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Reappraisal of the Transthoracic Echocardiographic Algorithm in Predicting Pulmonary Hypertension Redefined by Updated Pulmonary Artery Mean Pressure Threshold

ABSTRACT

Background: Although an adopted echocardiography algorithm based on tricuspid regurgitation jet peak velocity and suggestive findings for pulmonary hypertension has been utilized in the non-invasive prediction of pulmonary hypertension probability, the reliability of this approach for the updated hemodynamic definition of pulmonary hypertension remains to be determined. In this study, for the first time, we aimed to evaluate the tricuspid regurgitation jet peak velocity and suggestive findings in predicting the probability of pulmonary hypertension as defined by mean pulmonary arterial pressure > 20 mm Hg and > 25 mm Hg, respectively.

Methods: Our study group was comprised of the retrospectively evaluated 1300 patients (age 53.1 ± 18.8 years, female 62.1%) who underwent right heart catheterization with different indications between 2006 and 2018. All echocardiographic and right heart catheterization assessments were performed in accordance with the European Society of Cardiology/European Respiratory Society 2015 Pulmonary Hypertension Guidelines.

Results: Although tricuspid regurgitation jet peak velocity showed a significant relation with mean pulmonary arterial pressure in both definitions, suggestive findings offered a significant contribution only in predicting mean pulmonary arterial pressure ≥ 25 mm Hg but not for mean pulmonary arterial pressure > 20 mm Hg. In predicting the mean pulmonary arterial pressure > 20 mm Hg, tricuspid regurgitation jet peak velocity and suggestive findings showed an odds ratio of 2.57 (1.59-4.14, *P* < .001) and 1.25 (0.86-1.82, *P* = .16), respectively. In predicting the mean pulmonary arterial pressure ≥ 25 mm Hg, tricuspid regurgitation jet peak velocity, and suggestive findings showed an odds ratio of 2.33 (1.80- 3.04, *P* < .001) and 1.54 (1.15-2.08, *P* < .001), respectively. The tricuspid regurgitation jet peak velocity > 2.8 m/s and tricuspid regurgitation jet peak velocity > 3.4 m/s were associated with 70% and 84% probability of mean pulmonary arterial pressure > 20 mm Hg and 60% and 76% probability of mean pulmonary arterial pressure ≥ 25 mm Hg, respectively.

Conclusions: In contrast to those in predicting the mean pulmonary arterial pressure ≥ 25 mm Hg, suggestive findings did not provide a significant contribution to the probability of mean pulmonary arterial pressure > 20 mm Hg predicted by tricuspid regurgitation jet peak velocity solely. The impact of the novel mean pulmonary arterial pressure threshold on the echocardiographic prediction of pulmonary hypertension remains to be clarified by future studies.

Keywords: Echocardiography, pulmonary arterial pressure, pulmonary hypertension, redefinition, tricuspid regurgitation

INTRODUCTION

Since the first World Symposium on Pulmonary Hypertension (PH), PH has been arbitrarily defined as a mean pulmonary arterial pressure (mPAP) ≥ 25 mm Hg at rest, measured by right heart catheterization (RHC).[1,2] However, recent data suggest that mPAP > 20 mm Hg could be the upper limit of normal and has been significantly associated with increased risk for progression to overt PH, hospitalization, and mortality.[3-10] Therefore, the sixth PH World Symposium Task Force has proposed a 4 mm Hg reduction in the definitive threshold of the mPAP, without any

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changes in the pulmonary arterial wedge pressure (PAWP) < 15 mm Hg and pulmonary vascular resistance (PVR) ≥ 3 Wood units, other 2 measurement parameters of the precapillary PH definition.[11] Moreover, recently published European Society of Cardiology (ESC)/European Respiratory Society (ERS) 2022 PH Guidelines adopted a further reduction in PVR from 3 Wood units to > 2 Wood units in the hemodynamic definition of precapillary PH.[12]

However, whether a new mPAP threshold of PH increases the "new" prevalence of the patients with overall PH and precapillary PH, unnecessary RHC procedures, earlier initiation of pulmonary arterial hypertension (PAH)-targeted therapies in previously "borderline" precapillary PH, and surgical endarterectomy in chronic thromboembolic PH (CTEPH) remain to be determined in the absence of the reliable evidence.[9-13]

We have documented that the revised definition of PH compared with the previous definitive mPAP threshold resulted in a 9.8% increase in the diagnosis rates of overall PH, a 0.8% increase in precapillary PH, but only a 0.3% increase in combined pre–postcapillary PH.[13]

However, currently available echocardiographic screening algorithms have been targeted to predict the probability of mPAP ≥ 25 mm Hg in certain symptoms and signs which may be consistent with PH. Therefore, the need for a reappraisal of the echocardiographic cutoff values and suggestive findings in predicting the redefined target of mPAP might be considered as another unresolved issue.

In this study, we aimed to evaluate the probability of the currently available echocardiographic model in predicting the 2 different PH definitions based on hemodynamic criteria of mPAP > 20 mm Hg and PAP > 25 mm Hg, respectively.

METHODS

Our study group was comprised of the retrospectively evaluated 1300 patients (age 53.1 ± 18.8 years, female 807, 62.1%) who underwent RHC with different indications between 2006 and 2018, in accordance with the recommendations of the ESC/ERS 2009 and 2015 PH Guidelines.[1,2]

HIGHLIGHTS

- In this retrospective study, first time, we evaluated the European Society of Cardiology/European Respiratory Society 2015 Pulmonary Hypertension (PH) Guidelines echocardiographic screening algorithm based on tricuspid regurgitation jet peak velocity (TRVmax) and other suggestive findings for the predicted probability of PH as defined by mean pulmonary arterial pressure (mPAP) > 20 mm Hg and mPAP ≥ 25 mm Hg, respectively.
- In contrast to those for predicting the mPAP ≥ 25 mm Hg, suggestive echocardiographic findings did not provide a significant contribution to the probability of mPAP > 20 mm Hg being evaluated by TRVmax solely.
- The impact of the novel mPAP threshold on echocardiographic prediction of PH remains to be clarified by future prospective studies.

For hemodynamic definitions of PH on RHC according to the ESC/ERS 2015 PH Guidelines and sixth World Symposium PH, mPAP ≥ 25 mm Hg and mPAP > 20 mm Hg cutoff values have been utilized as diagnostic criteria for PH definitions, respectively.[1,2,11] For precapillary PH, PAWP ≤ 15 mm Hg and PVR ≥ 3 Wood units criteria have been included in both definitions. The overall study population has been subclassified according to the invasively measured mPAP ≤ 20 mm Hg/>20 mm Hg and mPAP < 25 mm Hg/≥ 25 mm Hg, and baseline demographics, clinical, echocardiographic, and hemodynamic characteristics were compared.[1,2,11,13]

The clinical and demographic characteristics of the patients were obtained from the hospital database and patient notes. The patients with missing files were excluded from the study. Demographic characteristics of the patients such as age and body mass index [weight, kg/(height, m^2)] were obtained from the patient files. Besides, as will be mentioned in detail below, transthoracic echocardiography and RHC data obtained from echocardiography and angiography/catheter laboratory applications were recorded from the hospital database.

Written informed consent was obtained from each participant if needed, and the study protocol was reviewed and approved by the Local Institutional Ethics Committee in accordance with the Declaration of Helsinki.

Evaluation with Echocardiography

A comprehensive transthoracic echocardiographic examination was performed in accordance with recommendations by current echocardiography and PH Guidelines by experienced dedicated cardiologists, before the RHC procedures and within the same day of the hemodynamic evaluation, if possible.[2,11,14,15] But, the hemodynamic data were not always obtained from the same-day catheter evaluations as the echo exam as a consequence of the nature of a retrospective study.

All patients underwent transthoracic echocardiography with Philips iE33 and Philips EPIQ 7-echocardiography device. The dimensions of the cardiac cavities, left ventricular posterior wall and interventricular wall thicknesses, left ventricular systolic functions (ejection fraction) and anatomical features of the heart valves, and functional features of the cardiac valves were evaluated routinely in all patients. Peak tricuspid regurgitation flow velocity was measured in 88% of all patients. In the 2015 ESC/ERS Guidelines, "presence of echo findings" was defined as the presence of at least 2 criteria from the 3 categories of "echo findings suggestive of PH," and we used the same definition in our study. Right ventricle/left ventricle (RV/LV) basal diameter ratio, flattening of the intraventricular septum (left eccentricity index), right ventricular output flow, Doppler acceleration time [pulmonary artery (PA) acceleration time], PA diameter, inferior vena cava (IVC) diameter, respiratory changes in IVC, and right atrium area were evaluated and recorded as suggestive echocardiographic findings. However, since the data regarding pulmonary regurgitation flow rate could not be obtained clearly, it was not included in the evaluation.

Evaluation with Right Heart Catheterization

Indications for RHC are as follows: hemodynamic verification and/or risk-based management of therapy in patients with symptoms compatible with PH and risk factors for PAH or CTEPH and without risk factors but with a moderate or high probability of PH according to echocardiographic examinations, hemodynamic verification and/or risk-based management in patients with heart failure, and evaluation before percutaneous interventions or surgical operations in patients with heart valve disease.

Right heart catheterization was performed at rest, without sedation, by experienced cardiologists. Prior to the procedure, the external pressure transducer was zeroed at the midpoint of the mid-seat line, anterior sternum, and bed surface in the supine patient. The pressure in PA, PA end position, RV, and right atrium was measured. All pressure measurements were made at the end of normal breathing. Blood samples were taken from the superior vena cava (upper and lower), IVC, right atrium (upper, middle, and lower), RV (apex, mid, and basal), and PA for oximetric measurements. Besides, oxygen (O_2) saturation in systemic arterial blood was also determined. In the case of a suspected left-to-right shunt, O_2 saturation was evaluated in steps. Cardiac output (CO) was measured by means of the indirect Fick method that uses the estimated values of O_2 uptake. Cardiac index was calculated as CO divided by body surface area, and PVR as mPAP minus PAWP divided by CO. Pulmonary artery wedge pressure measurement was measured in a subgroup of patients with mitral and/ or aortic valve stenosis or prosthetic mitral and/or aortic valves (2%). Direct measurement of LVEDP was preferred in the remainder. Transpulmonary pressure gradient, transsystemic pressure gradient, PVR, and systemic vascular resistance were calculated from the data obtained from RHC measurements.

Statistical Analysis

Whether the continuous variables were normally distributed or not was evaluated with a histogram. Normally distributed numerical variables were presented as mean ± SD and non-normal ones were presented as the median interquartile range (25^{th}-75^{th}). The *t*-test was used for normally distributed variables, and the Mann–Whitney *U*-test was used for non-normally distributed ones. Categorical variables were expressed as absolute numbers and percentages and compared with the chi-square test. A *P*-value < .05 was considered significant.

Two different models were created to evaluate the 2-stage echocardiographic study algorithm recommended by the ESC 2015 PH Guidelines for predicting catheter-derived assessments according to the previous (mPAP ≥ 25 mm Hg) and updated (mPAP > 20 mm Hg) hemodynamic definitions of PH, and predictive modeling was carried out with logistic regression analysis. In both models, the tricuspid regurgitation jet peak velocity (TRVmax) was measured by transthoracic echocardiography, and in addition to TRVmax, the echocardiographic findings [RV/LV basal diameter ratio, flattening of the intraventricular septum (left eccentricity index), right ventricular output flow, Doppler acceleration time (PA acceleration time), PA diameter, IVC diameter, respiratory changes in IVC, and right atrium area] suggestive of PH were included as variables. Model performances were measured with likelihood *X*2, *R*2, Brier scale, and C-index.

A nomogram was created as a result of the multiple logistic regression analysis with the coefficients in Model-1 and Model-2 in order to calculate the probability of invasively measured mPAP to be >20 mm Hg and ≥25 mm Hg by using TRVmax and the presence of other echocardiographic suggestive findings.

We also estimated the predicted probability of mPAP ≥ 25 mm Hg and mPAP > 20 mm Hg and plotted the predicted probability according to TRVmax and the presence of suggestive findings. The odds ratio (OR) was used to quantify the association between invasive mPAP > 20 mm Hg/mPAP ≥ 2 5 mm Hg and TRVmax and other suggestive findings.

Statistical evaluation was done with R version 4.0 (Austria, Vienna), "rms," and "ggplot2" packages.

RESULTS

The comparison of the basal characteristics and echocardiographic and hemodynamic findings of the patients according to mean PAP >20 mm Hg and ≥25 mm Hg is presented in Table 1.

The range of distribution for TRVmax on Doppler echocardiography and mPAP assessed by RHC is given in Figures 1A and B.

For invasively confirmed mPAP ≥ 25 mm Hg and mPAP > 20 mm Hg, log odds with TRVmax and suggestive echocardiographic findings are given in Figures 2A and B. Although TRVmax showed a significant relation with mPAP in both definitions, the presence of suggestive echocardiographic findings offered a significant contribution only in predicting mPAP ≥ 25 mm Hg but not for mPAP > 20 mm Hg.

In predicting the invasively confirmed mPAP > 20 mm Hg, TRVmax and suggestive findings showed an OR of 2.57 (1.59-4.14, *P* < .001) and 1.25 (0.86-1.82, *P* = .16), respectively (Table 2). In predicting the invasively confirmed mPAP ≥ 25 mm Hg, TRVmax and suggestive findings showed an OR of 2.33 (1.80-3.04, *P* < .001) and 1.54 (1.15-2.08, *P* < .001), respectively (Table 2).

Model performances were measured with likelihood *X*2, *R*2, Brier scale, and C-index. The Brier score, which is a quadratic proper scoring rule that combines calibration and discrimination, is higher for predicting mPAP ≥ 25 mm Hg than mPAP >20 mm Hg. Also *R*2 which is a useful measure of model performance when predicting a dichotomous outcome is higher for predicting mPAP ≥ 25 mm Hg than >20 mm Hg (Table 2).

For mPAP > 20 mm Hg and mPAP ≥ 25 mm Hg, probabilities of TRVmax were demonstrated in Figures 3A and B. The TRVmax > 2.8 m/s and TRVmax > 3.4 m/s were associated with 70% and 84% probability of mPAP > 20 mm Hg and 60% and 76% probability of mPAP ≥ 25 mm Hg, respectively.

Table 1. The Comparison of the Basal Demographic Characteristics, Echocardiographic, and Hemodynamic Findings of the Patients According to Mean PAP > 20 mm Hg and ≥ 25 mm Hg

Variables	Mean PAP ≤ 20 mm Hg (number: 276)	Mean PAP > 20 mm Hg (number: 1024)	*P*	Mean PAP < 25 mm Hg (number: 403)	Mean PAP ≥ 25 mm Hg (number: 897)	*P*
Basal characteristics						
Age	51.2 (37.8-60.8)	56.9 (45.8-64.9)	<.001	52.7 (39.7-61.9)	56.9 (46.1-65.0)	<.001
Gender, female	125 (45.3%)	403 (39.4%)	.07	173 (42.9%)	355 (39.6%)	.25
BMI (kg/ m^2)	24.97 (22.26-28.07)	25.80 (23.19-28.90)	.001	25.2 (22.8-28.07)	25.80 (23.14-29.00)	.018
BSA (m^2)	1.79 (1.67-1.90)	1.81 (1.68-1.96)	.005	1.80 (1.67-1.92)	1.81 (1.69-1.96)	.035
Heart rate (beats/min)	80 (72-87)	84 (76-91)	<.001	82 (72-88)	84 (77-91)	<.001
SaO_2 (%)	97 (95-98)	96 (93-97)	<.001	97 (95-98)	96 (93-97)	<.001
HF-rEF (1:0)	104 (38%)	494 (48%)	.002	155 (38%)	443 (49%)	<.001
HF-pEF (1:0)	6 (2%)	38 (4%)	.21	8 (2%)	36 (4%)	.061
Congenital heart disease (1:0)	60 (22%)	107 (10%)	<.001	83 (21%)	84 (9%)	<.001
COPD (1:0)	13 (5%)	50 (5%)	.906	24 (6%)	39 (4%)	.212
HT (1:0)	62 (22%)	227 (22%)	.916	94 (23%)	195 (22%)	.525
DM (1:0)	47 (17%)	199 (19%)	.379	72 (18%)	174 (19%)	.527
AF (1:0)	26 (9%)	158 (15%)	.011	41 (10%)	143 (16%)	.006
OAC use	54 (20%)	319 (31%)	<.001	84 (21%)	289 (32%)	<.001
Echocardiographic findings						
Suggestive echo finding (1:0)	49 (18%)	483 (47%)	<.001	86 (21%)	444 (50%)	<.001
Number of suggestive findings			<.001			<.001
0	227 (82%)	541 (53%)		317 (79%)	551 (50%)	0
1	22 (8%)	122 (12%)		33 (8%)	111 (12%)	1
2	13 (5%)	119 (12%)		27 (7%)	105 (12%)	2
3	6 (2%)	100 (10%)		11 (3%)	95 (11%)	3
4	6 (2%)	88 (9%)		12 (3%)	82 (9%)	4
5	0 (0%)	33 (3%)		1 (0%)	32 (4%)	5
6	2 (1%)	21 (2%)		2 (0%)	21 (2%)	6
TRVmax (m/s)	2.73 (2.50-3.16)	3.35 (2.9-3.87)	<.001	2.73 (2.50-3.16)	3.5 (3.0-4.0)	<.001
RV/LV >1 (1:0)	21 (8%)	284 (28%)	<.001	39 (10%)	266 (30%)	<.001
PAACT (msn)	95.0 (75.0-111.5)	68.5 (56.0-81.0)	<.001	88 (72-104)	67 (55-80)	<.001
PA diameter (cm)	2.5 (2.2-2.9)	3.0 (2.7-3.4)	<.001	2.55 (2.30-3.00)	3.10 (2.70-3.50)	<.001
Plethore (1:0)	13 (5%)	164 (16%)	<.001	24 (6%)	153 (17%)	<.001
Systolic PAP (mm Hg)	35 (30-45)	54 (40-69)	<.001	35 (30-45)	55 (45-70)	<.001
TAPSE (cm)	2.0 (1.6-2.5)	1.7 (1.3-2.1)	<.001	2.0 (1.5-2.4)	1.7 (1.3-2.0)	<.001
S' (cm/s)	12.0 (10.0-14.0)	10.5 (8.7-13.0)	<.001	11.0 (10.0-14.0)	10.15 (8.7-13.0)	<.001
Hemodynamic findings and definitions						
CO (L/min)	4.3 (3.7-5.1)	3.8 (3.1-4.6)	<.001	4.30 (3.70-5.10)	3.74 (3.00-4.60)	<.001
CI (L/min/ m^2)	2.40 (2.08-2.92)	2.06 (1.65-2.50)	<.001	2.4 (2.0-2.9)	2.0 (1.6-2.5)	<.001
PVR (Wood units)	1.0 (0.6-1.6)	4.0 (2.2-6.8)	<.001	1.1 (0.7-1.9)	4.4 (2.6-7.5)	<.001
SVR (Wood units)	18.6 (15.7-22.0)	20.0 (17.0-24.0)	<.001	18.75 (15.60-22.00)	20.30 (17.00-25.00)	<.001
TPG (mm Hg)	6 (3-8)	17 (10-26)	<.001	6 (3-10)	18 (11-28)	<.001
TSG (mm Hg)	85.0 (76.0-95.7)	79 (68-91)	<.001	85 (75-95)	79 (67-90)	<.001
Right atrial pressure (mm Hg)	5 (3-7)	8 (5-13)	<.001	5.0 (3.2-8.0)	9.0 (6.0-14.0)	<.001
Precapillary pulmonary vascular disease (PVR ≥3 Wood units, PCWP ≤15 mm Hg) [n (%)]	8 (2.8%)	318 (31%)	<.001	20 (5%)	306 (30%)	<.001
Postcapillary pulmonary vascular disease (PVR <3 Wood units, PCWP >15 mm Hg) [n (%)]	52 (18.8%)	223 (22%)	0.289	94 (23%)	181 (17.6%)	0.198
Combined pre—postcapillary pulmonary vascular disease (PVR ≥3 Wood units, PCWP >15 mm Hg) [n (%)]	3 (1%)	332 (32%)	<.001	6 (1.5%)	329 (32%)	<.001

While numerical data are expressed as median (interquartile range), categorical data are presented as absolute numbers and percentages (%).
AF, atrial fibrillation; BMI, body mass index; BSA, body surface area; CI, cardiac index; CO, cardiac output; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; HF-pEF, heart failure with preserved ejection fraction; HF-rEF, heart failure with reduced ejection fraction; HT, hypertension; LV, left ventricle; OAC, oral anticoagulant; PA, pulmonary artery; PAACT, pulmonary artery acceleration time; PAP, pulmonary arterial pressure; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; RV, right ventricle; *S'*, right ventricular PW tissue Doppler peak systolic velocity taken at the lateral tricuspid annulus; SaO_2, arterial oxygen saturation; SVR, systemic vascular resistance; TAPSE, displacement of the tricuspid annulus towards the apex in systole; TPG, transpulmonary pressure gradient; TRVmax, tricuspid regurgitation peak velocity; TSG, trans-systemic pressure gradient.

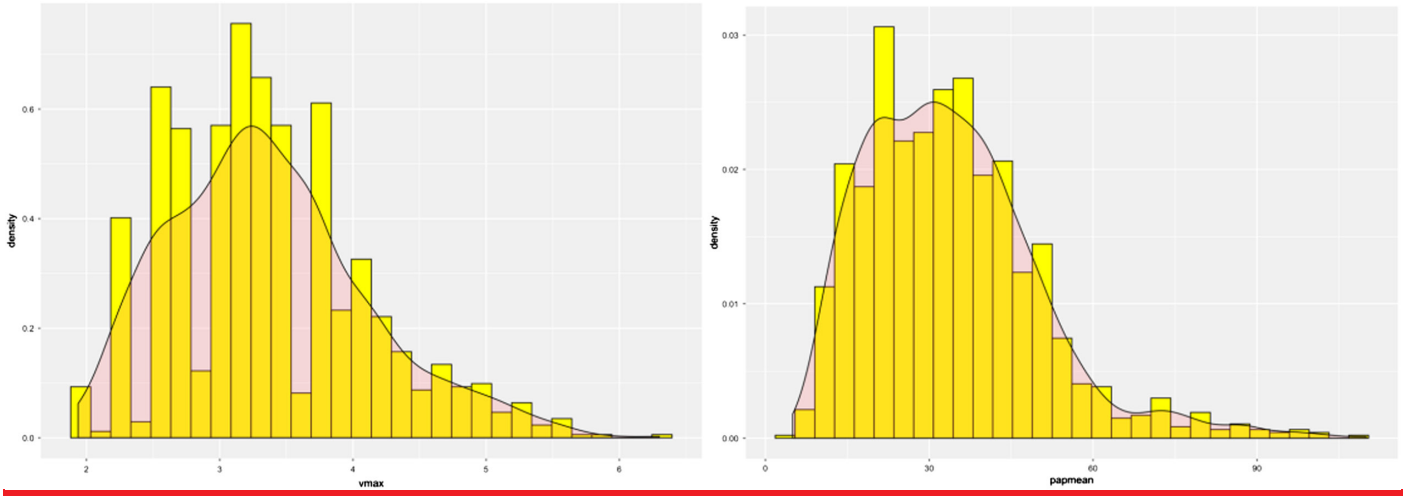


Figure 1. Distribution of the number of patients according to tricuspid regurgitation peak velocity (TRVmax) and mean pulmonary arterial pressure.

The clinical use of a nomogram is a simple and practical way to estimate the probability of post-test disease. For this reason, a nomogram was created as a result of the multiple logistic regression analysis with the coefficients in Model-1 and Model-2 in order to calculate the probability of invasively measured mPAP to be >20 mm Hg and ≥25 mm Hg by using TRVmax and the presence of other echocardiographic suggestive findings (Figure 4).

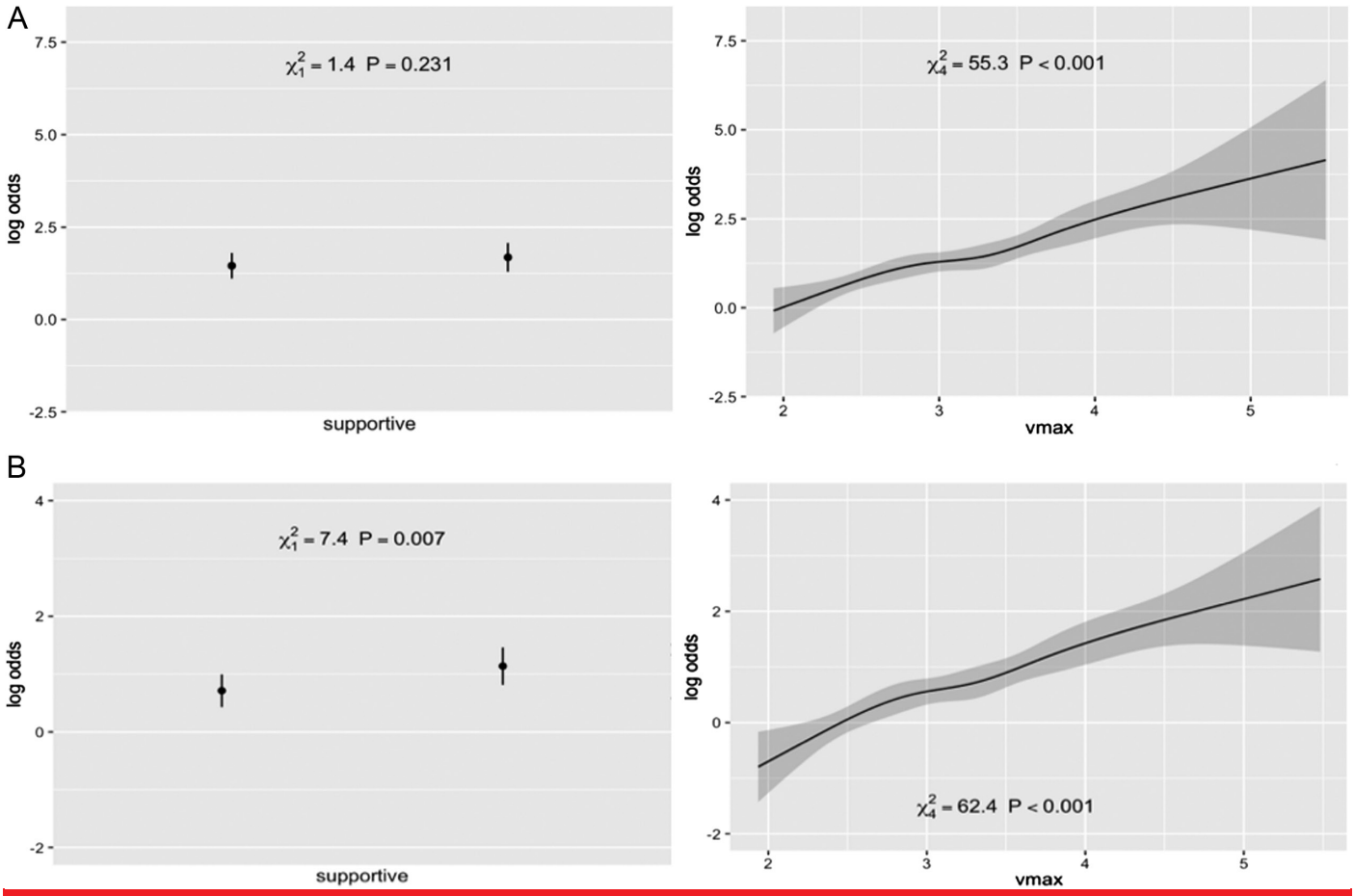


Figure 2. (A) The presence of suggestive echocardiographic findings and change in log-odds ratio in Model-1 (according to mean PAP > 20 mm Hg). (B) The presence of suggestive echocardiographic findings and change in log-odds ratio in Model-2 (according to mean PAP ≥ 25 mm Hg). PAP, pulmonary artery pressure.

Table 2. The Results of Logistic Regression Analysis Carried Out Separately for Model-1 and Model-2 and Model Performance Criteria

	Model-1 (mPAP > 20 mm Hg)			Model-2 (mPAP ≥ 25 mm Hg)		
Variable	**Odds ratio**	**CI**	***P***	**Odds ratio**	**CI**	***P***
TRVmax (m/s) (from 2.73 to 3.70)	2.57	1.59, 4.14	<.001	2.33	1.80, 3.04	<.001
Suggestive echo findings	1.25	0.86, 1.82	.16	1.54	1.15, 2.08	<.001
Performance measures of model						
R2	0.13			0.14		
Brier	0.134			0.188		
C-index	0.706			0.697		
Likelihood chi-square	93.64			118.56		

PAP, pulmonary arterial pressure; TRVmax, tricuspid regurgitation peak velocity.

To estimate the mean probability of PAP > 20 or mPAP ≥ 25 mm Hg in post-catheter evaluation in patients grouped according to the echocardiographic probability of PH, using the nomogram, the following steps should be followed:

- Step 1: Place the ruler over the patient's TRVmax reading lines and mark the intersection with an upper line,
- Step 2: Place the ruler over the values for suggestive echocardiographic findings and mark the intersection with an upper line,
- Step 3: Use a ruler to calculate the total scores and then read the probability of post-catheter evaluation in patients relative to the echocardiographic probability of PH.

For example, according to this nomogram, a patient with a TRVmax of 2.5 m/s and no suggestive echocardiographic findings would receive 32 points (32 + 0 points, respectively); for mPAP measured by RHC, the probability of > 20 mm Hg is 70%-75% and the probability of ≥ 25 mm Hg is 65%. In another example, a patient with a TRVmax of 5.0 m/s and suggestive echocardiographic findings would receive 78 points (70 + 8 points, respectively); for mPAP measured by RHC, the probability of > 20 mm Hg is 90%-95% and the probability of ≥ 25 mm Hg is 85%-90%.

When the data obtained after RHC were compared in the patient groups with the low, moderate, and high echocardiographic probability of PH before the diagnostic tests, the probability of mPAP > 20 mm Hg was found to be 68%, 76%, and 91% (mean), respectively, and the probability of mPAP ≥ 25 mm Hg was 50%, 65%, and 81% (mean), respectively (Figure 5A and B).

DISCUSSION

In this study, we evaluated the ESC/ERS echocardiographic screening algorithm based on TRVmax and other suggestive findings for the predicted probability of PH as defined by mPAP > 20 mm Hg and mPAP ≥ 25 mm Hg, respectively, for the first time. In contrast to those for predicting the mPAP ≥ 25 mm Hg, suggestive echocardiographic findings did not provide a significant contribution to the probability of mPAP > 20 mm Hg being evaluated by TRVmax solely. The TRVmax >2.8 m/s and TRVmax > 3.4 m/s were associated with 70% and 84% probability of mPAP > 20 mm Hg and 60% and 76% probability of mPAP ≥ 25 mm Hg, respectively.

Although RHC has been utilized as the method of choice for definitive diagnosis of PH, transthoracic echocardiography as a non-invasive, inexpensive, and widely available method has been used as the initial screening method for suspected population and in monitoring the treatment response and disease progression over time in patients with confirmed PH.[1,2,11,14,15] The TRVmax assessed by Doppler represents the phasic pressure gradient between the RV and right atrium at systole, and using the modified Bernoulli equation, RV systolic pressure can be estimated by adding the TR systolic pressure gradient to the estimated right atrial pressure.[2,14,15] This pressure is equal to systolic PA pressure (sPAP) in the absence of pulmonary stenosis. However, the accuracy of the Doppler estimates from TRVmax for invasively evaluated mPAP has remained an unmet need.[2,14,15] The reliability of right atrial pressure estimation is considered to be a major drawback of the TRVmax methods.[2,14,15] Moreover, the estimation of mPAP from TRVmax has been based on the assumption of linearity between sPAP and mPAP.[16-22] However, a large review including 29 studies revealed that the correlation between sPAPs estimated by Doppler and measured by RHC was only modest, with a summary correlation coefficient of 0.70 (95% CI 0.67-0.73), regardless of the disease severity.[23] Similarly, the diagnostic accuracy of the TRVmax method for PH proven by RHC was also reported to be modest, even using a cutoff value of 40 mm Hg which is the most commonly used threshold for sPAP by Doppler studies.[23]

The strong physiological linearity between sPAP and mPAP has been proven in several situations including exercise, pacing, treatment with inotropic agents or pulmonary vasodilators, and following heart or lung transplantation.[16,17,24,25] According to the empirical formula of the 2-pressure models, mPAP is defined by the following equation: mPAP = 2/3 × dPAP + 1/3 × sPAP, where dPAP refers to diastolic PA pressure.[26] The mPAP has been documented to be more sensitive to changes in dPAP as compared to those with sPAP.[16,26,27] The dPAP may represent distal vascular resistance more accurately than sPAP which is more dependent on the right ventricular ejection dynamics, PA compliance, and wave reflections.[16,26,27] Moreover, a new equation based on a simpler single-pressure model using a high-fidelity manometer was proposed: mPAP = 0.61 × sPAP + 2 mm Hg.[24] The sPAP was reported to account for 98% of mPAP variability.[24]

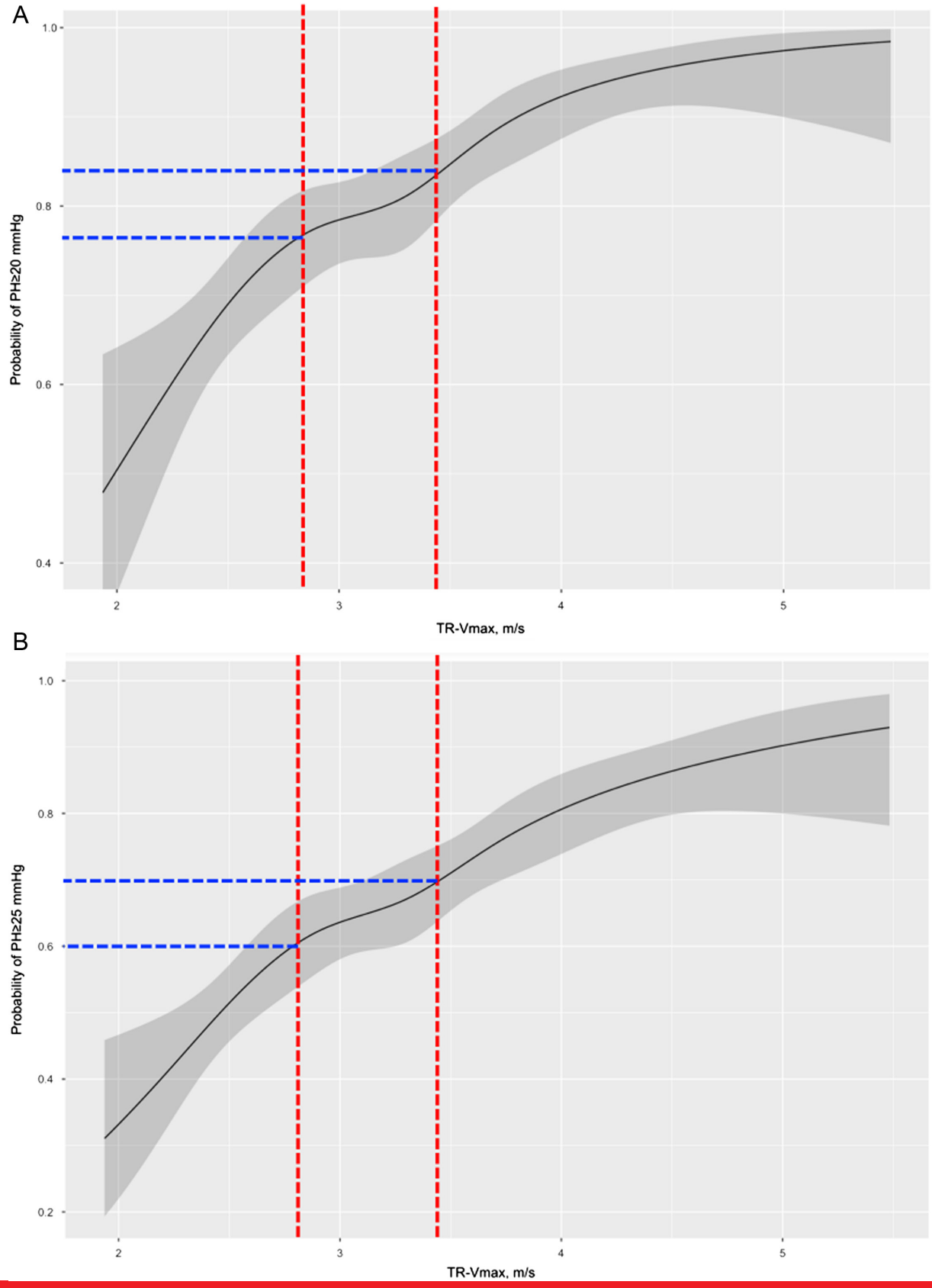


Figure 3. (A) According to Model-1, the probability of the mean PAP measured by right heart catheterization was > 20 mm Hg according to TRVmax measured in echocardiography. (B) According to Model-2, the probability of the mean PAP measured by right heart catheterization was ≥ 25 mm Hg according to TRVmax measured in echocardiography. PAP, pulmonary artery pressure; TRVmax, tricuspid regurgitation peak velocity.

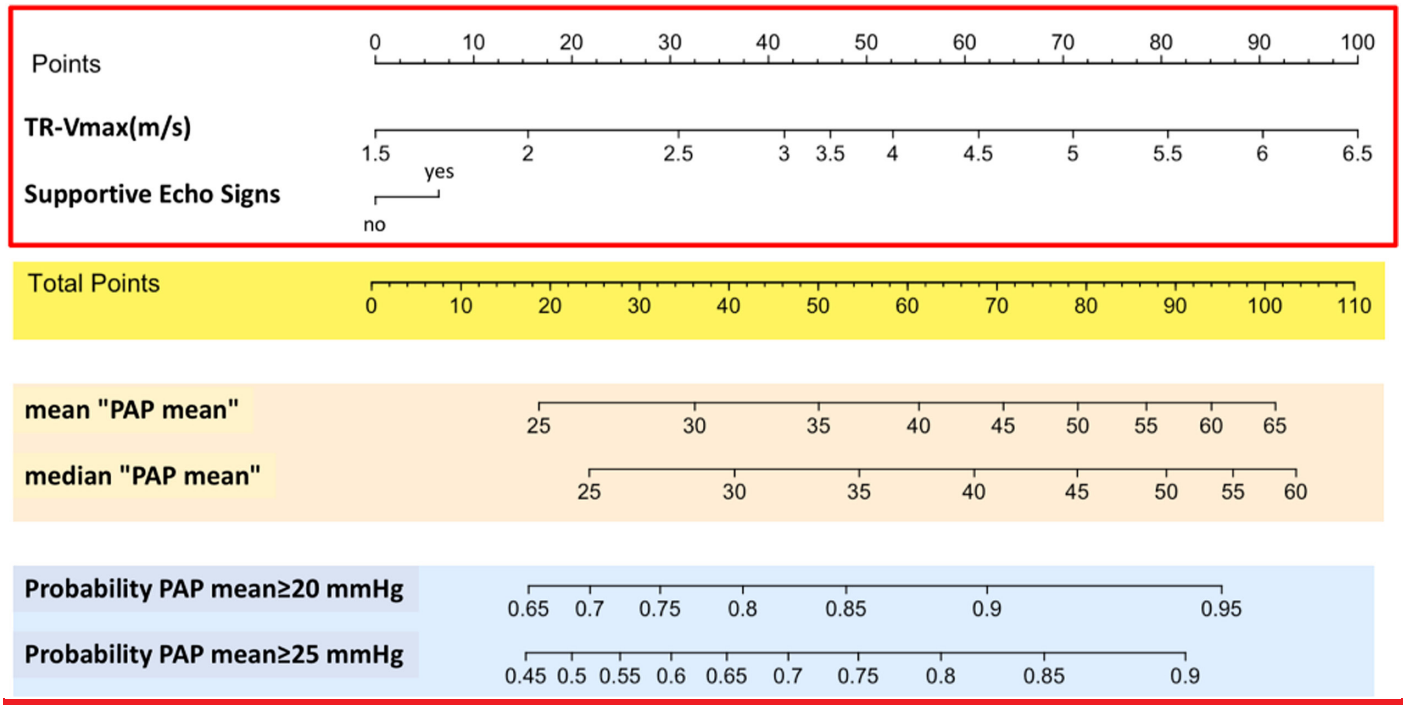


Figure 4. A nomogram developed for stepwise prediction of probability for mean pulmonary artery pressure > 20 and ≥ 25 mm Hg, respectively.

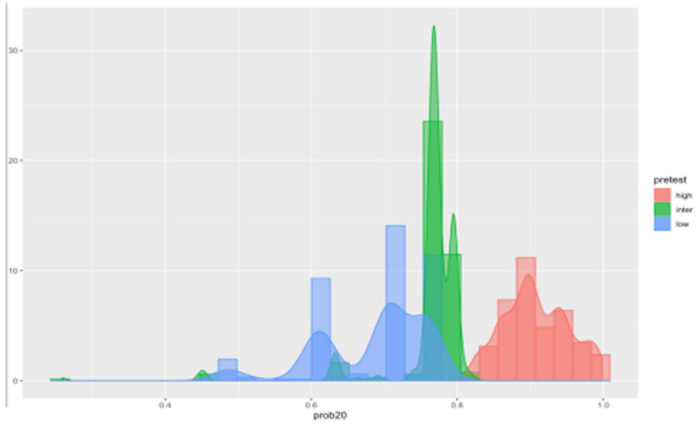
Several Doppler models based on TRVmax, RV outflow ejection time, or pulmonary regurgitant jet velocities have been developed for non-invasive estimation of the mPAP.[18-33,40,41] Although good and significant correlations were found between mPAP estimated by 4 widely used TRVmax formulas and mPAP measured by RHC ($r = 0.563$, $P < .001$ for all), the agreement between Doppler and RHC measures of mPAP was poor, regardless of the selected formula.[34] Two of those were underestimated, while the other 2 methods overestimated the invasively confirmed mPAP measures.[34] Therefore, the clinical relevance of mPAP estimates by TRVmax has been questioned, and ESC/ERS 2015 PH Guidelines recommended a 2-step echocardiographic algorithm combining the TR peak velocity at rest (instead of estimated sPAP) as the main variable for assigning the Doppler probability of PH with 7 additional echocardiographic variables from 3 categories addressing the right ventricular pressure overloading, accelerated and/or notched right ventricular ejection into the enlarged PA, and right atrial enlargement and plethora which are suggestive for PH.[2] We also utilized this definition based on the presence of at least 2 criteria from 3 categories of "echo findings suggestive of PH" including 7 parameters.

Besides a lot of new and unresolved issues raised after 4 mm Hg lowering the definitive mPAP threshold regarding uncertainties for management patterns in these patients with scleroderma, family members of hereditary PAH or asymptomatic carriers of gene mutations related to PAH, prevalent systemic to pulmonary congenital shunts, or chronic thromboembolic disease having mPAP between 21 and 25 mm Hg, the predictive value of the currently used echocardiographic model for the probability of PH in this patient population has yet to be evaluated.[11-13]

In the literature, various TRVmax cutoff values have been used in the evaluation before the diagnostic test in patients with suspected PH. In the study by Mukerjee et al.[35] in which Doppler echocardiography and cardiac catheterization were compared to distinguish the presence and absence of PAH in systemic sclerosis patients, various TRVmax thresholds were applied to test the sensitivity and specificity of the 2 techniques. It was observed that Doppler echocardiography was highly specific at high thresholds (97% with 3.35 m/s TRVmax), but as the threshold value increased, the rate of false negatives (42%) increased. It was reported in the study developed by Hachulla et al.[36] in which the efficacy of the algorithm based on TR velocity measurement with Doppler echocardiography for early diagnosis in systemic sclerosis patients was evaluated, that with the reduction of TRVmax cutoff to 2.5 m/s, 18 patients were diagnosed with PH according to the old definition (mPAP ≥ 25 mm Hg).[36] For this reason, it should be noted that there may be an increase in the rate of false negatives if the current TRVmax cutoff values are used in the evaluation of the echocardiographic probability in patients with suspected PH. In agreement with our results, these data suggest that in the era of the redefined mPAP threshold, the current TRVmax cut-off values alone may be sufficient for the assessment of echocardiographic probability in patients with suspected PH, and suggestive findings may not need to be investigated. On the other hand, this 4 mm Hg reduction in the definitive cutoff value of mPAP may also trigger seeking for lower TRVmax cutoff values with some new confirmative echocardiographic findings. For example, a low TAPSE/sPAP

A

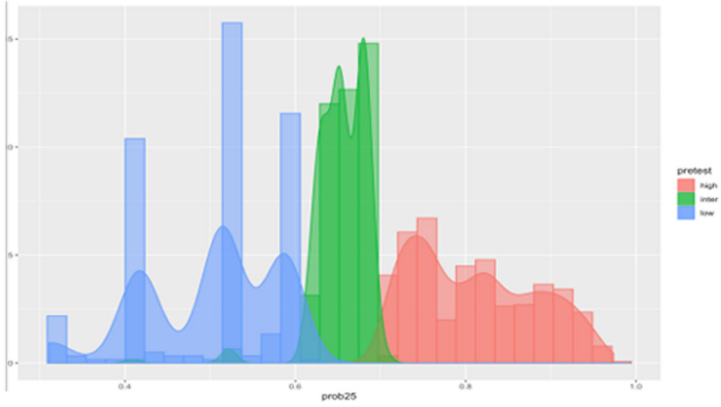
Peak tricuspid regurgitation velocity (m/s)	Presence of other echo 'PH signs'[a]	Echocardiographic probability of pulmonary hypertension
≤2.8 or not measurable	No	Low
≤2.8 or not measurable	Yes	Intermediate
2.9–3.4	No	
2.9–3.4	Yes	High
>3.4	Not required	



PAB>20 mmhg	low	intermediate	high
Prob min-max	0.48-0.77	0.26-0.82	0.81-0.99
Prob mean	0.68	0.76	0.91
Prob median	0.71 (0.61-0.76)	0.77(0.76-0.79)	0.90(0.88-0.94)

B

Peak tricuspid regurgitation velocity (m/s)	Presence of other echo 'PH signs'[a]	Echocardiographic probability of pulmonary hypertension
≤2.8 or not measurable	No	Low
≤2.8 or not measurable	Yes	Intermediate
2.9–3.4	No	
2.9–3.4	Yes	High
>3.4	Not required	



PAB>25 mmhg	low	intermediate	high
Prob min-max	0.31-0.61	0.41-0.70	0.70-0.97
Prob mean	0.50	0.65	0.81
Prob median	0.51 (0.42-0.59)	0.65(0.63-0.68)	0.81(0.75-0.87)

Figure 5. (A) The probability of mean PAP > 20 mm Hg in the post-catheter evaluation in patients grouped according to the echocardiographic probability of PH. (B) The probability of mean PAP ≥ 25 mm Hg in the post-catheter evaluation in patients grouped according to the echocardiographic probability of PH. PAP, pulmonary artery pressure; PH, pulmonary hypertension.

was reported as a straightforward non-invasive measure of RV-arterial coupling and RV diastolic stiffness in severe PH and was reported to be associated with a significantly worse prognosis.[37]

In a recent study based on the retrospective assessment of echocardiography and RHC data from a tertiary center registry, TR peak gradient (TRG) correlated modestly with sPAP measured on RHC in the whole cohort ($r = 0.671$, $P < .001$).[38] In stratified analysis, invasively evaluated sPAP showed a modest correlation with high TRG (>46 mm Hg; $r = 0.576$, $P < .001$) and a low correlation with TRG between 31 mm Hg and 46 mm Hg ($r = 0.208$, $P < .001$) but was not significantly correlated with low TRG (<31 mm Hg; $r = 0.128$, $P = 0.221$).[38] Tricuspid regurgitation peak gradient had slightly lower sensitivity, higher specificity, higher positive predictive value (PPV), and lower negative predictive values (NPV) for PH defined as mPAP > 20 mm Hg compared with PH defined as mPAP > 25 mm Hg. Positive and negative predictive values and diagnostic accuracy of TRG > 46 mm Hg were 95%, 39%, and 73%, respectively, for the new PH definition.[38] Lowering the TRG cutoff to < 31 mm Hg reduced the PPV to 89%. Accuracy was the highest (85%) using a TRG cutoff of 31 mm Hg, while there is extremely low specificity and a slight increase in sensitivity

without a substantial decrease in accuracy when the TRG was reduced below 31 mm Hg.[38] Although their data did not support lowering the TRG cutoff, we found that TRVmax cutoff values showed significant relation to mPAP > 20 mm Hg and mPAP ≥ 25 mm Hg, while the presence of additional echocardiographic findings offered a significant contribution only in predicting mPAP ≥ 25 mm Hg, but they were not necessary for mPAP > 20 mm Hg. Although the probability of mPAP ≥ 25 mm Hg was increased from 60% to 76% with TRVmax change from >2.8 m/s to >3.4 m/s, the probability of mPAP >20 mm Hg with the same cutoff values of TRVmax was higher—70% and 84%, respectively. Eventually, no change can be expected when TRVmax is <2.8 m/s and TRVmax is >3.4 m/s, whereas main changes seem to be associated with TRVmax between 2.8 m/s and 3.4 m/s. Moreover, it should be kept in mind that this 2-step echo model is based on a dichotomization across the TR jet peak velocity spectrum and in combination with suggestive echo findings. However, the correlation of the TRVmax with additional suggestive findings cannot validate the overall model, and a simple search for exploring the essentials of this model across the ESC/ERS 2015 and 2022 PH Guidelines, European Association of Cardiovascular Imaging 2015, and American Society of Cardiology 2010 Guidelines will confirm the absence of any validation for the whole model.[1,2,12,14] Instead, these definitions can be regarded as generally adopted pragmatic proposals. More interestingly, the number of suggestive findings was increased from 7 to 9 in the modified table of ESC/ERS 2022 PH Guidelines, and TAPSE/sPAP ratio < 0.55 was added to the first column of suggestive findings related to ventricles.[12] Although there is evidence for the value of each echo criterion in the diagnosis of PH, the grouping into 3 categories and the selection of the critical number have not yet been validated. Moreover, Ghio et al[39] reported that an echocardiographic approach integrating the TAPSE, TRG, and IVC was effective in stratifying the risk for all-cause mortality in PAH patients, whereas other echocardiographic measures such as right atrial area and pericardial effusion did not provide additional prognostic value.[39]

On the other hand, Gall et al[38] reported that the PPV of TRG for precapillary PH (mPAP > 20 mm Hg and PVR > 3 Wood units) was reported to be 85%. In patients with TRG < 46 mm Hg, TAPSE/TRG and TRG/right ventricular outflow tract acceleration time were documented to be superior to TRG alone in the diagnosis of newly defined precapillary PH.[38] In contrast to our results, they concluded that their data did not support lowering the TRG cutoff in the diagnosis for newly defined PH, and combining TRG with other echocardiographic parameters might improve the validity of echocardiographic screening in this setting.[38] However, all of the Doppler TRVmax and TRG and additive echocardiographic parameters in ESC/ERS 2015 and 2019 PH Guidelines have been proposed for initial screening of the overall PH but not for the prediction of precapillary PH. Hence, neither TAPSE/TRG nor TRG/right ventricular outflow tract acceleration time could be considered to be able to discriminate the precapillary versus postcapillary PH without a subsequent confirmative RHC evaluation.

Study Limitations

The retrospective nature of the analysis should be considered as the first limitation of this study. Because of a predefined population referred to RHC with different indications, a spectrum bias carrying the risk for distortions in a performance of a diagnostic test, and eventually, overestimation of the sensitivity and specificity of the Doppler assessments, could not be excluded. The lack of intra- and inter-observer variability analysis in echocardiographic measurements and ignoring the possible physiologic variabilities of the pulmonary vascular hemodynamics at sequential assessments as a confounding factor for comparisons between non-invasive and invasive mPAP measures might be the other limitations. Furthermore, we acknowledge that due to the nature of a retrospective study, hemodynamic data are not always obtained from same-day catheter evaluations as the echo examination, and we should confess that even a 24-hour time delay from echocardiographic evaluation to invasive assessment might be regarded as an inevitable limitation of a retrospective study because physiologic and hemodynamic variability within this time window might be considered as a potential confounder in comparing the 2 measure sets.

Moreover, recent changes in the hemodynamic definitions of precapillary and postcapillary PH seem to warrant new studies evaluating the values of non-invasive echocardiographic parameters in screening the overall PH and prediction of pre- versus postcapillary PH. However, because our analysis was targeted to the echocardiographic prediction of overall PH probability instead of its hemodynamic subtypes, results cannot be affected by recent reductions in the definitive PVR threshold.

CONCLUSIONS

In this study, we evaluated the echocardiographic screening algorithm for mPAP >20 mm Hg and mPAP ≥ 25 mm Hg. In contrast to those in predicting the mPAP ≥ 25 mm Hg, suggestive echocardiographic findings did not provide a significant contribution to the probability of mPAP > 20 mm Hg predicted by TRVmax solely. The TRVmax > 2.8 m/s and TRVmax > 3.4 m/s were associated with 70% and 84% probability of mPAP > 20 mm Hg and 60% and 76% probability of mPAP ≥ 25 mm Hg, respectively. Whether the 4 mm Hg reduction in the definitive threshold of mPAP may also require echocardiographic algorithms remains to be clarified by future studies.

Ethics Committee Approval: Ethics Committee decision date—decision number: 20.10.2020–2020/10/376; Kartal Koşuyolu High Specialization Training and Research Hospital Clinical Research Ethics Committee (2016-KAEK-112).

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İ.H.T., C.K.; Data Collection and/or Processing – S.T., H.C.T., Ö.Y.A., A.K., B. Kültürsay, B. Keskin, D.C., A.T.; Analysis and/or Interpretation – S.T., A.K., I.H.T.; Literature Review – S.T., H.C.T., Ö.Y.A., A.K., A.H., B. Kültürsay, B. Keskin, D.C., A.T., S.Ç.E., Ş.K., Z.B.; Writing – S.T., A.K., İ.H.T., C.K.; Critical Review – S.T., A.K., İ.H.T., N.Ö., C.K.

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