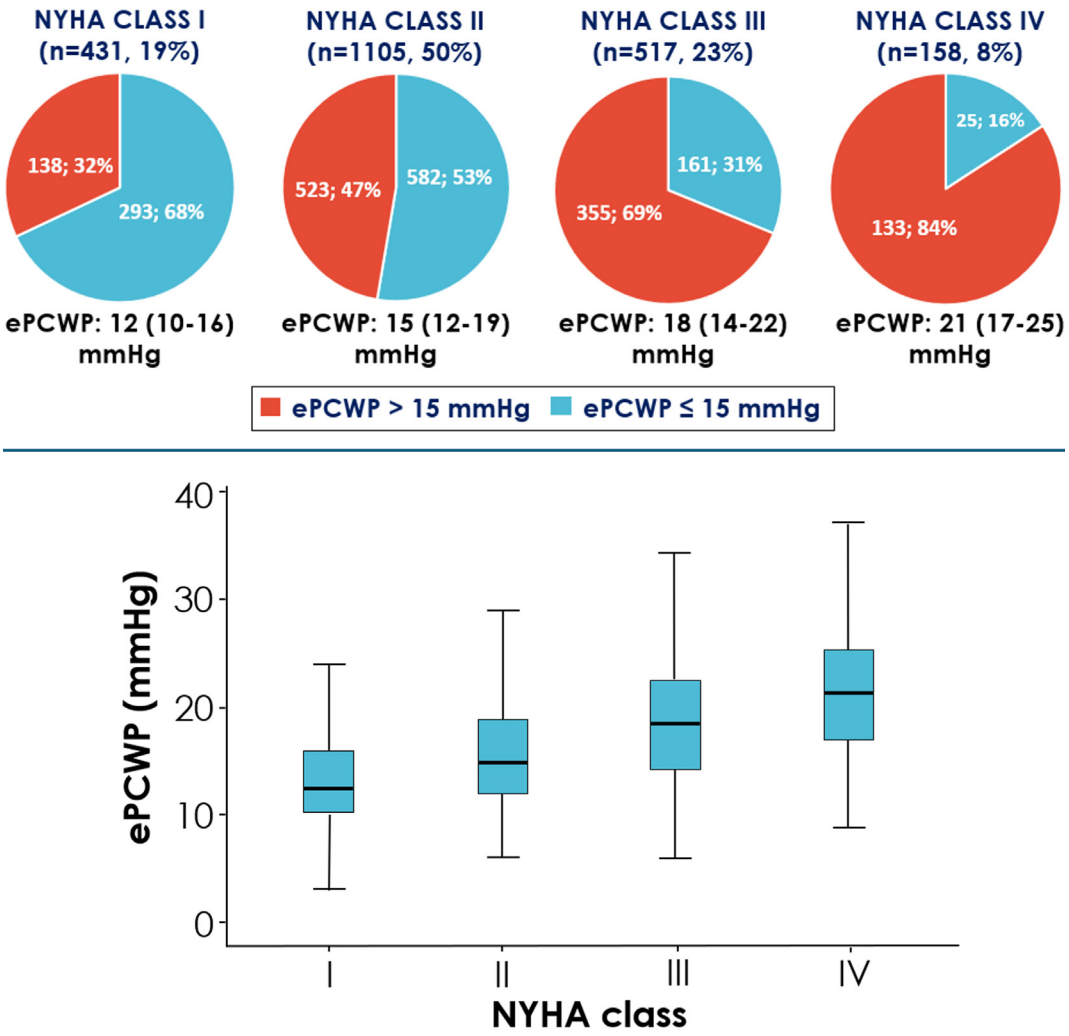

Figure 1 Relationship between ePCWP and NYHA functional class. *Upper panel*: Prevalence of increased ePCWP (>15 mm Hg) across NYHA classes. *Bottom panel*: Estimated PCWP values according to NYHA class. All post hoc comparisons were significant ($P < .001$).

Figure 3) and of the presence of AF at the time of the echocardiography (HR = 2.63 [95% CI, 1.96-3.54]; $P < .001$; Figure 4).

The prognostic significance of ePCWP was consistent also using the guideline-recommended 15 mm Hg cutoff (log-rank 125, $P < .001$; HR = 2.44 [95% CI, 2.09-2.85]; $P < .001$) and when considering the subpopulation ($n = 539$, 24%) in which simplified formulas for PCWP estimation were used (HR = 2.90 [95% CI, 2.15-3.91]; $P < .001$; Supplemental Figure 4).

Increased ePVR was associated with a higher risk of events (Supplemental Figure 5) but did not significantly improve risk prediction over ePCWP (Supplemental Figure 6).

As detailed in Table 2, at regression analysis ePCWP ($P = .001$), but not ePVR ($P = .07$), was an independent predictor of the primary end point (in a model adjusted for patient age, body mass index, NYHA class III to IV, AF, COPD, diabetes, hemoglobin, eGFR, NT-proBNP, TAPSE, and LVEF), also when considering only patients with AF ($P = .019$; Table 3) and when considering patients where simplified formulas for ePCWP calculation were used ($P = .003$; Supplemental Table 3). Notably, these findings were confirmed ($P = .037$) also when analyzing the study cohort without data imputation for hemoglobin, eGFR and NT-proBNP values ($n = 1,631$; Supplemental Table 4).

A multivariable model incorporating age, NYHA class III to IV, COPD, diabetes, hemoglobin, eGFR, NT-proBNP, TAPSE, and LVEF showed high prognostic accuracy at 6 months, moderate accuracy between 1 and 4 years, and modest accuracy at 5 years at Brier score analysis. The inclusion of ePCWP led to a consistent, albeit modest, improvement in accuracy, which increased over time (Supplemental Table 5).

The addition of ePCWP to this multivariable model improved risk prediction accuracy at likelihood ratio test (χ^2 difference = 22; $P < .001$; Figure 5).

When compared to the prognostic value of the guideline-recommended diastolic dysfunction grading, ePCWP was more accurate in predicting the risk of the primary end point (χ^2 difference = 73; $P < .001$; Figure 5) and stratified better patient risk at Kaplan-Meier analysis (log rank 151, $P < .001$ vs log rank 19, $P < .001$; Supplemental Figure 7).

Furthermore, ePCWP stratified patient risk across each diastolic dysfunction grade at univariate analysis, retaining prognostic accuracy

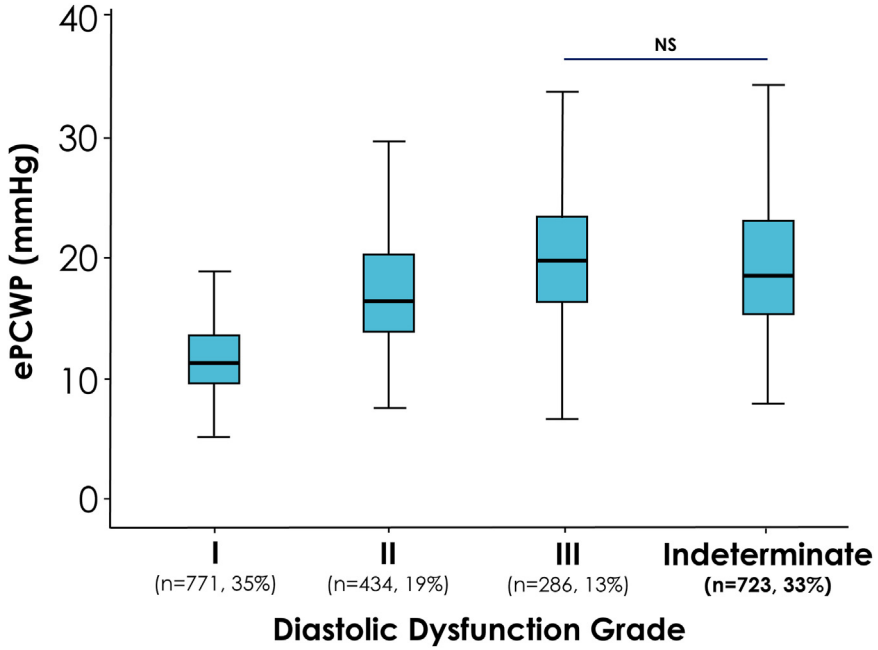

Figure 2 Estimated PCWP correlated with diastolic dysfunction grading. All post hoc comparisons (except for grade III vs indeterminate) were significant ($P < .001$).

also in indeterminate cases (grade I: HR = 1.13 [95% CI, 1.03-1.25]; $P = .010$; grade II-III: HR = 1.78 [95% CI, 1.38-2.30]; $P < .001$; indeterminate cases: HR = 2.62 [95% CI, 1.96-3.50]; $P < .001$).

Lastly, ePCWP outperformed both E/e' and LAVi in outcome prediction (ePCWP vs E/e': χ^2 difference = 86, $P < .001$; ePCWP vs LAVi: χ^2 difference = 73, $P < .001$), even when these parameters are considered together in a bivariate model (ePCWP vs LAVi + E/e': χ^2 difference = 19, $P < .001$; Supplemental Figure 9). Interestingly, these findings were confirmed both in the subpopulation with AF ($P < .001$) and in the subpopulation in which simplified formulas were used ($P = .001$).

DISCUSSION

This study represents the first evaluation of the clinical and prognostic significance of the echocardiographic estimates of PCWP and PVR, obtained through a recently validated algorithm,[19] in patients with HF and LVEF <50%.

Of note, ePCWP and ePVR were associated with both NYHA class and NT-proBNP levels as well as with a substantially higher risk of cardiac and all-cause death and of HF-related hospitalizations. However, only ePCWP was an independent predictor of the primary end point, improving model accuracy over other established clinical, biohumoral, and echocardiographic prognostic markers. Interestingly, the prognostic value of ePCWP was maintained across patient subgroups, including systolic and diastolic dysfunction strata, and in the subset with AF (Central Illustration).

In HF patients, LV diastolic pressure overload can increase hydrostatic pressure in pulmonary capillaries, causing pulmonary congestion and, consequently, dyspnea.[2] The NYHA classification, while widely used in clinical practice to assess symptoms severity, is inherently limited by its 4-category structure and its subjective nature, as dyspnea perception is influenced by several factors beyond hemodynamic congestion, including mobility, deconditioning, muscle wasting, central regulatory mechanisms, and pulmonary or neurological comorbidities.[2,31,32] Considering all these limitations, ePCWP manifested a robust relationship with NYHA class in this cohort, despite showing some expected overlap among the 4 NYHA classes. This noninvasive and quantitative assessment could therefore optimize the management of patients with dyspnea, potentially reducing the need for other invasive and costly procedures.[33,34]

Similarly, in this cohort, ePCWP correlated well with natriuretic peptides concentrations, another marker of hemodynamic overload.[1] Nevertheless, the assessment of individual natriuretic peptide levels may be influenced by factors such as hypoxia/ischemia, inflammation, or responses to other neurohormones, as well as by other confounders (e.g., renal function, aging, and body constitution).[35,36] Therefore, the integration of these values with ePCWP could yield a more comprehensive understanding of status of the individual patient, driving tailored therapeutic decisions.

Both the invasive measurement of PCWP through RHC and diastolic dysfunction evaluation through echocardiography have been previously associated with the risk of hospital admission and death in HF patients.[5-7,12] The present study confirmed these results, particularly highlighting a striking correlation between increased ePCWP values and HF hospitalizations (Figure 3). This suggests that ePCWP may be a useful tool for assessing the risk of these events, which deteriorate the patient's quality of life and impose significant costs on the healthcare system.

The efficacy of ePCWP in prognostic stratification decreased across LVEF tertiles. This decline can be attributed to the increasing impact of other concurrent prognostic factors as LVEF worsens. As LVEF declines, pathophysiological mechanisms such as myocardial fibrosis, adverse ventricular remodeling, and neurohormonal activation become more prominent. These factors, which are not directly related to diastolic dysfunction, significantly influence the prognosis in patients with reduced LVEF.[37] Additionally, factors such as low CO,

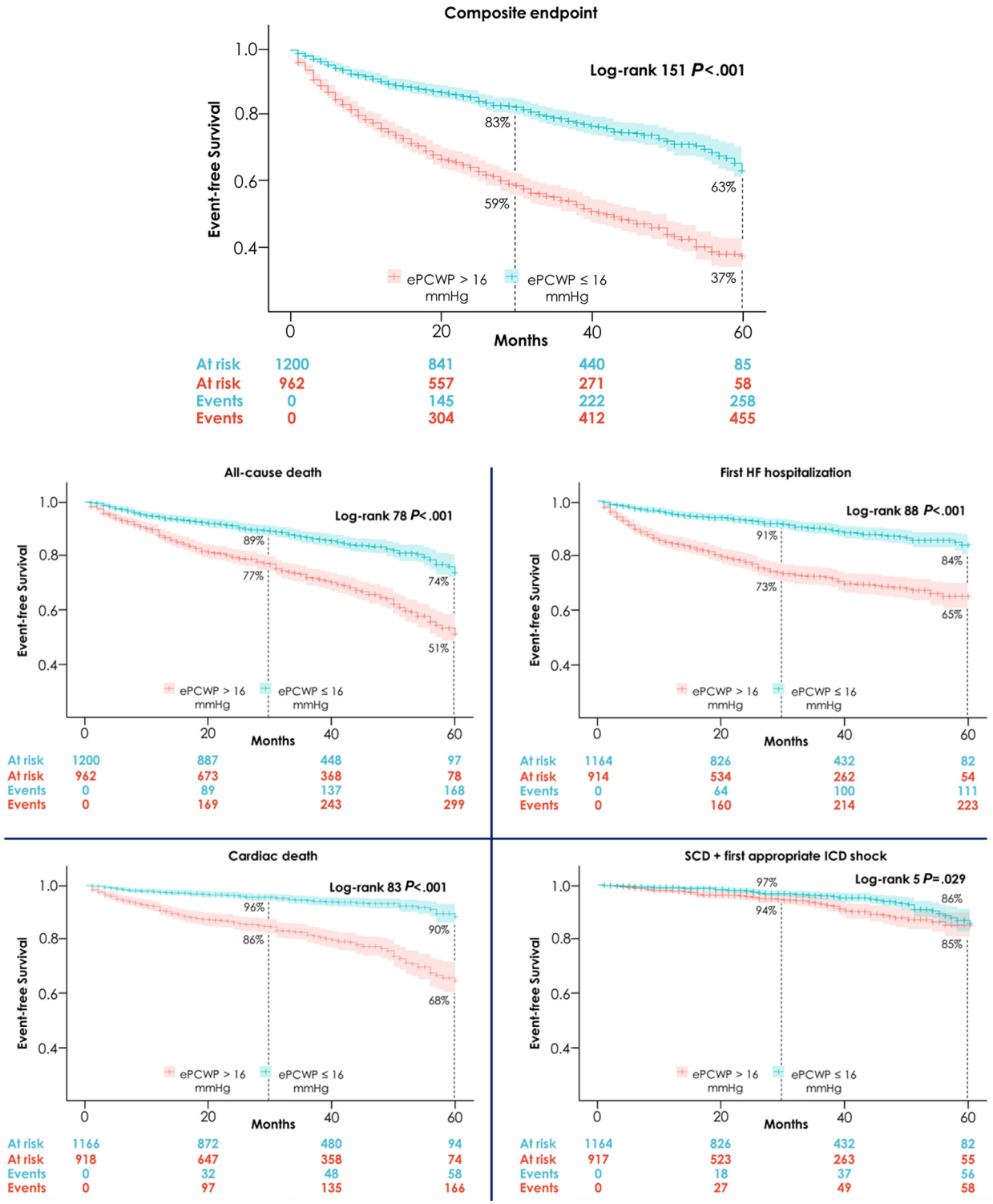

Figure 3 Kaplan-Meier curves for primary and secondary end points according to ePCWP. Patients with ePCWP >16 mm Hg showed a higher risk of the primary composite end point (all-cause death or first HF hospitalization) and of all the secondary end points (all-cause death, first HF hospitalization, cardiac death and heart transplantation or LVAD implantation, SCD, and first appropriate ICD shock).

cardiac cachexia, and increased susceptibility to infections further contribute to the complexity of prognosis in this population.[38]

Patients with augmented LV filling pressures can benefit from a more aggressive diuretic therapy, to ameliorate symptoms and reduce hospitalization and cardiovascular deaths.[39] Moreover, some recent trials suggested the potential beneficial effect of some modern HF drugs on LV filling pressures, namely sacubitril/valsartan and SGLT2 inhibitors.[40-42] These medications allow for a reduction in the

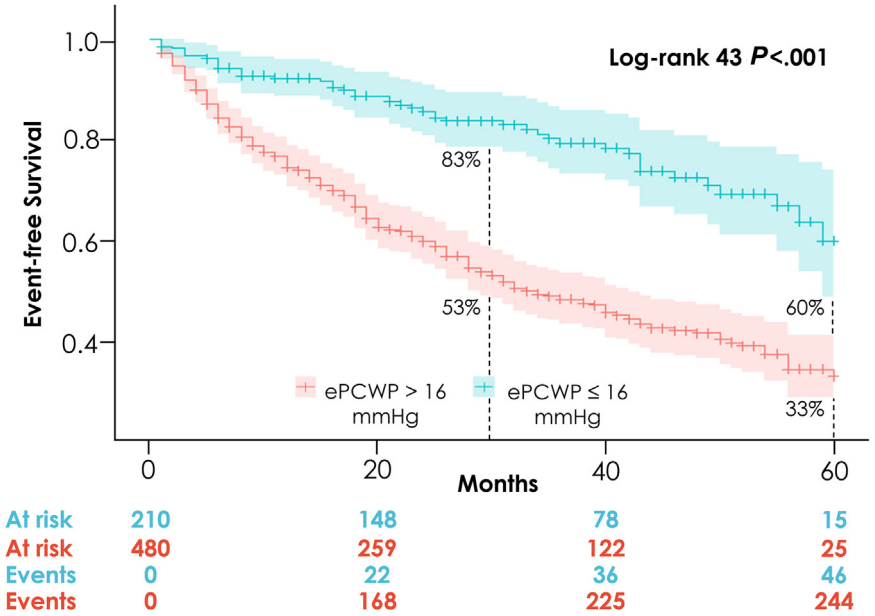

Figure 4 Kaplan-Meier curves for the primary end point according to ePCWP in patients with AF. The prognostic value of estimated ePCWP was maintained in patients with AF.

dosage of traditional diuretics, representing a significant therapeutic resource for patients with elevated ePCWP.

Compared with ePCWP, ePVR showed a less robust association with the severity of the dyspnea. This is not surprising considering that pulmonary vascular remodeling in HF, due to backward transmission of elevated LV filling pressures on the right side of the heart, could mitigate the severity of pulmonary congestion and dyspnea, at least in a first stage, until right ventricular function deteriorates.[2,32]

The 2016 American Society of Echocardiography/European Association of Cardiovascular Imaging algorithm to assess diastolic function has previously shown good prognostic performance.[13,43] Nevertheless, this algorithm retains important drawbacks: (1) it provides a qualitative assessment of LV filling pressures; (2) it may not be applied to patients with AF; and (3) it yields a significant number of indeterminate cases.[10,19] The relatively higher proportion of indeterminate cases in this cohort (33%) compared to previous studies

Table 2 Multivariable Cox regression analyses for the primary end point

	Univariable model			Multivariable model		
Predictors	HR	95% CI	*P*	HR	95% CI	*P*
Age, years	**1.05**	**1.04-1.05**	**<.001**	**1.02**	**1.01-1.03**	**<.001**
Sex, male	1.06	0.89-1.25	.52	—	—	—
BMI, kg/m^2	**0.98**	**0.97-0.99**	**.019**	0.99	0.97-1.01	.13
Ischemic etiology	1.13	0.98-1.30	.10	—	—	—
NYHA class III-IV	**2.56**	**2.22-2.95**	**<.001**	**1.33**	**1.12-1.56**	**0.001**
AF	**1.35**	**1.17-1.58**	**<.001**	1.03	0.88-1.22	.70
Hypertension	1.05	0.92-1.22	.46	—	—	—
COPD	**1.91**	**1.60-2.27**	**<.001**	**1.46**	**1.22-1.75**	**<.001**
Diabetes	**1.37**	**1.18-1.60**	**<.001**	**1.19**	**1.01-1.39**	**.033**
Hb, g/dL	**0.79**	**0.76-0.83**	**<.001**	**0.93**	**0.89-0.97**	**.002**
eGFR, mL/min/m^2	**0.98**	**0.97-0.98**	**<.001**	**0.99**	**0.98-0.99**	**<.001**
Log (NT-proBNP), ng/L	**3.18**	**2.80-3.61**	**<.001**	**1.38**	**1.14-1.67**	**.001**
TAPSE, mm	**0.92**	**0.91-0.94**	**<.001**	**0.97**	**0.95-0.99**	**.001**
LVEF, %	**0.97**	**0.96-0.97**	**<.001**	**0.98**	**0.97-0.99**	**.05**
ePCWP, mm Hg	**1.08**	**1.07-1.10**	**<.001**	**1.03**	**1.01-1.04**	**.001**
ePVR, WU	**1.43**	**1.33-1.54**	**<.001**	1.09	0.99-1.21	.07

BMI, Body mass index; *Hb*, hemoglobin; *LVEDVi*, LV end-diastolic volume index.
Bold type indicates statistical significance.

Table 3 Multivariable Cox regression analyses for the primary endpoint in patients with AF (n = 684)

Predictors	Univariable model			Multivariable model		
	HR	95% CI	*P*	HR	95% CI	*P*
Age, years	**1.05**	**1.03-1.06**	**<.001**	**1.02**	**1.01-1.04**	**.001**
Sex, male	0.84	0.65-1.10	.18	—	—	—
BMI, kg/m^2	0.99	0.96-1.01	.23	—	—	—
Ischemic etiology	1.23	0.98-1.53	.07	—	—	—
NYHA class III-IV	**2.51**	**2.01-3.13**	**<.001**	**1.45**	**1.15-1.84**	**.002**
Hypertension	0.88	0.70-1.09	.24	—	—	—
COPD	**1.39**	**1.05-1.86**	**.024**	**1.38**	**1.05-1.83**	**.023**
Diabetes	1.20	0.95-1.52	.12	—	—	—
Hb, g/dL	**0.80**	**0.75-0.85**	**<.001**	**0.89**	**0.84-0.95**	**<.001**
eGFR, mL/min/m^2	**0.98**	**0.96-0.97**	**<.001**	**0.99**	**0.98-0.99**	**<.001**
Log (NT-proBNP), ng/L	**4.43**	**3.51-5.58**	**<.001**	**1.85**	**1.35-2.54**	**<.001**
TAPSE, mm	**0.92**	**0.90-0.95**	**<.001**	0.98	0.95-1.01	.14
LVEF, %	**0.97**	**0.96-0.98**	**<.001**	1.00	0.98-1.01	.80
ePCWP, mm Hg	**1.09**	**1.07-1.11**	**<0.001**	**1.03**	**1.01-1.05**	**.019**
ePVR, WU	**1.27**	**1.12-1.44**	**<.001**	1.12	0.97-1.29	.11

BMI, Body mass index; *Hb*, hemoglobin.
Bold type indicates statistical significance.

(17%-20%)[11] may be partially attributed to the inclusion of patients with AF, whereas most other studies excluded these patients.

The use of ePCWP may overcome such limitations. Indeed, by providing a quantitative estimate of LV filling pressures, it may be more informative in the single patient. Furthermore, through the use of validated simplified formulas, ePCWP is evaluable in nearly all patients, independently of the severity of LV dysfunction or the presence of AF.[19] Although ePCWP estimated using simplified formulas exhibits a slightly weaker correlation with invasive PCWP measurement,[19] it maintained high predictive accuracy and served as an independent prognostic marker, enabling risk stratification even in the absence of certain echocardiographic parameters.

Due to the complexity of guideline algorithms and their limited applicability in certain clinical scenarios, diastolic dysfunction grading in current practice is often inferred from a limited set of parameters, primarily E/e′ and LAVi. However, multiple studies have demonstrated that neither of these indices alone provides sufficiently accurate assessments of diastolic function.[44] In our cohort, ePCWP outperformed both E/e′ and LAVi in predicting outcomes, even in patients with AF. Moreover, ePCWP proved to be easily obtainable in nearly all patients without prolonging examination time, making it a valuable tool for routine assessment of LV filling pressure with both strong diagnostic and prognostic utility.

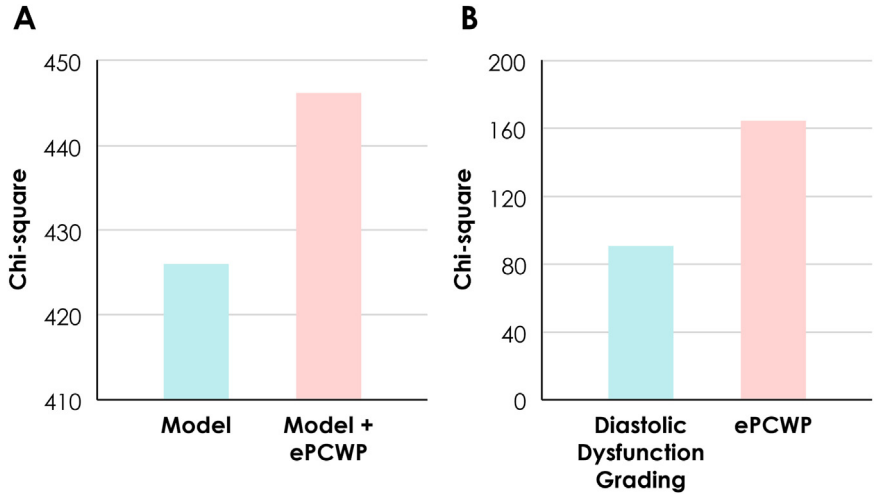

Figure 5 Estimated PCWP improves risk prediction of a clinical multivariable model and outperforms current diastolic dysfunction grading. **(A)** The addition of ePCWP to a clinical multivariable model (including patient age, NYHA class III-IV, AF, COPD, diabetes, hemoglobin, eGFR, NT-proBNP, TAPSE, and LVEF) yielded a significant improvement in risk prediction. **(B)** Estimated PCWP outperformed current diastolic dysfunction grading in outcome prediction. $P < .001$ for all comparisons.

Recently, another algorithm to estimate PCWP with echocardiography has been shown to retain prognostic value in a retrospective study, despite being validated against RHC only in a small subset of patients ($n = 53$) and being less strongly correlated to the invasive measure of PCWP compared to that used in this study ($R = 0.67$ vs $R = 0.85$).[45] While the inclusion of pulmonary vein systolic pressure as a key parameter of the algorithm may limit its external applicability, patients exhibiting AF and/or significant mitral valve disease were excluded, leaving a gap in the validity of that approach within a substantial portion of HF patients.

A recent study proposed a cardiac magnetic resonance–based approach for estimating PCWP (ePCWP).[46] However, its accuracy was found to be inferior to that of comprehensive echocardiographic assessment. Moreover, cardiac magnetic resonance remains a costly technique with limited availability in many cardiology centers worldwide, further restricting its clinical applicability.

While in this study (including patients with left-sided heart disease) ePVR did not improve risk prediction over ePCWP, recent evidence suggests that this may not be true in patients with pulmonary hypertension.[47] Indeed, the lack of predictive value of PVR should be interpreted with caution, as posttreatment hemodynamics were not available in this investigation.[48] Additionally, the presence of other conditions associated with precapillary pulmonary hypertension (e.g., COPD, thromboembolic disease, obstructive sleep apnea) may have acted as confounders, potentially influencing outcome results; besides, only a relatively small proportion of patients in our cohort had significantly elevated ePVR values, thus reducing its statistical power in multivariable analysis. The possibility of obtaining a quantitative estimate of both PCWP and PVR may thus prove its value in other specific populations.

Study Limitations

Due to the cross-sectional study design, the possible implications of longitudinal changes in ePCWP and PVR, particularly following therapeutic changes, remain to be investigated.

As detailed in the methods section, the study population consisted of patients with HF and LVEF <50%. Future studies should confirm the clinical and prognostic value of the proposed formulas in patients with HFpEF, specific cardiomyopathies, or other groups of pulmonary hypertension.

Owing to the retrospective design, a significant proportion of missing biohumoral data required mean imputation to enhance the statistical power of the multivariable analysis; nonetheless, our findings remained consistent even without data imputation, confirming their validity and robustness. In a similar fashion, due to the use of the echocardiographic data reported at the time of the examination, novel parameters related to diastolic function such as left atrial strain or global longitudinal strain were not reported because they were missing in most patients. While future studies should investigate the interactions between these measures and ePCWP and ePVR, which may be complementary, the use of deformation imaging remains scarce (<40%) in the routine practice, as recently reported by an international survey, mainly because of time constraints, low reproducibility, and intervendor variability.[49]

The presence of B lines, that is, another index of pulmonary extravascular congestion, was not assessed in this study. While previous evidence found only modest correlation between PCWP and B lines count,[50] ePCWP, as a quantitative measure of intravascular congestion, might provide deeper insight into patient hemodynamics, being less influenced by possible confounders such as primitive lung diseases, nephrotic syndrome, and systemic sclerosis.[51]

CONCLUSION

These findings demonstrate the robust clinical and prognostic significance of the echocardiographic estimates of PCWP (and, to a lesser extent, PVR) in patients with HF and LVEF <50%. These parameters, measurable in nearly all patients, correlate with symptoms and natriuretic peptides levels and are strongly associated with the risk of adverse events over time.

Importantly, compared to the 2016 guidelines algorithm for the assessment of diastolic dysfunction, the proposed approach provides a quantitative evaluation of LV filling pressures, even in AF patients, drastically reducing the rate of indeterminate cases and improving the accuracy in risk prediction.

If routinely obtained in the outpatient setting, this information can facilitate early identification of high-risk patients, potentially reducing the need of RHC and enabling a tailored therapeutic approach to improve hemodynamic status and, ultimately, *quoad vitam* and *quoad valetudinem* prognosis.

DATA AVAILABILITY

The data underlying this article cannot be shared publicly due to the privacy of individuals that participated in the study. The data will be shared on reasonable request to the corresponding author.

CONFLICT OF INTEREST

None.

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None.

SUPPLEMENTARY DATA

Supplementary data related to this article can be found at https://doi.org/10.1016/j.echo.2025.04.005.

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