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Accuracy and diagnostic performance of doppler echocardiography to estimate mean pulmonary artery pressure in heart failure

Alva Björkman BSc[1] | Lars H. Lund MD, PhD[2] | Ulrika Ljung Faxén MD, PhD[2,3] |
Per Lindquist PhD[4] | Ashwin Venkateshvaran PhD[2] (iD)

[1] Department of Clinical Physiology, Karolinska Institutet, Stockholm, Sweden

[2] Department of Medicine, Cardiology Unit, Department of Clinical Physiology, Karolinska Institutet, Stockholm, Sweden

[3] Perioperative Medicine and Intensive Care, Karolinska University Hospital, Stockholm, Sweden

[4] Department of Clinical Physiology, Surgical & Perioperative sciences, Umeå University, Umeå, Sweden

Correspondence
Ashwin Venkateshvaran PhD, FASE, FESC, Department of Cardiovascular Research, Karolinska University Hospital, 17176, Sweden.
Email: ashwin.venkateshvaran@ki.se

Abstract

Background: Multiple echocardiographic algorithms have been proposed to estimate mean pulmonary artery pressure (PAP_M) and assess pulmonary hypertension (PH) likelihood. We assessed the accuracy of four echocardiographic approaches to estimate PAP_M in heart failure (HF) patients undergoing near-simultaneous right heart catheterization (RHC), and compared diagnostic performance to identify PH with recommendation-advised tricuspid regurgitation peak velocity (TRV_{max}).

Methods: We employed four validated echocardiographic algorithms incorporating tricuspid regurgitation peak or mean gradient, pulmonary regurgitation peak gradient, and right ventricular outflow tract acceleration time to estimate PAP_M. Echocardiographic estimates of right atrial pressure were incorporated in all algorithms but one. Association and agreement with invasive PAP_M were assessed. Diagnostic performance of all algorithms to identify PH was evaluated and compared with the recommended TRV_{max} cut-off.

Results: In 112 HF patients, all echocardiographic algorithms demonstrated reasonable association (r = .41–.65; $p < 0.001$) and good agreement with invasive PAP_M, with relatively lower mean bias and higher precision observed in algorithms that incorporated tricuspid regurgitation peak or mean gradient. All methods demonstrated strong ability to identify PH (AUC = .70–.80; $p < 0.001$) but did not outperform TRV_{max} (AUC = .84; $p < 0.001$). Echocardiographic estimates of right atrial pressure were falsely elevated in 30% of patients.

Conclusions: Echocardiographic estimates demonstrate reasonable association with invasive PAP_M and strong ability to identify PH in HF. However, none of the algorithms outperformed recommendation-advised TRV_{max}. The incremental value of echocardiographic estimates of right atrial pressure may need to be re-evaluated.

KEYWORDS
pulmonary hypertension, right heart catheterization, tricuspid regurgitation peak velocity

1 | INTRODUCTION

Pulmonary hypertension (PH) is common in heart failure (HF)[1] and is associated with poor prognosis.[2] Passive downstream elevations in left heart pressures often combined with pulmonary arteriolar remodeling are seen both in HF with preserved (HFpEF) and reduced ejection fraction (HFrEF) and carry therapeutic implications.[3] PH is defined as per current recommendations as a mean pulmonary artery pressure (PAP_M) $\geq$ 25 mm Hg at rest, measured during right heart catheterization (RHC).[4] In recent years, expert groups have recommended a revised cut-off as PAP_M > 20 mm Hg.[5,6] Although definite diagnosis necessitates an invasive evaluation of PAP_M, Doppler echocardiography is routinely employed to screen for PH and evaluate hemodynamic severity during follow-up. Multiple approaches to estimate PAP_M using echocardiography have been previously proposed.[7–13] Most algorithms incorporate elements of Doppler analysis obtained from tricuspid regurgitation (TR),[7,10,11,13] pulmonary regurgitation (PR)[9] or flow across the right ventricular outflow tract (RVOT)[8,14] into empirical relationships to obtain PAP_M. However, the accuracy of these approaches to estimate invasive PAP_M in the specific setting of HF has not been studied. Further, current ESC recommendations do not advise use of any echocardiographic algorithms to assess PAP_M but instead recommend the use of tricuspid regurgitation peak velocity (TRV_{max}) cut-off > 2.8 m/sec to assign PH probability.[4] Availability of alternative echocardiographic approaches that represent invasive PAP_M could potentially replace TRV_{max} during screening, and may even obviate the need for invasive assessment.

With this background, we aimed to study the feasibility and accuracy of four different echocardiographic algorithms to estimate PAP_M in a retrospective analysis of HF subjects undergoing near-simultaneous RHC. Further, we wished to compare the diagnostic performance of these algorithms with recommendation-based TRV_{max} to identify PH.

2 | METHODS

2.1 | Study population

Echocardiographic examinations of consecutive patients with clinically judged HF referred for RHC to the Karolinska University Hospital between 2014 and 2018 were retrospectively reviewed. All subjects were hemodynamically stable during assessment and medical therapy was suitably titrated. Patients in atrial fibrillation or with significant arrhythmias and/or poor echocardiographic image quality precluding accurate measurement were excluded. Thereafter, subjects with isolated pre-capillary alterations on RHC were excluded from the analysis. The study was approved by the local ethics committees (DNR 2008/1695-31) and all patients provided written informed consent.

2.2 | Echocardiographic evaluation

All patients underwent comprehensive echocardiography employing a Vivid E9 ultrasound system (GE Ultrasound, Horten, Norway) by a single experienced echocardiographer (AV) in keeping with current recommendations.[15] 2D gray-scale images were acquired at 50–80 frames/sec and Doppler tracings were recorded using a sweep speed of 100 mm/sec. Three consecutive heart cycles were acquired in sinus rhythm. TR was measured with Continuous wave Doppler, considering the most optimal signal obtained from multiple echocardiographic windows. PR was obtained with Continuous wave Doppler from the parasternal short-axis view at the level of the semi-lunar valves. Right ventricular outflow tract flow was obtained by placing a 5-mm Pulsed Doppler signal in the RVOT just proximal to the pulmonic valve. All images were subsequently exported and analyzed offline (EchoPAC PC, version 11.0.0.0 GE Ultrasound, Waukesha, Wisconsin, USA) by an experienced, credentialed echocardiographer blinded to catheterization data.

A summary of approaches employed to evaluate PAP_M are illustrated in Figure 1. Broadly, PAP_M was evaluated using four different algorithms taking into consideration evaluation of TR,[7,10] PR,[9] and RVOT acceleration time ($RVOT_{AT}$).[8] Applying the approach postulated by Aduen et al.,[7] PAP_M was estimated by adding TR mean pressure gradient to recommended estimates of right atrial pressure (RAP) obtained from inferior vena cava (IVC) size and collapsibility.[15] The second approach by Chemla et al. calculated PAP_M from estimated systolic pulmonary artery pressure (PAP_S) obtained by adding the gradient corresponding with peak TR velocity (TRV_{max}) to IVC-estimated RAP using the relationship $PAP_M = .61 \times PAP_S + 2$ mm Hg.[10] In the third approach (Abbas and colleagues), PAP_M was estimated by adding gradients obtained from peak PR velocity to corresponding IVC-estimated RAP.[9] Finally, in the fourth approach proposed by Dabestani et al., $RVOT_{AT}$ was defined during systole as time in milliseconds from beginning of flow to peak velocity. PAP_M was then calculated as $PAP_M = 90 - (.62 \times RVOT_{AT})$ when AT < 120msec and $79 - (.45 \times RVOT_{AT})$ when AT $\geq$ 120msec.[8]

2.3 | Invasive evaluation

Echocardiographic examinations were followed by RHC within a 1-hour period. Pharmacological status was unaltered between echocardiography and catheterization. RHC was performed by experienced operators blinded to echocardiography examinations using a 6F Swan Ganz catheter employing jugular or femoral vein access. After suitable calibration with the zero-level set at the mid-thoracic line, pressure measurements were taken from the right atrium (RA), right ventricle (RV), and pulmonary artery (PA) during end-expiration. Five to 10 cardiac cycles were acquired and all pressure tracings were stored and analyzed offline using a standard hemodynamic software package (WITT Series III, Witt Biomedical Corp., Melbourne, FL, USA).
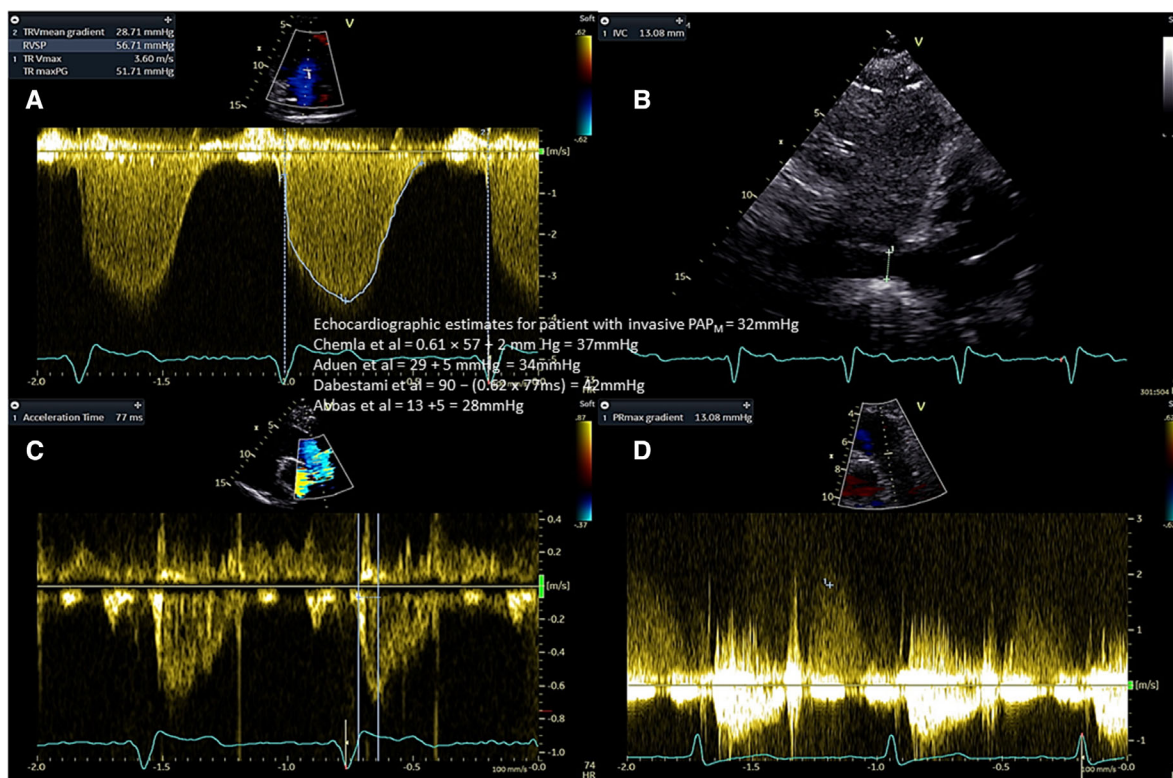
FIGURE 1 Illustration of echocardiographic estimates in a patient with invasive PAPM = 32 mm Hg. (A) Tricuspid regurgitation CW Doppler spectrum was analyzed to assess TRV_{max} (Chemla et al.) and TR mean gradient (Aduen et al.), (B) IVC size and collapse to estimate RAP (Chemla et al., Aduen et al., Abbas et al.), (C) RVOT acceleration time assessed by PW Doppler (Dabestami et al.), (D) PR peak gradient assessed by CW Doppler (Abbas et al.). Resultant echocardiographic estimates for each algorithm are provided

2.4 | Statistical analysis

Normality was tested using the Shapiro-Wilk test and visually reaffirmed using QQ plots. Continuous variables were expressed as mean ± SD for parametric variables or median (inter-quartile range) for non-parametric variables and categorical variables were expressed as numbers and percentage. Correlations between Doppler PAP_M approaches and corresponding invasive measurements were performed using the Pearson's 2-tailed test (correlation between two continuous variables). Accuracy was defined as the difference of the mean bias and precision as the spread of data points between echocardiographic and invasive measurements on Bland-Altman analysis. Receiver operating characteristics (ROC) curve was employed to illustrate diagnostic potential of both TRV_{max} and echocardiographic algorithms. Sensitivity, specificity, negative predictive value (NPV) and positive predictive value (PPV) were measured. IBM SPSS statistics version 23.0 was employed for analysis.

3 | RESULTS

3.1 | Study population

Of 212 enrolled in the study, 45 patients with atrial fibrillation and 46 with pacemaker therapy were first excluded. Nine patients were subse-

quently excluded after RHC revealed isolated pre-capillary alterations. Ultimately, 112 patients (60 ± 16 years; 46% Female) were included in the analysis. Baseline characteristics are presented in Table 1. All subjects demonstrated signs and symptoms of HF, elevated NTproBNP and objective evidence of LV systolic and/or diastolic function. Echocardiographic and invasive data of the cohort is presented in Table 2. LV EF was reduced (< 50%) in 55 (49%) of the patients. Patients had elevated filling pressures represented by elevated mitral E/e', dilated LA volumes and elevated PA systolic pressure. Further, the cohort demonstrated elevated PA systolic, diastolic, mean pressures (PAP_S, PAP_D, and PAP_M respectively), mean pulmonary capillary wedge pressures ($PAWP_M$) and increased pulmonary vascular resistance (PVR) on RHC. Sixty-five patients (58%) demonstrated PH, as defined by $PAP_M \geq 25$ mm Hg in keeping with current recommendations. Seventy-eight patients (70%) demonstrated PH when the revised $PAP_M > 20$ mm Hg cut-off was considered.

3.2 | Feasibility and accuracy of doppler PAP_M algorithms

Echocardiographic assessment of PAP_M was most feasible employing the approach considering $RVOT_{AT}$ introduced by Dabestani et al.[14] (86% of patients could have PAP_M assessed using this method), followed by TR-derived assessments by Chemla et al.[10] (84%) and Aduen

TABLE 1 Characteristics of patient population

	All patients (n = 112)
Demographics	
Age (years)	60 ± 16
Female	51 (46)
Medical history	
Diabetes	20 (18)
Hypertension	68 (61)
Hypercholesteremia	36 (32)
NYHA Class	
I/II/III/IV	11/18/77/6
	(10/16/69/5)
Clinical assessment	
Heart rate (bpm)	69 ± 14
Body surface area (m^2)	1.92 ± .2
Systolic blood pressure (mm Hg)	117 ± 24
Diastolic blood pressure (mm Hg)	66 ± 13
Laboratory	
NTproBNP (ng/L)	1450 (395:2730)
Hemoglobin (g/L)	131 ± 98
Serum creatinine (μmol/L)	98 ± 37
Diagnosis	
Restrictive cardiomyopathy	9 (8)
Dilated cardiomyopathy	30 (27)
Hypertrophic cardiomyopathy	4 (4)
Ischemic cardiomyopathy	17 (15)
Multifactorial	48 (43)
Myocarditis	4 (3)

Data presented as mean ± SD/ median (Q1;Q3) or number (%).
Abbreviations: NYHA, New York heart association function class; NTproBNP, N-terminal pro b-type natriuretic peptide.

TABLE 2 Invasive and echocardiographic data of patient population

	All (n = 112)
Right heart catheterization	
PAWP$_M$ (mm Hg)	17 ± 8
PAP$_S$ (mm Hg)	45 ± 18
PAP$_D$ (mm Hg)	18 ± 9
PAP$_M$ (mm Hg)	29 ± 12
RAP$_M$ (mm Hg)	8 ± 6
RVP$_S$ (mm Hg)	44 ± 18
RVP$_D$ (mm Hg)	10 ± 6
PVR (WU)	2.7 ± 1.9
TPG (mm Hg)	12 ± 7
CO (L/min)	4.7 ± 1.6
Echocardiography	
Left heart	
LVIDd (mm)	55 ± 13
LVEDV (ml)	157 ± 90
LV mass (gm)	221 ± 96
LVEF (%)	46 ± 20
LV E/e' average	14 ± 6
LAVI (ml/m^2)	47 ± 17
Right heart	
RVIDd (mm)	40 ± 8
TAPSE (mm)	17 ± 5
RVSP (mm Hg)	48 ± 17
RA area (cm^2)	20 ± 7

Data presented as mean ± SD or number (%).
p-value represents difference between RA reservoir strain subgroups.
Abbreviations: PAWP, pulmonary capillary wedge pressure, PAP$_M$, mean pulmonary artery pressure; PAP$_D$, diastolic pulmonary artery pressure; RAP, right atrial pressure; RVP, right ventricular pressure; PVR, pulmonary vascular resistance; TPG, transpulmonary gradient; CO, cardiac output; LVIDd, left ventricular internal diameter during end-diastole; LVEDV, left ventricular end-diastolic volume; EF, ejection fraction; RVID, right ventricular internal diameter end-diastole; TAPSE, tricuspid annular plane systolic excursion; TRV$_{max}$, tricuspid regurgitation max velocity; RVSP, right ventricular systolic pressure; LAVI, left atrial volume index.

et al.[7] (81%). PAP$_M$ estimated using the PR-derived approach (Abbas et al.[9]) was least feasible of the four methods (53%). All echocardiographic PAP$_M$ algorithms demonstrated a moderately significant correlation with invasive variables (r = .41–.65; *p* < 0.001 for all) (Figure S1). The method proposed by Aduen et al.[7] demonstrated the strongest correlation with invasive PAP$_M$ (r = .65; *p* < 0.001), comparable with recommendation-based TRV$_{max}$ (r = .64; *p* < 0.001). Agreement between each echocardiographic approach and RHC was studied using Bland-Altman analysis (Figure 2). Echocardiography demonstrated good accuracy to represent invasive pressures in the methods employing TR gradients (Aduen et al.[7] and Chemla et al.[10]), as seen in relatively low bias between echocardiography and RHC (bias = +2.4 and -2.4 mm Hg, respectively). Moderate precision was observed with limits of agreement (mean value ± 1.96 x SD) in the range of ±20 mm Hg for both methods. Relatively higher systematic error between diagnostic modalities was observed for approaches by Dabestani et al.[14]

(that employed RVOT$_{AT}$) that overestimated invasive measurements (bias = +4.2 mm Hg) and Abbas et al.[9] (that employed PR peak velocity) that underestimated invasive measurements (bias = -6.1 mm Hg). Relatively wider limits of agreement were seen in both algorithms.

3.3 | Diagnostic performance of echocardiographic algorithms to identify PAP$_M$ ≥ 25mm Hg

Recommendation-based TRV$_{max}$ demonstrated strong discriminatory ability to identify invasive PAP$_M$ ≥ 25 mm Hg (AUC = .84, CI .76–.91; *p* < 0.001) (Figure 3A). All echocardiographic approaches
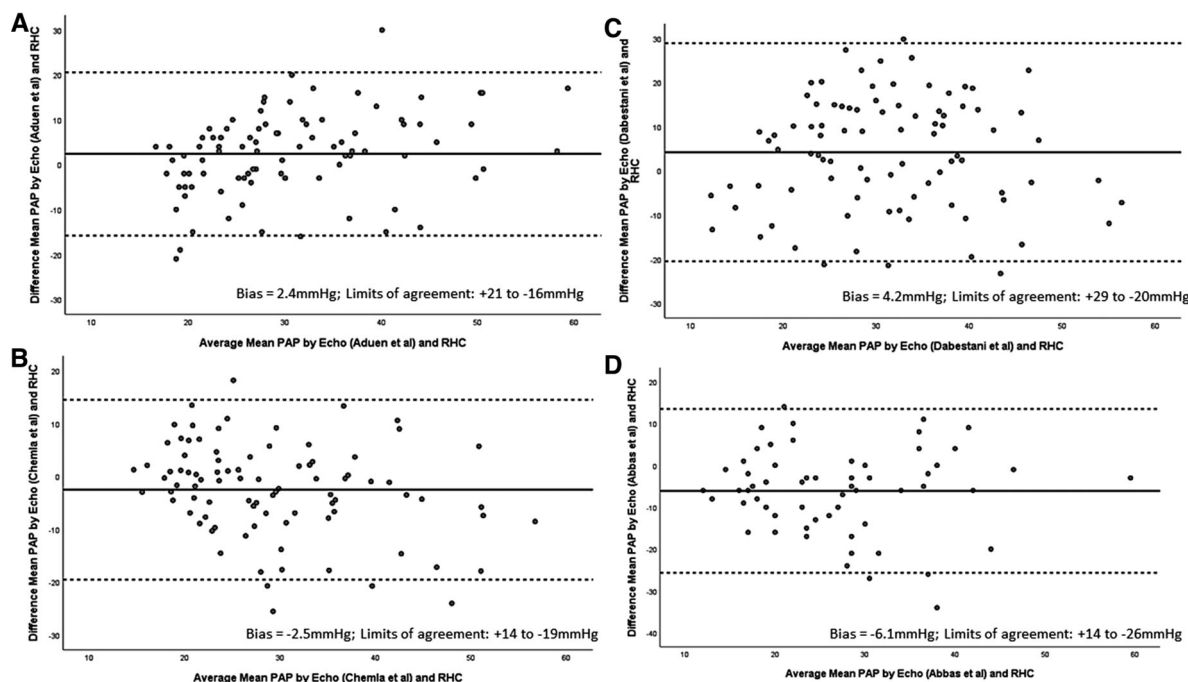
FIGURE 2 Bland-Altman plots illustrating agreement between echocardiographic algorithms and invasive PAPM measurements
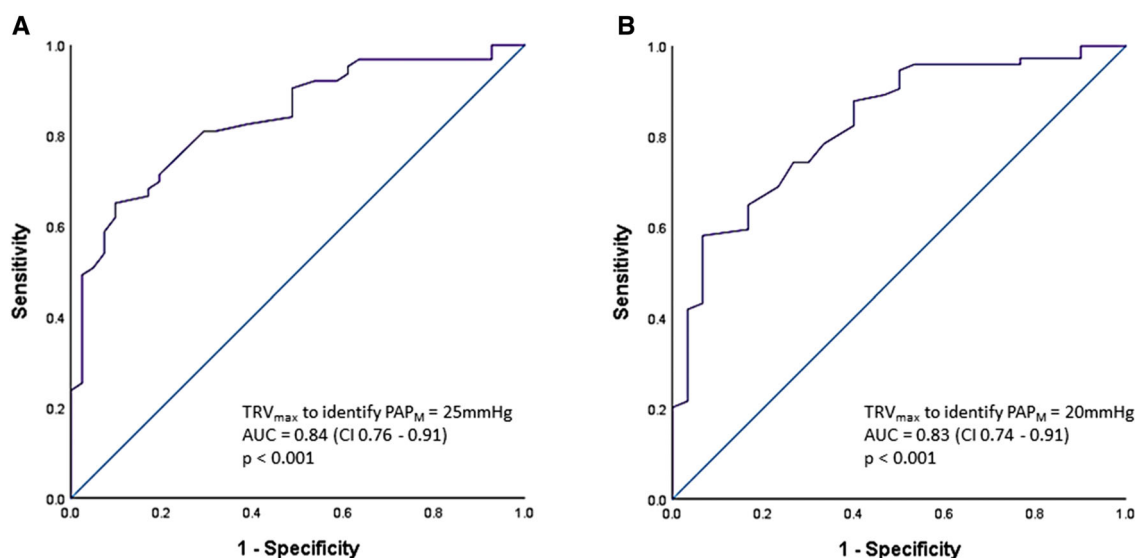

FIGURE 3 Receiver operator characteristics analysis illustrating diagnostic performance of TRV_{max} to identify (A) $PAP_M \geq 25$ mm Hg and (B) $PAP_M > 20$ mm Hg

demonstrated moderate to strong discrimination (AUC range .70–.80; $p < 0.001$ for all) with the Chemla et al. algorithm[10] demonstrating strongest diagnostic performance (AUC = .80, CI .71–.89; $p < 0.001$) (Figure 4). Sensitivity, Specificity, PPV, and NPV of TRV_{max} and algorithms to identify invasive $PAP_M \geq 25$ mm Hg are presented in Table 3. The recommended TRV_{max} cut-off of 2.8 m/sec demonstrated 83% sensitivity and 61% specificity to identify $PAP_M \geq 25$ mm Hg. At a cut-off of 25 mm Hg, PAP_M derived by Aduen et al.[7] and Dabestani et al.[14] demonstrated low specificity (38% and 35%, respectively) and Abbas et al.,[9] low sensitivity (48%). The only algorithm to show compara-

ble, strong, balanced sensitivity and specificity was that proposed by Chemla et al.[10] (78% sensitivity and 67% specificity).

3.4 | Diagnostic performance of echocardiographic algorithms to identify $PAP_M > 20$ mm Hg

When a revised, lowered PH cut-off was considered, TRV_{max} continued to demonstrate strong diagnostic ability (AUC = .83, CI .74–.91; $p < 0.001$) (Figure 3B) when compared with other echocardiographic
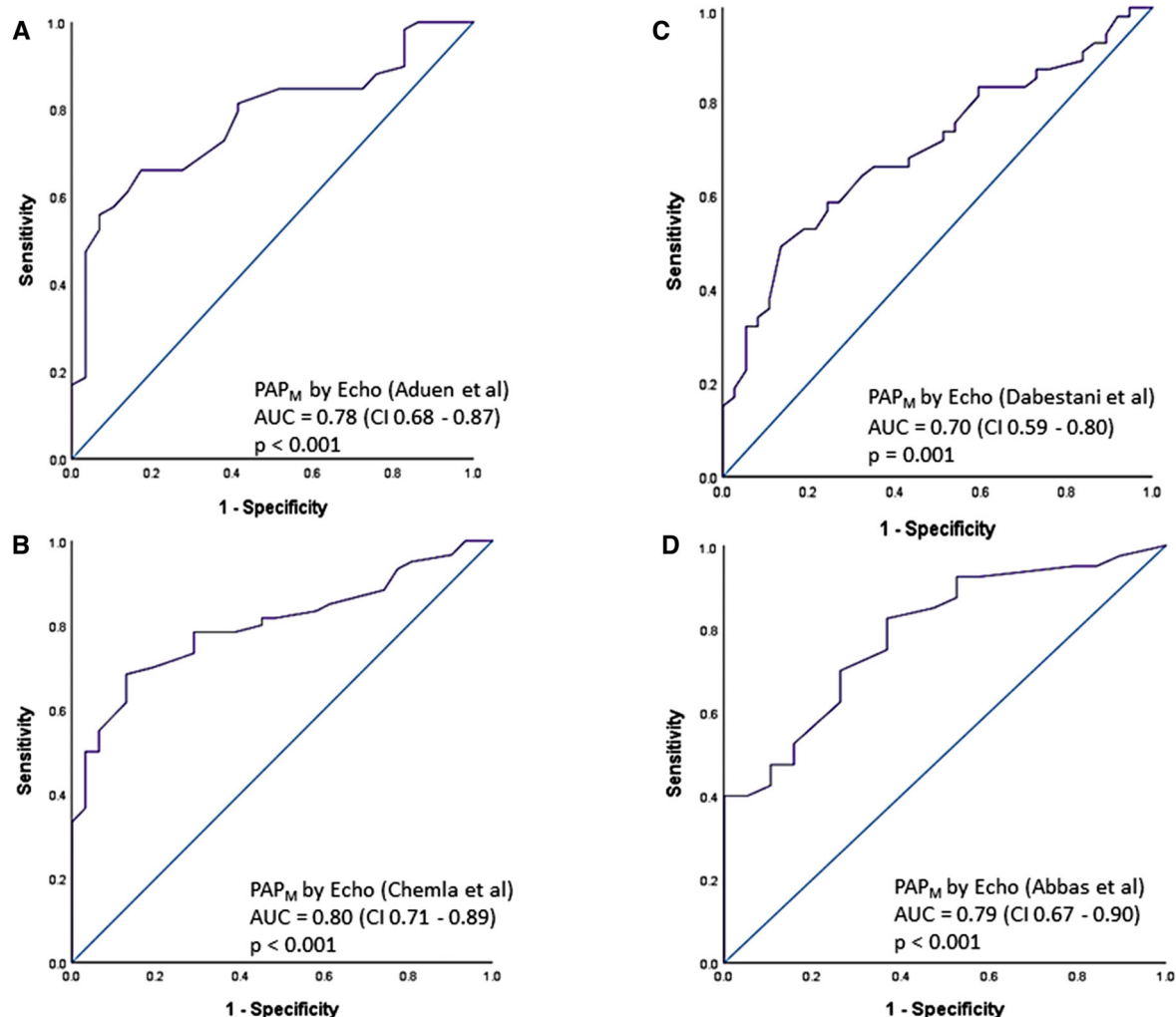
FIGURE 4 Receiver operator characteristics analysis illustrating diagnostic performance of echocardiographic algorithms to identify $PAP_M \geq$ 25 mm Hg

TABLE 3 Sensitivity, specificity, positive predictive value, negative predictive value for recommendation-based cut-off in addition to echocardiographic algorithms to identify invasive $PAP_M \geq$ 25 mm Hg

Method	Cut off	Sensitivity (%)	Specificity(%)	Positive predictive value (%)	Negative predictive value (%)
Aduen et al.	25 mm Hg	85	38	74	55
Chemla et al.	25 mm Hg	78	67	80	63
Dabestani et al.	25 mm Hg	83	35	63	61
Abbas et al.	25 mm Hg	48	84	86	43
TRV_{max}	2.8 m/sec	83	61	77	69

approaches (AUC range .67–.71; $p < 0.05$) (Figure S2). At a cut-off of 2.8 m/sec, TRV_{max} demonstrated 78% sensitivity and 68% specificity to identify invasive $PAP_M > 20$ mm Hg. Specificity was generally low for all echocardiographic methods (17%–35%) with the exception of the algorithm proposed by Abbas et al.[9] (64% sensitivity, 67% specificity) (Table S1)

3.5 | Accuracy of echocardiographic right atrial pressure estimates

Echocardiographic RAP employing IVC size and collapse were incorporated to calculate PAP_M in all echocardiographic algorithms with the exception of the approach postulated by Dabestani et al.[12] In 107

subjects (96%) with interpretable images, RAP estimated by IVC was elevated (8 or 15 mm Hg) in 78% subjects ($n = 83$, RAP = 8 mm Hg in 43 and 15 mm Hg in 40 subjects). However, false positives were frequent, as seen in 12 of 40 patients (30%) with significantly elevated RAP estimated by echocardiography (15 mm Hg) that had normal invasive RAP (≤ 7 mm Hg).

4 | DISCUSSION

To the best of our knowledge, this is the first study to evaluate the accuracy of multiple echocardiographic algorithms to estimate PAP_M and study diagnostic performance to identify PH in the specific setting of HF. All four echocardiographic algorithms demonstrated reasonable association and good agreement with RHC, with generally lower bias seen in algorithms considering tricuspid mean or peak gradient. However, none of the echocardiographic algorithms outperformed TRV_{max} to identify PH in the ROC analysis.

The accuracy of echocardiographic algorithms to estimate pulmonary artery pressures has been a matter of debate. Earlier studies suggest that echocardiography frequently over- or underestimates invasive pulmonary pressures and should not be relied upon.[16,17] More recent studies, however, have emphasized results of Bland-Altman analyses that display low bias between echocardiographic and invasive measurements, suggesting that Doppler estimates are highly accurate for population studies.[18,19] Our data suggests that accuracy of echocardiographic estimates may also vary based on approach utilized. Minimal bias was observed in methods that incorporated TRV_{max}, corroborating an earlier study employing high-fidelity catheters that suggests that the most accurate estimate of PAP_M is obtained by assessment of systolic PA pressures alone.[20] Higher systemic bias with invasive measurements and lower precision reflected in wider limits of agreement employing both PI (Abbas et al.[9]) and $RVOT_{AT}$ (Dabestani et al.[14]) seen in this study may, at least in part, be attributable to smaller patient cohorts ($n = 23$ and 39, respectively) and less severe clinical presentations in the original studies. As seen in the Bland-Altman plots, a greater dispersion of points is observed at higher mean values of PAP_M, suggesting that these methods may be less reliable in the setting of severe PH. The cohort examined by Abbas et al. demonstrated a $PAP_M = 25$ (range 10–57) mm Hg and $PAWP_M = 15$ (range 2–38) mm Hg, suggesting a milder hemodynamic presentation compared with cohort in our study.[9] Dabestani et al. do not present corresponding values in their cohort, but suggest a PAP_M range, that is, relatively lower than that in our study with lower PH cut-off (20 mm Hg).[14] Additionally, the empirical algorithms presented using this method may demonstrate limited utility in the setting of severely elevated PAP_M, as alluded to in certain comparative studies evaluating multiple echocardiographic approaches.[21] Despite displaying relatively lower precision and agreement with invasive measurements, both the abovementioned methods demonstrated good diagnostic ability to identify PH in our cohort. Uninterpretable TR signals are frequent in HF,[22] have been reported in as many as 39% of subjects and may present a limitation to echocardiographic evaluation of PH.[23] In our study, TRV_{max} could not be adequately assessed in 14% and velocity-time integral in 19% of patients, emphasizing the diagnostic role for methods that do not necessitate TR jet interrogation.

Early identification of PH in HF has direct consequences on treatment and prognosis. Despite reasonable to strong diagnostic ability to identify PH, none of the echocardiographic algorithms outperformed TRV_{max} on ROC analysis, irrespective of hemodynamic definition of PH. This finding is contrary to a recent comparative report where the chosen echocardiographic algorithms showcased generally superior performance as compared with TRV_{max}.[21] The authors suggest in the abovementioned study that algorithms that consider estimates of right atrial pressure in addition to TRV_{max} demonstrate generally stronger correlation with invasive measurements and superior diagnostic performance when compared with TRV_{max} alone. This was substantiated by data from their study where right atrial pressure > 15 mm Hg estimated by echocardiography demonstrated highest odds ratio for invasively confirmed PH. In the setting of HF, echocardiographic estimates of right atrial pressure are frequently falsely elevated and sole reliance on the IVC to estimate RAP may be misleading.[24] In our study, close to one in three patients with elevated RAP estimated by echocardiography demonstrated normal corresponding invasive pressures suggesting that these estimates are frequently inaccurate and may not necessarily contribute to stronger performance of derived PAP_M variables as earlier suggested.[9,21] Echocardiographic estimates of RAP_M have been incorporated into empirical derivations of PAP_M in all but one selected PAP_M algorithms in this study. This may play a role in the observed lower performance when compared with TRV_{max} alone, but needs to be further examined.

The use of fluid-filled catheters instead of high-fidelity manometer-tipped catheters for pressure measurement might introduce additional error and may be considered a limitation in this study. Retrospective analysis of echocardiographic data did not permit a closer inspection factors leading to lower feasibility of certain algorithms included in this comparative analysis. Finally, we did not employ agitated saline bubble contrast to strengthen TR jet signal as this is not part of routine protocol in our laboratory.

5 | CONCLUSIONS

In the setting of HF, echocardiographic estimates of PAP_M are highly feasible, demonstrate reasonable association and good agreement with invasive measurements. Despite displaying strong ability to identify PH, none of the methods outperformed recommendation-proposed TRV_{max} cut-off > 2.8 m/sec.

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