

Improving echocardiographic subclassification of pulmonary hypertension: Relating the tricuspid regurgitation velocity to estimated pulmonary artery wedge pressure

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Abstract

Background

Pulmonary hypertension (PH) has heterogeneous etiologies requiring different treatments, making accurate subclassification essential. Pre-capillary PH is distinguished from post-capillary PH through measurement of pulmonary arterial wedge pressure (PAWP) at right heart catheterization (RHC), an invasive procedure with limited availability. Echocardiography enables non-invasive estimation of pulmonary pressure utilizing the peak tricuspid regurgitation velocity (TRV_{max}) but subclassification of PH remains challenging.

The ratio of TRV_{max} to left atrial strain (ePLAGS) has been proposed as a non-invasive discriminative tool but may be confounded by right ventricular dysfunction. Recently, a quantitative echocardiographic equation for estimating PAWP (ePAWP) has shown good agreement with invasive measurements. We hypothesized that relating TRV_{max} to ePAWP could improve discrimination of pre- and postcapillary PH.

Aim

To assess the diagnostic accuracy of TRV_{max} /ePAWP in the identification of pre-capillary PH and to compare its performance with ePLAGS.

Materials and methods

In this retrospective study, 83 patients with echocardiographic signs of PH ($TRV_{max} > 2.8$ m/s) were identified in the Karolinska-Umeå hemodynamic (KARUM) database, which includes 481 patients referred for RHC and echocardiography. Patients with non-sinus rhythm, severe tricuspid regurgitation, more than moderate mitral valve disease or insufficient echocardiographic data were excluded. The diagnostic performance of TRV_{max} /ePAWP and ePLAGS was evaluated using receiver operating characteristic (ROC) analysis, with area under the curve (AUC) comparison using DeLong's test.

Results

TRV_{max} /ePAWP showed moderate discriminatory ability to identify pre-capillary PH (AUC of 0.71 [95% CI: 0.58-0.83]). The highest diagnostic odds ratio of 10.9 was observed at a threshold of 0.32 m/s/mmHg (PPV: 0.82; NPV: 0.71; specificity: 0.96; sensitivity: 0.30). Compared to TRV_{max} /ePAWP, ePLAGS showed worse discriminatory ability ($p=0.046$) with an AUC of 0.51 [95% CI: 0.38–0.63].

Conclusion

$\text{TRV}_{\text{max}}/\text{ePAWP}$ demonstrated moderate diagnostic accuracy for identifying pre-capillary PH and showed potential as a rule-in marker, outperforming ePLAGS.

1. Background

Pulmonary hypertension (PH) is a severe condition with a wide range of aetiologies, in which elevated pulmonary arterial pressure (PAP) results from increased pulmonary vascular resistance (PVR) and decreased pulmonary vascular compliance (PVC) (1). A fundamental distinction is made between pre-capillary PH, where elevated PAP results from pulmonary vascular disease and isolated post-capillary pulmonary hypertension (IpcPH), where elevated PAP is caused by elevated left ventricular filling pressure (LVFP) (2). Additionally, these two entities can co-exist in combined pre- and post-capillary pulmonary hypertension (CpcPH) (2). It is essential to correctly identify the PH subtype, as treatment strategies differ (3). Delayed diagnosis of pre-capillary PH is common and can potentially lead to a worsened prognosis and patient distress (4, 5).

The reference method for diagnosing PH is right heart catheterization (RHC), in which a catheter is introduced through a vein into the right heart chambers and the pulmonary circulation, allowing for haemodynamic measurements. These include right atrial pressure (RAP), PAP and pulmonary artery wedge pressure (PAWP), which closely reflects mean left atrial pressure (LAP). It also enables the calculation of cardiac output (CO) and PVR (6). RHC is an invasive procedure, albeit with a low rate of severe complications and mortality, and its limited availability highlights the need for more accessible and reliable diagnostic methods (7).

According to the 2022 update of the ESC/ERS Guidelines, PH is defined as a mean PAP (mPAP) exceeding 20 mmHg at rest and is further subclassified into pre- capillary PH, IpcPH and CpcPH according to PAWP and PVR (*Table 1*) (3). Transthoracic echocardiography is recommended as the primary screening modality, while RHC remains necessary for the definitive diagnosis (3).

Table 1. Subclassification of pulmonary hypertension according to the 2022 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension.

	mPAP (mmHg)	PVR (WU)	PAWP (mmHg)
Pre-capillary PH	>20	>2	≤15
CpcPH	>20	>2	>15
IpcPH	>20	≤2	>15

Abbreviations: CpcPH: combined post- and pre-capillary pulmonary hypertension; IpcPH: isolated post-capillary pulmonary hypertension; mPAP: mean pulmonary artery pressure; PAWP: pulmonary artery wedge pressure; Pre-capillary PH: pre-capillary pulmonary hypertension; PVR: pulmonary vascular resistance.

Echocardiography can be used to estimate PAP, including systolic pulmonary artery pressure (sPAP) (8). Echocardiographically estimated sPAP correlates with invasive measurements and has shown good performance in identifying PH (9, 10) although its precision has been questioned (11, 12). The estimation of sPAP requires the presence of tricuspid regurgitation (TR) and is based on Doppler assessment of its peak velocity (TRV_{max}). By applying the modified Bernoulli equation ($\Delta P = 4 \times TRV_{max}^2$ in m/s), the systolic pressure gradient between the right ventricle and the right atrium can be estimated. sPAP can then be derived by adding ΔP to estimated RAP (13). However, echocardiographic estimation of RAP – based on inferior vena cava (IVC) dimensions – has been shown to overestimate invasively measured RAP, and its role in improving TRV_{max} -based sPAWP estimations remains uncertain due to conflicting results (10, 12).

Subclassification of PH using echocardiography remains challenging. Several approaches have been evaluated, demonstrating varying diagnostic performance (14-18). Among these, Scalia et al. introduced an echocardiographic parameter (ePLAR) to differentiate pre-capillary PH from IpcPH in patients with invasively confirmed PH. ePLAR was derived by dividing TRV_{max} by the ratio of mitral peak early velocity to early diastolic myocardial velocity (E/e') as a surrogate for left ventricular filling pressure (LVFP). ePLAR was demonstrated to identify isolated pre-capillary PH with good accuracy (19). However, E/e' alone has been shown to have a limited correlation with LVFP (20, 21), and the currently recommended European Association of Cardiovascular Imaging (EACVI) algorithm for the evaluation of LVFP has also shown insufficient diagnostic accuracy (20).

Venkateshvaran et al. employed left global atrial strain (LA-GS), an echocardiographic parameter shown to be superior to E/e' , as a surrogate for LVFP (22). As a result, the TRV_{max} to LA-GS ratio (ePLAGS) demonstrated higher diagnostic accuracy than ePLAR in distinguishing precapillary from postcapillary PH in patients with invasively confirmed PH (23). LA-GS has been incorporated in the most recent interpretative algorithm for the assessment of diastolic function by the American Society of Echocardiography (ASE). However, its diagnostic performance has been questioned (24).

As an alternative approach, a quantitative echocardiographic equation for estimating PAWP (ePAWP) has been described. The estimation is based on indexed left atrial volume (LAVi), early mitral inflow (mitral E) and pulmonary vein systolic velocity (PVs) (*Equation 1*). ePAWP demonstrated good agreement with invasive PAWP and a superior diagnostic performance in identifying elevated filling pressures than the ASE/EACVI algorithm (13, 25). We hypothesize that the diagnostic accuracy in discriminating precapillary from postcapillary PH could be further improved by relating TRV_{max} to ePAWP ($TRV_{max}/ePAWP$).

Equation 1

$$ePAWP = 0.179 \times LAVi (mL/m^2) + 2.672 \times \frac{\text{mitral } E (m/s)}{PVs (m/s)} + 2.7$$

2. Aim

The aim of this study is to describe the diagnostic accuracy of $TRV_{max}/ePAWP$ in the identification of precapillary PH and to compare its diagnostic performance with ePLAGS.

3. Materials and methods

3.1 Design

The study was conducted as a retrospective analysis of data from the Karolinska-Umeå hemodynamic database (KARUM).

3.2 Study population

The KARUM hemodynamic database includes 481 patients consecutively referred to PH-centres at Karolinska University Hospital (2014-2018) or Norrlands University Hospital (2010-2015) for RHC due to dyspnoea, advanced heart failure, suspected pulmonary arterial hypertension (PAH) or follow-up for verified PAH. The inclusion criterion for the present study was

echocardiographic signs of PH defined as $TRV_{max} > 2.8$ m/s. Exclusion criteria are (1) non-sinus rhythm, (2) severe tricuspid regurgitation, (3) more than moderate mitral regurgitation or stenosis and (4) insufficient echocardiographic data for the calculation of ePAWP or ePLAGS.

3.3 Methods

Echocardiographic examination

Echocardiographic examinations were performed in all patients by experienced sonographers in accordance with a standardized protocol (26). The echocardiographic examinations were conducted within three hours of the RHC using the Vivid E9 ultrasound system (GE Ultrasound, Horten, Norway). All acquired images were subsequently analysed by experienced personnel blinded to the results from the RHC using the EchoPAC PC software (version 11.0.0.0, GE Ultrasound, Waukesha, Wisconsin).

Right heart catheterization

All patients underwent RHC within 3 hours from the echocardiographic examination. The procedure was performed by experienced personnel who were blinded to the echocardiographic results. The femoral or jugular vein was used to introduce a 6F Swan-Ganz catheter. After calibrating the transducer to zero, pressure measurements were recorded during end-expiration during five to ten heart cycles from right atria, right ventricle and pulmonary artery. All measurements were analysed using a hemodynamic software package (WITT Series III, Witt Biomedical Corp., Melbourne, FL).

3.4 Statistical analysis

Baseline patient characteristics will be described as mean with standard deviation, if normally distributed, or otherwise as median with interquartile range for continuous variables. Comparison of group means will be performed using the student t-test. Comparisons of medians between groups will be performed using the Kruskal-Wallis test followed by Dunn's post hoc test with Bonferroni adjustment for multiple comparisons. Proportional differences between groups will be assessed using chi-square test. Receiver operating characteristic (ROC) analysis will be used to evaluate the diagnostic performance of TRV_{max} /ePAWP and TRV_{max} /ePLAGS respectively in detecting precapillary PH, defined as $mPAP > 20$ mmHg, $PAWP \leq 15$ mmHg and $PVR > 2$. The results will be reported as the area under the curve (AUC) with 95% confidence interval (CI). Comparison between AUCs will be performed using DeLong's test for correlated ROC curves. A p-value < 0.05 will be considered statistically significant. Statistical analysis will be performed using R version 4.2.1 (R Core 239 Team, Vienna, Austria).

3.5 Ethical considerations

The original study and inclusion of patients in the KARUM database was approved by the local ethics committees (Karolinska 2024-02861-01 and Umeå 007-092M). All patients provided written informed consent.

The patients included in the KARUM database underwent only clinically justified examinations based on their symptomatology. The present study solely includes pre-existing, pseudonymized data and will therefore have no negative implications for the study participants. The participants cannot, however, be expected to benefit from the study either. For future patients the study has the potential to contribute to earlier diagnosis of precapillary PH, which may lead to improved prognosis and reduced suffering.

4. Results

4.1 Patient population

Out of 481 eligible patients included in the KARUM database, 313 individuals had $TRV_{max} > 2,8$ m/s, and were therefore eligible for inclusion. Of these, 84 individuals were excluded due to non-sinus rhythm, 3 due to severe tricuspid regurgitation and 11 due to more than moderate mitral regurgitation. Lastly, 132 individuals were excluded because of missing echocardiographic parameters, predominantly PVs measurements, which were unavailable in 130 of eligible individuals. Consequently, 83 individuals were included. (*Figure 1*). Out of the included 83 patients, PH was confirmed by RHC in 65 patients; 30 with pre-capillary PH, 25 with CpcPH, 7 with IpcPH, and 3 who did not meet the diagnostic criteria for any of these subtypes (*Table 2*).

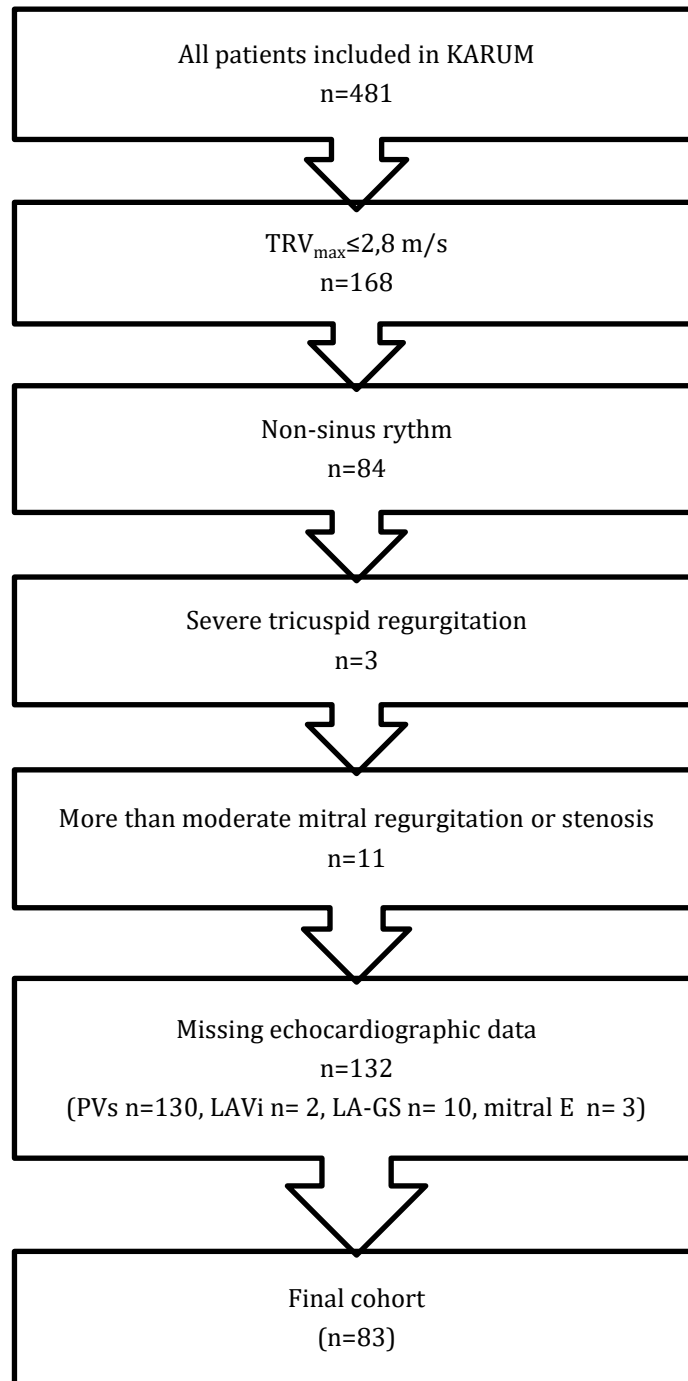


Figure 1. Flowchart of study selection

Abbreviations: LA-GS: left atrial strain; LAVi: indexed left atrial volume; mitral E: early mitral inflow; PVs: pulmonary vein systolic velocity

4.2 Baseline characteristics

No significant differences were observed among the PH categories with respect to age, sex, NT-proBNP levels, or the prevalence of diabetes mellitus or hypertension. However, body mass index (BMI) was modestly lower in patients with pre-capillary PH compared with those with CpcPH

(adjusted $p = 0.04$). Regarding invasive hemodynamic measurements, PVR was higher in patients with pre-capillary PH than in those with IpcPH (adjusted $p < 0.001$) or undefined PH (adjusted $p = 0.014$), while no statistically significant difference was observed relative to the CpcPH group. PAWP was significantly lower in the pre-capillary PH group compared with both the CpcPH (adjusted $p < 0.001$) and IpcPH groups (adjusted $p < 0.001$). Among echocardiographically derived parameters, ePAWP was higher in the CpcPH group than in the pre-capillary PH group (adjusted $p = 0.02$), whereas no other statistically significant differences were observed among the PH categories. LA-GS was significantly reduced in the CpcPH (adjusted $p = 0.002$) and IpcPH (adjusted $p = 0.004$) groups compared with patients with normal sPAP (*Table 2*).

Table 1 Baseline characteristics of patient population. Data presented as median (interquartile range) or number (%).

	No PH	CpcPH	PrecapPH	lpcPH	Undefined PH	p
Individuals	18	25	30	7	3	
Age (years)	75 (69-78)	68 (60-78)	69 (62-78)	58 (38- 69)	70 (62-73)	0.33
Male gender	8 (44)	9 (36)	8 (27)	4 (57)	1 (33)	0.55
Height (cm)	170 (163- 177)	169 (160- 174)	167 (164- 172)	168 (166- 178)	176 (175- 180)	0.30
BMI (kg/m2)	26.8 [22.6- 28.7)	29.8 (24.4- 34.5)	24.8 (20.7- 27.9)	26.9 (23.3- 29.6)	32.3 (28.5- 32.8)	0.04
DM	3 (17)	9 (36)	3 (10)	2 (29)	0 (0)	0.14
HT	13 (72)	18 (72)	14 (47)	3 (43)	2 (67)	0.22
SBP (mmHg)	140 (128- 155)	133 (120- 143)	133 (110-140)	140 (98- 156)	129 (124- 130)	0.50
NTproBNP (ng/L)	321 (101- 479)	604 (270- 2450)	699 (253- 1540)	1665 (921- 2199)	431 (368- 802)	0.19
PVR (WU)	1.6 (1.4- 2.5)	3.2 (2.7- 4.9)	4.3 (3.1- 5.2)	1.8 (1.6- 1.9)	1.4 (1.2-1.7)	<0.001
PAWP (mmHg)	10.5 (7.3- 12.8)	22.00 (18.0- 24.0)	10.0 (7.0- 13.0)	23.0 (19.5- 24.5)	13.0 (13.0- 14.0)	<0.001
ePAWP (mmHg)	12.4 (10.6- 14.2)	15.6 (14.0- 19.6)	12.8 (10.6- 16.6)	18.1 (15.0- 21.9)	12.5 (11.8- 13.0)	0.001
LA-GS (%)	25 (18- 31)	11 (8- 17)	16 (9- 23)	10 (4- 13)	27 (20- 29)	<0.001
TRVmax/ePAWP	0.24 (0.21- 0.30)	0.21 (0.17- 0.25)	0.28 (0.23- 0.35)	0.18 (0.15- 0.23)	0.25 (0.22- 0.28)	0.003
ePLAGS	0.13 (0.09-0.17)	0.32 (0.19- 0.52)	0.24 (0.17- 0.34)	0.29 (0.25- 0.86)	0.11 (0.11, 0.19)	<0.001

Abbreviations: BMI: body mass index; ePAWP: echocardiographically estimated pulmonary artery wedge pressure; LA-GS: left atrial global strain; NT-proBNP: N-terminal pro–brain natriuretic peptide; PAWP: pulmonary artery wedge pressure; PVR: pulmonary vascular resistance; sPAP: systolic pulmonary artery pressure.

4.3 Diagnostic accuracy of TRV_{max}/ePAWP and ePLAGS

TRV_{max}/ePAWP showed a moderate discriminatory ability to identify pre-capillary PH with an AUC of 0.71 (95% CI: 0.58-0.83) (*Figure 2*). The optimal threshold, determined by maximizing Youden's index, was 0.26 m/s/mmHg ($J = 0.35$), corresponding to a sensitivity of 0.63, a specificity of 0.72, a positive predictive value (PPV) of 0.41, a negative predictive value (NPV) of 0.87 and a diagnostic odds ratio (DOR) of 4.38. The highest DOR of 10.93 was observed at a threshold of 0.32 m/s/mmHg, corresponding to a PPV of 0.82, an NPV of 0.71, positive likelihood ratio (LR+) of 7.95, a specificity of 0.96 and a sensitivity of 0.30 (*Table 3*).

ePLAGS demonstrated no discriminatory ability for identifying patients with pre-capillary PH, with an area under the curve (AUC) of 0.51 (95% CI: 0.38–0.63) (*Figure 2*). The highest DOR observed was 2.16, corresponding to a PPV of 0.41, an NPV of 0.75, a sensitivity of 0.83 and a specificity of 0.30 at a threshold of 0.15 m/s/mmHg while the optimal threshold according to Youden's index was 0.16 m/s/mmHg ($J = 0.14$), corresponding to a sensitivity of 0.80 and a specificity of 0.34 (*Table 4*).

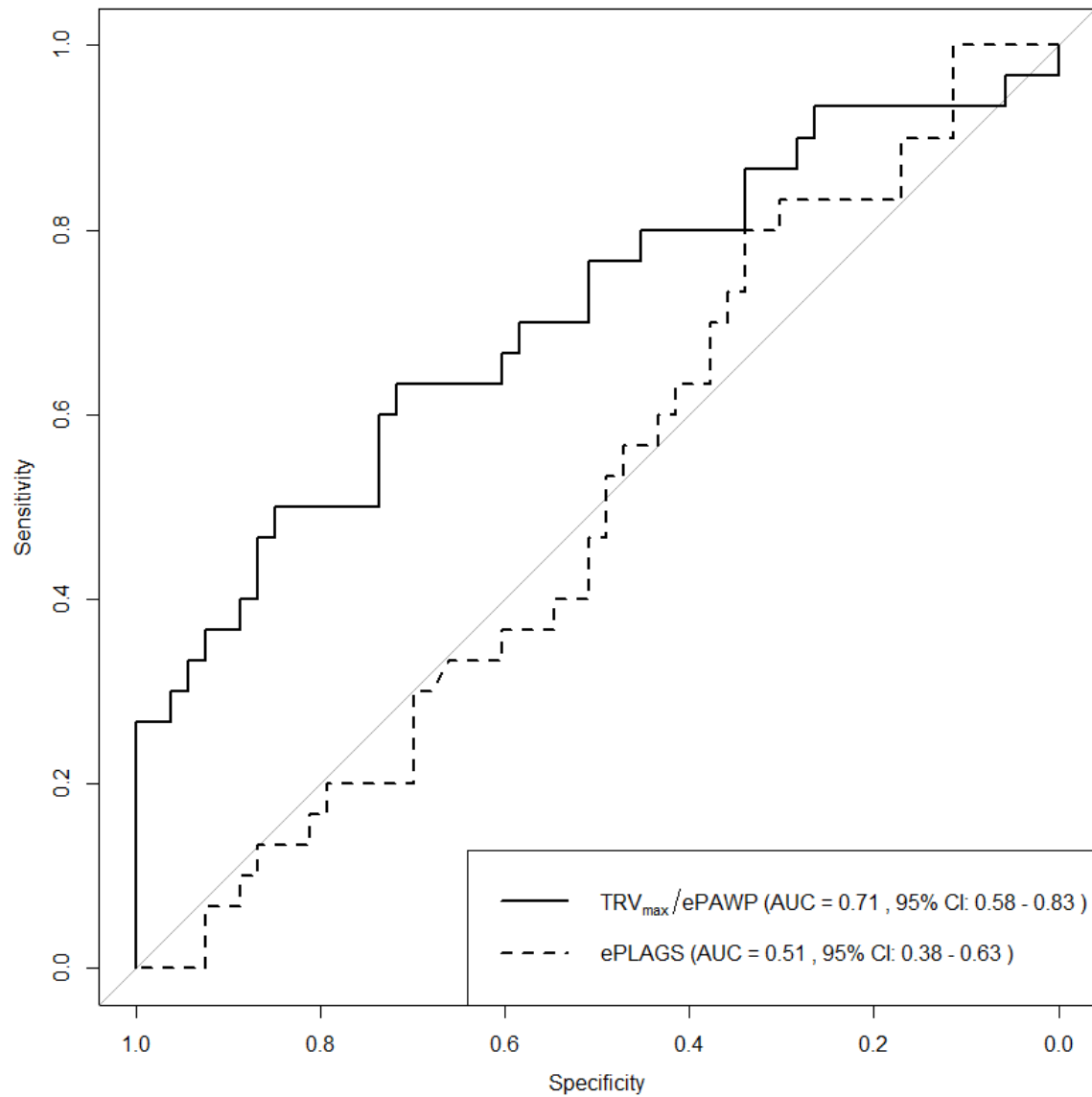


Figure 2. Receiver operating characteristic (ROC) curves comparing the diagnostic performance of TRV_{max}/ePAWP and ePLAGS for identifying pre-capillary PH. DeLong's test demonstrated that the area under the curve (AUC) for TRV_{max}/ePAWP was significantly higher than that for ePLAGS ($p = 0.046$, 95% CI 0.004-0.393).

Table 3: Diagnostic performance of TRV_{max}/ePAWP at different thresholds.

Threshold	Sensitivity	Specificity	PPV	NPV	LR+	LR-	DOR
-Inf	1.00	0.00	0.36		1.00	Inf	Inf
0.13	0.97	0.06	0.37	0.75	1.02	0.59	1.74
0.16	0.93	0.25	0.41	0.87	1.24	0.27	4.55
0.21	0.80	0.43	0.44	0.79	1.41	0.46	3.07
0.24	0.67	0.60	0.49	0.76	1.68	0.55	3.05
0.26	0.57	0.74	0.55	0.75	2.15	0.59	3.64
0.29	0.47	0.85	0.64	0.74	3.09	0.63	4.92
0.30	0.37	0.92	0.73	0.72	4.86	0.69	7.09
0.32	0.30	0.96	0.82	0.71	7.95	0.73	10.93
0.34	0.27	1.00	1.00	0.71	Inf	0.73	Inf

Abbreviations: DOR: diagnostic odds ratio; LR+: positive likelihood ratio; LR-: negative likelihood ratio; NPV: negative predictive value; PPV: positive predictive value.

Table 4: Diagnostic performance of ePLAGS at different thresholds.

Threshold	Sensitivity	Specificity	PPV	NPV	LR+	LR-	DOR
0.10	0.90	0.11	0.36	0.67	1.01	0.88	1.15
0.15	0.83	0.30	0.40	0.76	1.19	0.55	2.16
0.16	0.80	0.34	0.41	0.75	1.21	0.59	2.06
0.21	0.57	0.47	0.38	0.66	1.07	0.92	1.17
0.31	0.33	0.66	0.36	0.64	0.98	1.01	0.97
0.44	0.17	0.81	0.33	0.63	0.88	1.03	0.86
0.64	0.10	0.89	0.33	0.64	0.88	1.01	0.87
0.80	0.07	0.92	0.33	0.64	0.88	1.01	0.88
1.91	0.00	0.96	0.00	0.63	0	1.04	0
Inf	0.00	1.00		0.64	Inf	1.00	Inf

Abbreviations: DOR: diagnostic odds ratio; LR+: positive likelihood ratio; LR-: negative likelihood ratio; NPV: negative predictive value; PPV: positive predictive value.

5. Discussion

The present study demonstrates that pre-capillary PH can be identified echocardiographically using the $\text{TRV}_{\max}/\text{ePAWP}$ ratio with a moderate diagnostic accuracy. A $\text{TRV}_{\max}/\text{ePAWP}$ threshold of 0.32 m/s/mmHg provided high specificity (0.96) with a positive likelihood ratio of 7.95, suggesting potential utility as a rule-in marker, although sensitivity remained limited. The clinical relevance of these findings is supported by the unfavourable prognosis associated with pre-capillary PH, the prevalent diagnostic delay, and the availability of therapeutic strategies that differ substantially from those for other forms of PH (3, 4). Non-invasive, widely accessible methods for reliably triaging patients for RHC are therefore of critical importance.

In our cohort, $\text{TRV}_{\max}/\text{ePAWP}$ outperformed ePLAGS, which demonstrated limited discriminative ability. These results contrast with a previous study reporting moderate to good diagnostic accuracy for ePLAGS in pre-capillary PH (23). Similarly, Scalia et al showed good diagnostic accuracy for the ratio $\text{TRV}_{\max}/\text{E}/\text{e}'$ in identifying pre-capillary PH (19). Notably, in both studies, analyses were restricted to patients with invasively confirmed PH, which is a plausible explanation for the differing result. By including all patients with echocardiographically suspected PH, defined as a $\text{TRV}_{\max} > 2.8$ m/s, our study offers a more clinically relevant evaluation of the method and its potential applicability in routine clinical practice.

A potential explanation for the lack of discriminatory ability of LA-GS may be that LA-GS is reduced not only in the presence of left ventricular diastolic dysfunction (27), but also as an indirect consequence of right ventricular dysfunction in PH (28). In the latter case, it has been hypothesized that reduced preload, due to ventricular interdependence, contributes to decreased LA-GS (28).

Several factors may contribute to the limited diagnostic performance of $\text{TRV}_{\max}/\text{ePAWP}$. The use of $\text{TRV}_{\max}$ as a surrogate for pulmonary pressure is subject to inherent limitations (11, 29); notably, within the context of the present study, it has been shown to frequently misclassify subjects in the KARUM database (12).

Atrial enlargement, a key component in the estimation of ePAWP, is not specific to elevated filling pressures and may persist despite normalization of PAWP, potentially leading to misclassification. (27, 30). Conversely, excluding atrial volume may yield a more accurate estimate of PAWP. Lindow et al. derived an equation for PAWP estimation without atrial volume (ePAWP-NOLA), which showed slightly lower bias but similar precision compared with ePAWP (31). Future studies could explore this approach to improve the diagnostic performance of $\text{TRV}_{\max}/\text{ePAWP}$.

The sample size was relatively small, and a substantial proportion of patients were excluded due to missing echocardiographic measurements, mainly PVs. The reason for this is unknown.

Previous studies have reported high feasibility, suggesting that larger cohorts could be studied in the future (32). Furthermore, the requirement for invasive procedures may have influenced the size of the study population. Also, patients with non-sinus rhythm or significant valvular heart disease were excluded, limiting the generalizability of $TRV_{max}/ePAWP$ to these populations.

Key strengths of the study include the contemporaneous performance of echocardiography and RHC, which minimizes variation in filling pressures due to factors such as medications, neurohormonal influences or fluid status. Additionally, the study design enabled evaluation of $TRV_{max}/ePAWP$ in a clinically relevant context using echocardiographic data alone, allowing assessment of its performance in a real-world setting. Furthermore, this approach permitted evaluation across the full spectrum of pulmonary hypertension subtypes.

6. Conclusion

$TRV_{max}/ePAWP$ demonstrated moderate diagnostic accuracy for identifying pre-capillary PH and showed potential as a rule-in marker, outperforming ePLAGS.

5. References

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