



Early View

Original research article

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Echocardiographic probability of pulmonary hypertension: a validation study

Michele D'Alto¹, Marco Di Maio², Emanuele Romeo¹, Paola Argiento¹, Ettore Blasi¹, Alessandro Di Vilio¹, Gaetano Rea³, Antonello D'Andrea⁴, Paolo Golino¹, Robert Naeije⁵.

(1) Department of Cardiology, University "L. Vanvitelli" - Monaldi Hospital, Naples, Italy

(2) Department of Medicine, Surgery and Dentistry, University of Salerno, Baronissi (Salerno), Italy.

(3) Radiology Unit, Monaldi Hospital, Naples, Italy

(4) Unit of Cardiology and Intensive Coronary Care, "Umberto I" Hospital, Nocera Inferiore, Italy.

(5) Department of Pathophysiology, Free University of Brussels, Brussels, Belgium.

Correspondence:

Dr Michele D'Alto, MD, PhD

Piazzale Ettore Ruggieri, 1

80131, Naples, Italy

Phone: +390817064198; fax +390817064275

Email: mic.dalto@tin.it

Take home message:

Echocardiography with measurement of direct and indirect signs as suggested by the 2015 ERS/ESC guidelines can still be used to assess the probability of pulmonary hypertension and pulmonary vascular disease according renewed definitions.

Abstract

Background. According to current guidelines, the diagnosis of pulmonary hypertension (PH) relies on echocardiographic probability followed by right heart catheterization. How echocardiography predicts PH recently re-defined by a mean pulmonary artery pressure (mPAP) >20 mmHg instead of ≥ 25 mmHg and pulmonary vascular disease defined by a pulmonary vascular resistance (PVR) >3 or >2 Wood units has not been established.

Methods. A total of 278 patients referred for PH underwent a comprehensive echocardiography followed by a right heart catheterization. Fifteen patients (5.4%) were excluded because of insufficient quality echocardiography.

Results. With PH defined by a mPAP >20 mmHg, 23 patients had no PH, 146 had pre-capillary and 94 post-capillary PH. At univariate analysis, maximum velocity of tricuspid regurgitation (TRV) ≥ 2.9 and ≤ 3.4 m/s, left ventricle (LV) eccentricity index >1.1 , right ventricle (RV) outflow tract (OT) notching or acceleration time <105 ms, RV-LV basal diameter >1 and PA diameter predicted PH, whereas inferior vena cava diameter and right atrial area did not. At multivariable analysis, only TRV ≥ 2.9 m/s independently predicted PH. Additional independent prediction of PVR >3 Wood units was offered by LV eccentricity index >1.1 and RVOT acceleration time <105 ms and/or notching, but with no improvement of optimal combination of specificity and sensibility or positive prediction.

Conclusions. Echocardiography as recommended in current guidelines can be used to assess the probability of re-defined PH in a referral center. However, the added value of indirect signs is modest and sufficient quality echocardiographic signals may not be recovered in some patients.

Key words: Pulmonary hypertension; right ventricle; echocardiography; tricuspid regurgitation; pulmonary flow; heart failure.

Introduction

The diagnosis of pulmonary hypertension (PH) rests on a step-by-step approach to define a clinical probability and is eventually confirmed by a right heart catheterization (1). Doppler echocardiography is an important component of this strategy. This procedure allows for the estimation of mean pulmonary artery pressure (mPAP) from the maximum velocity of tricuspid regurgitation (TRV), the acceleration time (AT) of right ventricular outflow tract (RVOT) flow-velocity and early pulmonary regurgitation velocity, and offers indirect PH assessment by 2-dimensional (2D) vascular and cardiac measurements (2). The 2015 European Respiratory Society (ERS)/European Society of Cardiology (ESC) guidelines for the diagnosis and treatment of PH stated that a TRV <2.8 m/s or undetectable would be associated with a low probability PH, a TRV between 2.9 and 3.4 m/s with an intermediate probability and a TRV >3.4 m/s with a high probability of PH (3,4). The guidelines also considered indirect signs of PH consisting in pulmonary artery (PA) or inferior vena cava (IVC) diameters, early pulmonary regurgitation velocity, RVOT-AT and systolic notching, left ventricle (LV) eccentricity index, right ventricle (RV)/LV basal diameter and right atrial (RA) area. A TRV-based intermediate or even low probability of PH would become higher probability in the presence of 2 indirect signs (3,4).

Pulmonary hypertension used to be defined by a mPAP ≥ 25 mmHg and pulmonary vascular disease by a pulmonary vascular resistance (PVR) >3 Wood units (3,4). There has been a proposal at the 5th World Symposium on PH (WSPH) held in Nice in 2018 to redefine PH by a mPAP >20 mmHg and pulmonary vascular disease by a PVR >3 Wood units (5). A mPAP of 20 mmHg is the upper limit of normal (6) and population studies have shown that higher than normal values are with a decreased survival (7). A lower cut-off could also be considered for PVR. A PVR of approximately 2 Wood units is the upper limit of normal (8) and higher values are also associated with a decreased survival (9).

The echocardiographic prediction of PH and/or pulmonary vascular disease based these redefined cut-off values is being assessed. A recent retrospective study on a large patient population concluded that a TRV of 3.4 m/s (RV-RA pressure gradient of 46 mmHg) remained a valid cut-off value for the prediction of PH defined by a mPAP >20 mmHg, but that lowering the threshold of TRV to 2.9 m/s (RV-RA pressure gradient of 31 mmHg) reduced its positive prediction value to below 89 % (10). The authors also showed that prediction of pulmonary vascular disease by mPAP >20 mmHg combined to a PVR >3 Wood units by TRV was improved when combined with tricuspid annular plane excursion (TAPSE) or RVOT-AT (10).

The purpose of the present study on patients referred for PH who underwent quasi-simultaneous non-invasive and invasive assessments was to assess the echocardiographic measurements listed in current guidelines prediction of PH and pulmonary vascular disease defined by either a mPAP >20 mmHg, a mPAP \geq 25 mmHg, a PVR >2 Wood units and a PVR >3 Wood units.

Methods

A total of 396 consecutive patients were referred to the Pulmonary Hypertension Unit of Monaldi Hospital (Naples, Italy) between January 1, 2018, and Dec 31, 2019 for a suspicion of PH. All of them underwent a clinical evaluation including a comprehensive echocardiography. Among them, 278 underwent a right heart catheterization. In 15 of these patients (5.4%) the echocardiography was of insufficient quality for further analysis (6 because of a poor acoustic window and 9 because of an inadequate TRV signal). Thus, 263 patients of this contemporary cohort were retrospectively evaluated in the present study. All the patients gave an informed consent to the study which complied with the Declaration of Helsinki and was approved by the Institutional Review Board of Monaldi Hospital of Naples, Italy (Protocol n. 18201).

Right heart catheterization was performed at rest, without sedation, by two experienced cardiologists (M.D. and E.R.). Measurements of systolic, mean and diastolic PAP (sPAP, mPAP and dPAP respectively), right atrial pressure (RAP), and pulmonary artery wedge pressure (PAWP) were taken at end-expiration. Cardiac output (CO) was measured by thermodilution using an average of at least three measurements. Cardiac index (CI) was calculated as CO divided by body surface area (BSA), and pulmonary vascular resistance (PVR) as mPAP minus PAWP divided by CO. PH was diagnosed by a mPAP ≥ 25 mmHg, post-capillary PH by a PAWP > 15 mm Hg and combined pre- and postcapillary PH by a PAWP > 15 mmHg and a PVR > 3 Wood units, in agreement with the 2015 ERS/ESC guidelines.

A comprehensive transthoracic echocardiographic examination was performed *quasi simultaneously* (within 1 hour) of right heart catheterization following international recommendations (11) by experienced dedicated cardiologists (P.A. and A.D.) using commercially available equipment, as previously described (12,13).

Categorical data were expressed as counts and proportions, and the between group comparisons were made using chi squared or Fisher's exact tests. The normality of each continuous variable was tested with the Shapiro-Wilk test. Non-normal variables were expressed as median [interquartile range], and the differences between medians were tested with Kruskal-Wallis test. Normally distributed variables were expressed as mean \pm standard deviation and the difference between means were tested with the t tests or the analysis of variance. No correction for multiple comparisons was applied. A univariate logistic regression analysis was used for the association between echocardiographic estimates of PAP (TRV, RVOT-AT or notching and maximum velocity of early PA regurgitation) and indirect signs of PH (PA diameter, or IVC diameter and inspiratory collapsibility, LV eccentricity index, RV-LV basal diameter and RA area and either a mPAP > 20 mmHg, and mPAP ≥ 25 mmHg, a

PVR >3 WU and a PVR >2 WU. A multivariate analysis was performed to identify independent echocardiographic predictors of each of these cut-off values. False positives and negatives, areas under ROC curves (AUC), sensitivities and specificities and positive/negative prediction values were determined for each of the direct or indirect PH predictors and for TRV plus one or more other independent echocardiographic PH predictors. Invasive and noninvasive estimates of mPAP and PAWP were compared using a Bland and Altman analysis (14).

Results

The anthropomorphic, functional, hemodynamic and echocardiographic data of the 263 patients included in the study are shown in tables 1 and 2. Of note, in these tables the distribution of data relies on the 2015 ERS/ESC guidelines cut-off values for the diagnosis of PH, that is a mPAP ≥ 25 mmHg and a PVR >3 WU.

Of the 129 patients with pre-capillary PH, 84 had pulmonary arterial hypertension (PAH) (67 idiopathic, 11 connective tissue disease-associated, and 6 with closed congenital cardiac shunts), 36 PH on chronic lung diseases, 4 had chronic thrombo-embolic PH, and 5 had “high-flow” PH defined as mPAP ≥ 25 mmHg and a PVR <3 WU. A total of 94 patients had PH on heart failure (38 isolated post-capillary PH, and 56 combined post- and pre-capillary PH. Among the 40 non-PH patients: 22 had a heart failure, 11 with preserved (HFpEF), 7 with mid-range (HFmrEF) and 4 with reduced (HFrEF) ejection fraction, 4 had a moderate-to severe primary tricuspid regurgitation, 3 a moderate-to-severe pacemaker-related tricuspid regurgitation, 4 a history of pulmonary embolism, 5 patients a chronic lung disease and 7 a connective tissue disorder.

As shown in Table 1, PH patients had worse functional class and lower cardiac output, and by definition increased mPAP and PVR compared to no-PH patients. The post-capillary PH patients showed lower mPAP, lower PVR and by definition increased PAWP compared to pre-capillary PH patients.

As shown in Table 2, almost all echocardiographic features were altered in PH patients, with small differences between echocardiographic and catheterization estimates of sPAP, increased PA dimensions, increased RV and RA dimensions in pre-capillary PH, and shortened RVOT-AT and/or notching. Of note, LV ejection fraction was essentially preserved and E/e' ratio were increased in the post-capillary PH group, in keeping with predominantly HFpEF and HFmrEF diagnosis.

The re-definition of PH by a mPAP >20 mmHg decreased the "no PH" group to 23 and increased the pre-capillary PH group to 146 patients, while the post-capillary PH group remained unchanged. The between groups distributions of anthropomorphic, functional, hemodynamic and echocardiographic data remained similar.

The uni- and multivariable of echocardiographic predictors of mPAP >20 mmHg are shown in Table 3. All the patients with a TRV >3.4 m/s had PH. At univariate analysis, TRV ≥ 2.9 m/s and ≤ 3.4 m/s, RV/LV basal diameter >1.0, LV eccentricity index >1.1 and RVOT-AT <105 ms or notch and PA diameter >25 mm were significantly associated with PH, while early diastolic PA regurgitation velocity >2.2 m/s, IVC diameter >21 mm or no inspiratory collapse, and RA area >18 cm² were not. At multivariable analysis, only TRV ≥ 2.9 m/s predicted mPAP >20 mmHg.

The uni- and multivariable of echocardiographic predictors of PH defined by mPAP ≥ 25 mmHg are shown in Table 4. All the patients with a TRV >3.4 m/s had PH. At univariate analysis, the same echocardiographic measurements were significantly associated with PH, but with in addition an early

PA regurgitation velocity of 2.2 m/s. At multivariable analysis TRV ≥ 2.9 m/s and ≤ 3.4 m/s, LV eccentricity index >1.1 and PA diameter >25 mm independently predicted PH.

The uni- and multivariable of echocardiographic predictors of mPAP >20 mmHg and PVR > 2 Wood units are shown in Table 5. At univariate analysis, TRV ≥ 2.9 m/s and ≤ 3.4 m/s or >3.4 m/s, LV eccentricity index >1.1 , early PA diastolic regurgitation >2.2 m/s, PA diameter >25 mm, IVC diameter >21 mm with decreased inspiratory collapse, RA area and RVOT-AT <105 ms or notching were significantly associated with a mPAP >20 mmHg and PVR >2 Wood units. At multivariable analysis, TRV ≥ 2.9 and ≤ 3.4 m/s or >3.4 m/s, LV eccentricity index >1.1 , RVOT-AT <105 ms or notching and IVC diameter >21 mm with decreased inspiratory collapse independently predicted mPAP >20 mmHg and PVR >2 Wood units.

The uni- and multivariable of echocardiographic predictors of mPAP ≥ 25 mmHg and PVR >3 Wood units are shown in Table 6. At univariate analysis, all the echocardiographic measurements were significantly associated with mPAP ≥ 25 mmHg and PVR >3 Wood units. At multivariable analysis, TRV ≥ 2.9 and ≤ 3.4 m/s or >3.4 m/s, LV eccentricity index >1.1 , RVOT-AT <105 ms or notching independently predicted mPAP ≥ 25 mmHg and PVR >3 Wood units.

The number of false negatives or positives, true negatives and positives, AUC, sensitivity, specificity, positive and negative predictive values of independent predictors of PH defined either by mPAP ≥ 20 mmHg, mPAP ≥ 25 mmHg, mPAP ≥ 20 mmHg and PVR >2 Wood units and mPAP ≥ 25 mmHg and PVR >3 Wood units are shown in Table 7. The best AUC was always obtained with TRV ≥ 2.9 m/s.

The incremental predictive value of one or more indirect signs in addition to peak TRV either >3.4 m/s or ≥ 2.9 m/s to predict PH defined by a mPAP >20 mmHg, mPAP ≥ 25 , mPAP >20 mmHg and PVR >2 Wood units and mPAP ≥ 25 mmHg and PVR >3 Wood units are shown in Table 8. In particular, for the prediction of mPAP ≥ 20 mmHg and PVR >2 Wood units, using 2.9 m/s as cut off for TRV, the best AUC was observed with addition of 1 indirect echo signs and the positive predictive value was 100% is with the presence of 2 indirect echo signs. Using 3.4 m/s as cut off for TRV the best AUC was not improved by the addition of indirect signs and the PPV near 100%.

The areas under the ROC curves for different cut-off values of TRV for the prediction of mPAP >20 mmHg, mPAP ≥ 25 mmHg, mPAP >20 mmHg + PVR >2 Wood units and mPAP ≥ 25 mmHg + PVR >3 Wood units are illustrated in Figure 1. Specificity increased but sensitivity decreased for TRV-derived predictions of either pressure or resistance with increased TRV cut-off values. The highest combination of sensitivity and specificity was obtained with a TRV cut-off value of 3.1 m/s.

A Bland and Altman analysis comparing mPAP measured at right heart catheterization or calculated from TRV at echocardiography showed a small bias of -2 mmHg, suggesting good accuracy, but an upper limit of agreement of 11 mmHg and a lower limit of agreement of 15 mmHg, suggesting limited precision.

A Bland and Altman analysis comparing PAWP measured at right heart catheterization or calculated from the E/e' ratio at echocardiography showed as well small bias of 0.02 mmHg, suggesting good accuracy, but limits of agreement of 10 mmHg, suggesting limited precision.

Discussion

The present results validate previously proposed echocardiographic strategy to predict PH in the 2015 ERS/ESC guidelines with a central role for TRV and added value of other estimates of PAP or PA, IVC or right heart chamber dimensions.

Pulmonary hypertension re-defined by a mPAP >20 mmHg was independently predicted either by a TRV >3.4 m/s or by a TRV ≥ 2.9 m/s and ≤ 3.4 m/s alone. Pulmonary vascular disease was independently predicted by TRV >3.4 m/s or by a TRV ≥ 2.9 m/s and ≤ 3.4 m/s with addition of 3 indirect signs to predict a PVR >3 Wood units or 3 indirect signs to predict a PVR >2 Wood units. However, the added value of indirect signs to predict pulmonary vascular disease in this patient population referred with a high clinical suspicion of PH and pulmonary vascular disease was modest.

Pulmonary hypertension used to be defined by a mPAP ≥ 25 mmHg (2,3) but it was proposed at the most recent WSPH held in Nice in 2018 to decrease this cut-off value to 20 mmHg (5). This proposal was based on the reasoning that a mPAP >20 mmHg is higher than normal (6) and associated with a decreased life expectancy (7). The renewed PH definition by a mPAP >20 mmHg has already entered clinical practice (15). Interestingly, a PVR >3 Wood units remained requested for the diagnosis of pre-capillary PH (or pulmonary vascular disease) (3-5) while it has been shown that a PVR of 2 Wood units is the upper limit of normal (8) and higher values are associated with decreased life expectancy (9). Therefore, in this study we assessed the echocardiographic predictors of PH and/or pulmonary vascular disease with consideration of all 4 cut-off values. We expect the lower cut-off values for mPAP and PVR to be used for the diagnosis of PH in the coming future.

Echocardiography allows for the estimation of mPAP based on either TRV, RVOT flow-velocity pattern or PA early regurgitation velocity (2). It is generally considered that TRV is the method of choice, with RVOT-AT and PA regurgitation serving as supportive measurements or internal controls (2,12). Several studies have shown that PAP calculated from a TRV or invasively measured are well correlated but with a dispersion resulting in an excessive proportion of false positive or negative diagnosis of PH (6,12,16,17). In fact, a Bland and Altman analysis in these studies invariably shows an only small bias around 2 mmHg, indicating accuracy but rather wide limits of agreement up to 20 mmHg and more indicating insufficient precision for individual decision making (7,12,16,17). Hence the reasoning behind the 2015 ERS/ESC guidelines to implement alternative assessments of PAP pressures as supportive measurements or internal controls. It is interesting that the added value of these supporting measurements was not significant for a TRV >3.4 m/s or significant but small for a TRV ≥ 2.9 m/s and ≤ 3.4 m/s in the present patient population, and only to identify increased PVR especially when the diagnostic cut-off was brought down to 2 Wood units. This may be explained by the fact that PVR is better than PAP to estimate RV afterload and its effects on right heart remodeling (18,19).

The cut-off values of echocardiographic measurements to predict PH as defined in the 2015 ERS/ESC guidelines were derived from known limits of normal and an estimated safety margin (2-4). One could wonder whether decreased cut-off values for PH or pulmonary vascular disease would not require adapted echocardiographic thresholds. There has been one study on a large patient population suggesting that this strategy actually reduces the positive predictive value of the measurements (6). A TRV threshold of 2.9 m/s corresponds to a sPAP of 34 mmHg and a mPAP of 22 mmHg recalculated respectively using the Bernoulli equation and estimate of RAP (20) and an equation based on the known proportionality between sPAP and mPAP (21). A TRV threshold of 2.9 m/s can be considered as the upper limit of normal as defined in large population studies (22,23). The TRV of 3.4 m/s corresponds to a sPAP of 46 mmHg and a mPAP of approximately 30 mmHg, which is

definitely much higher than normal (22,23). The best (ROC-derived) cut-off value of TRV to predict PH in the present study was 3.1 m/s. It is not surprising therefore that there is no added value of indirect echocardiographic signs to predict PH based a higher cut-off value.

The present study has several limitations. The first is a referral bias as the patients were sent to an expert PH center with the request to perform a right heart catheterization for a suspicion of PH. Therefore, the pre-test probability was high, which likely resulted in spuriously high positive predictions from echocardiographic TRV measurements. However, this referral bias is inevitable, as the echocardiography followed by invasive assessment would not be possible in a general unselected population, but may vary from one community to another and thus modulate the universal validity of the present's study conclusions. The second is that the patients were suspected of PH based on different definitions, which could also affect pre-test probability assessment. The third may be that measurements of pulmonary vascular pressures with fluid-filled catheters and cardiac output assessed by thermodilution compare with almost no bias but with large limits of agreement to gold standard high-fidelity micro-manometer-tipped catheters and the Fick method (22). However, our study is representative of "real life" expert PH center as required for diagnosis and treatment of pulmonary vascular diseases and considered in the ERS/ESC guidelines (2,3). The fourth is that the echocardiographic prediction of PH is not possible in every patient with a suspicion of PH. If needed, an alternative imaging modality such as by cardiac magnetic resonance may have to be implemented in these patients. Finally, the study assessed to echocardiographic cut-off values to estimate low vs intermediate or high probability of PH as disposed in the 2015 ERS/ESC guidelines, without however a reevaluation of these probability categories.

In conclusion, the echocardiographic prediction strategy of PH as defined in the 2015 ERS/ESC guidelines is valid for the new definition of PH based on a mPAP >20 mmHg. The clinical probability of pulmonary vascular disease by either a PVR >3 or >2 Wood units can adequately be assessed by

the same combination of measurements, with however more indirect signs when a cut-off value for PVR of 2 Wood units is to be taken into consideration.

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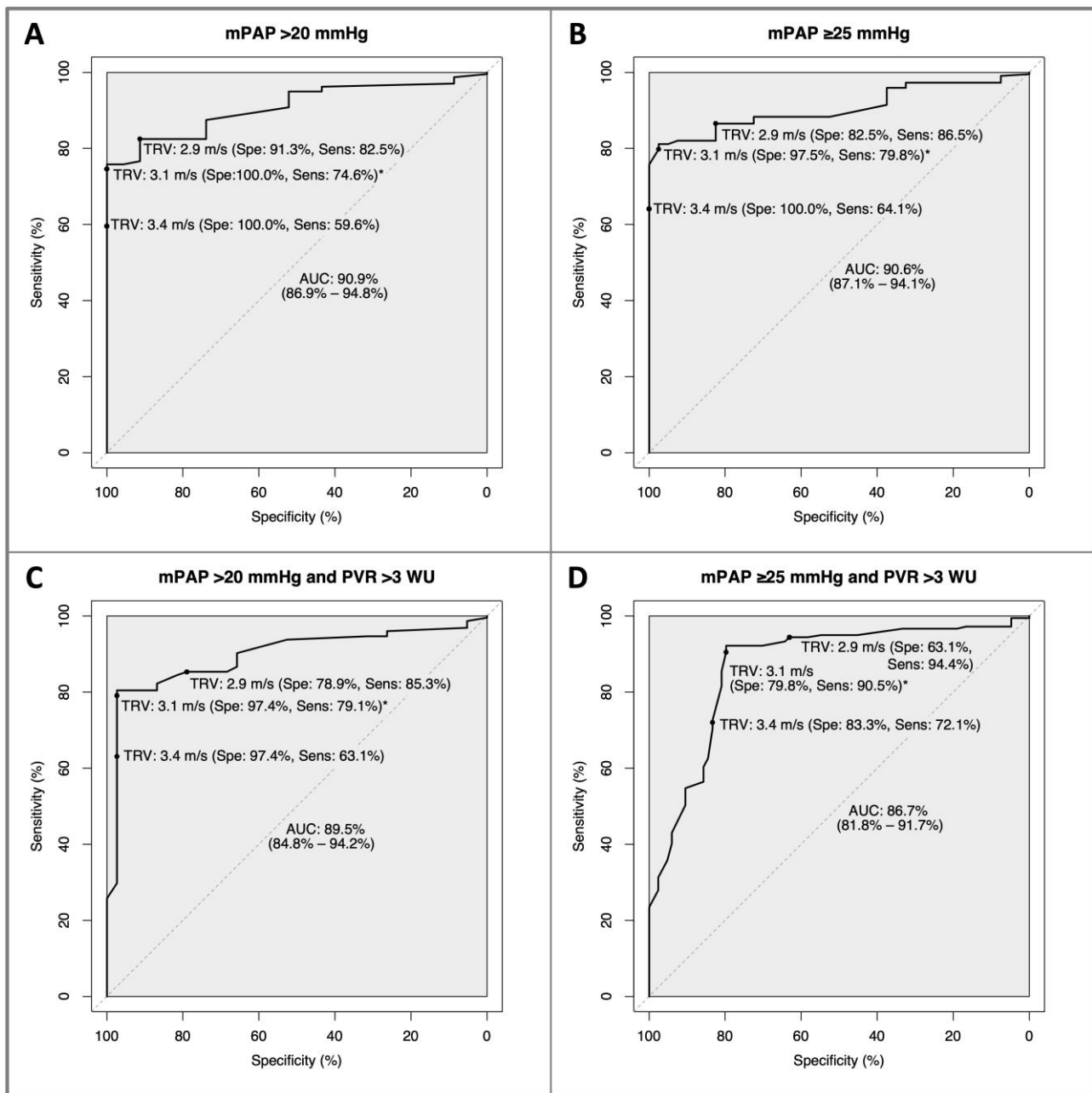
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Figure 1.



Receiver-operator (ROC) curves for the predictions of mean pulmonary artery pressure (mPAP) ≥ 25 mmHg, mPAP ≥ 20 mmHg, mPAP ≥ 25 mmHg and pulmonary vascular resistance (PVR) > 3 Wood units (WU) and mPAP ≥ 20 mmHg and PVR > 2 WU by increasing cut-off values for the maximum velocity of tricuspid regurgitation (TRV). Increasing the TRV cut-off increased the sensitivity but decreased the specificity of the predictions. In all cases the areas under the curves exceeded 80%.

Abbreviations: see tables 7-8. *Best cut-off value

Table 1: Demographic, functional and invasive hemodynamic data of overall population and differences between patients with and without pulmonary hypertension (PH) defined as mean pulmonary artery pressure (mPAP) ≥ 25 mmHg.

Variables	Overall	No PH (mPAP <25 mmHg)	PH (mPAP ≥ 25 mmHg)	Pre-capillary PH (mPAP ≥ 25 mmHg and PAWP ≤ 15)	Post-capillary PH (mPAP ≥ 25 mmHg and PAWP >15)	P*	P**
n	263	40	223	129	94		
Sex (m), n (%)	94 (35.7)	7 (17.5)	87 (39.0)	42 (32.6)	45 (47.9)	0.015	0.030
Weigh (kg), mean (SD)	70.6 (11.2)	64.8 (7.7)	71.6 (11.4)	69.0 (11.7)	75.2 (10.0)	<0.001	<0.001
Height (cm), median [IQR]	164.0 [160.0, 168.0]	160.0 [155.0, 161.0]	165.0 [160.0, 170.0]	164.0 [157.0, 168.0]	167.0 [161.2, 172.0]	<0.001	<0.001
BSA (m²), mean (SD)	1.8 (0.2)	1.7 (0.1)	1.8 (0.2)	1.7 (0.2)	1.8 (0.1)	<0.001	<0.001
Age (years), median [IQR]	57.0 [48.0, 64.0]	58.5 [54.0, 65.2]	57.0 [46.0, 63.0]	56.0 [45.0, 65.0]	59.0 [50.2, 62.0]	0.053	0.476
NYHA functional class, n (%)						<0.001	0.110
1	18 (6.8)	15 (37.5)	3 (1.3)	2 (1.6)	1 (1.1)		
2	111 (42.2)	25 (62.5)	86 (38.6)	56 (43.4)	30 (31.9)		
3	131 (49.8)	0 (0.0)	131 (58.7)	68 (52.7)	63 (67.0)		
4	3 (1.1)	0 (0.0)	3 (1.3)	3 (2.3)	0 (0.0)		
Cardiac index (l/min/m²), median [IQR]	2.7 [2.2, 3.2]	3.2 [2.9, 3.4]	2.5 [2.1, 3.1]	2.5 [2.1, 3.2]	2.5 [2.2, 3.0]	<0.001	0.290

Cardiac output (l/min), mean (SD)	4.7 (1.2)	5.2 (0.8)	4.6 (1.2)	4.6 (1.2)	4.7 (1.2)	0.004	0.515
RAP (mmHg), median [IQR]	8.0 [7.0, 11.0]	6.0 [5.0, 7.2]	9.0 [7.0, 11.0]	9.0 [6.0, 11.0]	9.0 [8.0, 11.0]	<0.001	0.130
PVR (WU), median [IQR]	4.6 [2.8, 7.2]	2.5 [2.0, 2.9]	5.2 [3.4, 7.8]	7.1 [4.8, 10.1]	3.6 [2.3, 5.0]	<0.001	<0.001
PVRi (WU*m²), median [IQR]	8.0 [4.7, 12.1]	4.1 [3.4, 4.6]	9.1 [6.1, 13.5]	11.8 [8.2, 18.3]	6.7 [4.3, 8.9]	<0.001	<0.001
mPAP (mmHg), median [IQR]	36.0 [28.0, 46.0]	20.0 [18.0, 22.0]	39.0 [32.0, 48.0]	40.0 [33.0, 51.0]	37.0 [31.0, 44.8]	<0.001	0.023
PAWP (mmHg), median [IQR]	10.0 [8.0, 19.0]	8.0 [6.0, 9.0]	11.0 [8.0, 21.0]	9.0 [7.0, 10.0]	21.0 [19.0, 24.0]	<0.001	<0.001
HR (bpm), median [IQR]	80.0 [70.0, 88.5]	73.0 [69.8, 85.0]	81.0 [72.0, 89.0]	81.0 [70.0, 86.0]	81.0 [75.2, 95.0]	0.070	0.194

*no PH vs PH, ** Pre-capillary vs post-capillary PH.

BSA: body surface area; HR: heart rate; IQR: interquartile range; mPAP: mean pulmonary artery pressure; NYHA: New York Heart Association; PVR: pulmonary vascular resistance; PVRi: pulmonary vascular resistance index; PAWP: pulmonary artery wedge pressure; RAP: right atrial pressure; SD: standard deviation; WU: Wood units.

Table 2: Mean (SD) of echocardiographic data of overall population and differences between patients with and without pulmonary hypertension (PH) defined as mean pulmonary artery pressure (mPAP) \geq 25 mmHg.

Variables	Overall	No PH (mPAP <25 mmHg)	PH (mPAP \geq25 mmHg)	Pre-capillary PH (mPAP \geq25 mmHg and PAWP \leq15)	Post- capillary PH (mPAP \geq25 mmHg and PAWP >15)	P*	P**
n	263	40	223	129	94		
RV diastolic area (cm²), median [IQR]	18.0 [14.0, 26.0]	26.5 [17.0, 30.0]	17.0 [13.8, 24.5]	18.8 [14.0, 27.3]	15.7 [13.0, 19.8]	<0.001	0.001
RV systolic area (cm²), median [IQR]	12.0 [9.0, 18.0]	15.5 [11.0, 18.0]	11.5 [9.0, 18.0]	13.0 [9.5, 19.0]	10.4 [8.0, 16.0]	0.032	0.004
FAC (%), median [IQR]	30.0 [22.3, 40.8]	39.6 [35.2, 43.8]	27.7 [20.8, 38.9]	27.0 [20.3, 40.0]	28.6 [23.1, 38.8]	<0.001	0.634
RA area (cm²), median [IQR]	15.0 [12.0, 20.0]	14.0 [11.9, 16.5]	15.5 [12.2, 20.0]	18.0 [13.0, 23.0]	14.0 [12.0, 16.0]	0.106	<0.001
TAPSE (mm), median [IQR]	19.0 [14.0, 22.0]	21.0 [17.8, 22.0]	18.0 [14.0, 22.0]	17.0 [14.0, 22.0]	19.0 [16.0, 22.0]	0.010	0.020

E/e', median [IQR]	7.5 [5.7, 11.4]	6.0 [5.1, 7.3]	8.0 [6.0, 12.2]	6.6 [5.3, 8.0]	12.7 [10.5, 15.9]	<0.001	<0.001
Peak TRV (m/s), median [IQR]	3.5 [2.9, 4.0]	2.8 [2.7, 2.9]	3.7 [3.2, 4.1]	3.9 [3.4, 4.2]	3.5 [2.9, 3.9]	<0.001	<0.001
LVTD (mm), median [IQR]	47.0 [44.0, 51.0]	45.0 [44.0, 53.0]	47.0 [44.0, 51.0]	47.0 [43.0, 51.0]	47.0 [44.0, 51.8]	0.723	0.191
LVTS (mm), median [IQR]	29.0 [26.0, 34.0]	27.0 [25.0, 34.2]	29.0 [26.0, 34.0]	29.0 [25.0, 34.0]	29.0 [27.0, 33.0]	0.045	0.397
IVS (mm), median [IQR]	10.0 [10.0, 11.0]	10.0 [9.8, 12.0]	10.0 [10.0, 11.0]	10.0 [10.0, 11.0]	11.0 [9.0, 12.0]	0.861	0.823
LV EF (%), median [IQR]	60.0 [55.0, 63.0]	61.0 [57.0, 63.2]	60.0 [55.0, 62.0]	59.0 [55.0, 61.0]	60.0 [55.0, 64.0]	0.045	0.145
PA (mm), median [IQR]	24.0 [22.0, 29.0]	19.5 [18.0, 24.0]	26.0 [22.0, 31.0]	25.0 [22.0, 32.0]	26.0 [23.0, 30.5]	<0.001	0.597
RVOT-AT (ms), median [IQR]	92.0 [85.0, 102.0]	102.0 [96.5, 113.0]	90.0 [85.0, 100.0]	89.0 [84.0, 99.0]	92.0 [85.5, 111.8]	<0.001	0.108

*no PH vs PH, ** Pre-capillary vs post-capillary PH.

E/e': ratio between early mitral inflow velocity and mitral annular early diastolic velocity; FAC: fractional area change; IQR: interquartile range; IVS: interventricular septum; LV EF: left ventricular ejection fraction; LVTD: left ventricular transverse diameter in diastole; LVTS: left ventricular transverse diameter in systole; PA: pulmonary artery; PH: pulmonary hypertension; PW: posterior wall; RA: right atrium; RV: right ventricle; RVOT-AT: Right ventricular outflow tract acceleration time; SD: standard

deviation; sPAP: systolic pulmonary pressure; TAPSE: tricuspid annular plane systolic excursion; TRV: tricuspid regurgitation velocity; WU: Wood units.

Table 3: Univariable and multivariable logistic regression testing all direct and indirect echocardiographic signs of PH as predictors of mPAP >20 mmHg. Frequencies of these echocardiographic findings in patients with and without mPAP >20 mmHg are also shown.

Signs of PH	Level	mPAP ≤20 mmHg n (%)	mPAP >20 mmHg n (%)	OR univariable	OR multivariable
n		23	240		
Peak tricuspid regurgitation velocity (m/s)	<2.9	21 (33.3)	42 (66.7)	-	-
	≥2.9 and ≤3.4	2 (3.5)	55 (96.5)	13.75 (3.75-89.01, p=0.001)	13.75 (3.75-89.01, p=0.001)
	>3.4	0 (0.0)	143 (100.0)	NA	NA
RV/LV basal diameter ratio	<1.0	19 (12.3)	136 (87.7)	-	-
	>1.0	4 (3.7)	104 (96.3)	3.63 (1.32-12.81, p=0.023)	NS
LV eccentricity index	≤1.1	17 (14.4)	101 (85.6)	-	-
	>1.1	6 (4.1)	139 (95.9)	3.90 (1.56-11.13, p=0.006)	NS
RV outflow Doppler acceleration time (ms)/ midsystolic notching	≥105 and no notch	14 (24.1)	44 (75.9)	-	-
	<105 or notch	9 (4.4)	196 (95.6)	6.93 (2.86-17.62, p<0.001)	NS

Early diastolic pulmonary regurgitation velocity (m/sec)	≤2.2	21 (10.2)	184 (89.8)	-	-
	>2.2	2 (3.4)	56 (96.6)	3.20 (0.90-20.37, p=0.124)	NS
Pulmonary artery diameter (mm)	≤25	18 (12.9)	121 (87.1)	-	-
	>25	5 (4.0)	119 (96.0)	3.54 (1.36-11.00, p=0.015)	NS
Inferior cava diameter (mm)/ inspiratory collapse	≤21 or no decreased collapse	20 (10.3)	175 (89.7)	-	-
	>21 and decreased collapse	3 (4.4)	65 (95.6)	2.48 (0.81-10.76, p=0.154)	NS
Right atrial area (end-systole, cm²)	≤18	18 (10.1)	160 (89.9)	-	-
	>18	5 (5.9)	80 (94.1)	1.80 (0.69-5.61, p=0.262)	NS

Multivariable model metrics: AIC = 103.5, C-statistic = 0.89, Hosmer-Lemeshow test: p=1.00.

Abbreviations: see Table 2

NA: not applicable; OR: odds ratio.

Table 4: Univariable and multivariable logistic regression testing all direct and indirect echocardiographic signs of PH as predictors of mPAP \geq 25 mmHg. Frequencies of these echocardiographic findings in patients with and without mPAP \geq 25 mmHg are also shown.

Signs of PH	Level	mPAP <25 mmHg n (%)	mPAP \geq 25 mmHg n (%)	OR univariable	OR multivariable
n		40	223		
Peak TRV (m/s)	<2.9	33 (52.4)	30 (47.6)	-	-
	\geq 2.9 and \leq 3.4	7 (12.3)	50 (87.7)	7.86 (3.24-21.40, p<0.001)	7.42 (2.88-21.49, p<0.001)
	>3.4	0 (0.0)	143 (100.0)	NA	NA
RV/LV basal diameter ratio	<1.0	33 (21.3)	122 (78.7)	-	-
	>1.0	7 (6.5)	101 (93.5)	3.90 (1.75-9.95, p=0.002)	NS
LV eccentricity index	\leq 1.1	30 (25.4)	88 (74.6)	-	-
	>1.1	10 (6.9)	135 (93.1)	4.60 (2.21-10.35, p<0.001)	3.81 (1.49-10.59, p=0.007)
RVOT-AT (ms)/ midsystolic notching	\geq 105 and no notch	17 (29.3)	41 (70.7)	-	-
	<105 or notch	23 (11.2)	182 (88.8)	3.28 (1.59-6.68, p=0.001)	NS
Early diastolic pulmonary regurgitation velocity (m/sec)	\leq 2.2	37 (18.0)	168 (82.0)	-	-
	>2.2	3 (5.2)	55 (94.8)	4.04 (1.39-17.18, p=0.024)	NS
PA diameter (mm)	\leq 25	31 (22.3)	108 (77.7)	-	-
	>25	9 (7.3)	115 (92.7)	3.67 (1.73-8.51, p=0.001)	3.87 (1.50-10.87, p=0.007)
Inferior cava diameter (mm)/ inspiratory collapse	\leq 21 or no decreased collapse	33 (16.9)	162 (83.1)	-	-
	>21 and decreased collapse	7 (10.3)	61 (89.7)	1.78 (0.79-4.56, p=0.195)	NS
RA area (end-systole, cm²)	\leq 18	31 (17.4)	147 (82.6)	-	-
	>18	9 (10.6)	76 (89.4)	1.78 (0.84-4.15, p=0.153)	NS

Multivariable model metrics: AIC =125.2, C-statistic =0.93, Hosmer-Lemeshow test: p =0.825. NA: not applicable; OR: odds ratio; for other abbreviations see table 2.

Table 5: Univariable and multivariable logistic regression testing all direct and indirect echocardiographic signs of PH as predictors of mPAP >20 mmHg and PVR >2 WU. Frequencies of these echocardiographic findings in patients with and without mPAP >20 mmHg and PVR >2 WU are also shown.

Signs of PH	Level	<i>mPAP</i> ≤ 20 <i>mmHg</i> and/or <i>PVR</i> ≤ 2 <i>WU</i>	<i>mPAP</i> > 20 <i>mmHg</i> and <i>PVR</i> > 2 <i>WU</i>	OR univariable	OR multivariable
n		38	225		
Peak TRV (m/s)	< 2.9	30 (47.6)	33 (52.4)	-	-
	≥ 2.9 and ≤ 3.4	7 (12.3)	50 (87.7)	6.5 (2.7-17.7, p<0.001)	5.08 (2.0-14.7, p=0.001)
	> 3.4	1 (0.7)	142 (99.3)	129.1 (26.2- 2340.1, p<0.001)	57.0 (10.9- 1052.4, p<0.001)
RV/LV basal diameter ratio	< 1.0	27 (17.4)	128 (82.6)	-	-
	> 1.0	11 (10.2)	97 (89.8)	1.9 (0.9-4.1, p=0.104)	NS
LV eccentricity index	≤ 1.1	25 (21.2)	93 (78.8)	-	-
	> 1.1	13 (9.0)	132 (91.0)	2.7 (1.3-5.8, p=0.006)	2.8 (1.1-8.0, p=0.042)
RVOT-AT (ms)/ midsystolic notching	≥ 105 and no notch	23 (39.7)	35 (60.3)	-	-
	< 105 or notch	15 (7.3)	190 (92.7)	8.3 (4.0-17.8, p<0.001)	4.24 (1.6-11.6, p=0.003)
Early diastolic pulmonary regurgitation velocity (m/sec)	≤ 2.2	35 (17.1)	170 (82.9)	-	-
	> 2.2	3 (5.2)	55 (94.8)	3.8 (1.3-16.1, p=0.033)	NS
PA diameter (mm)	≤ 25	26 (18.7)	113 (81.3)	-	-
	> 25	12 (9.7)	112 (90.3)	2.1 (1.1-4.6, p=0.041)	NS
Inferior cava diameter (mm)/ inspiratory collapse	≤ 21 or no decreased collapse	35 (17.9)	160 (82.1)	-	-
	> 21 and decreased collapse	3 (4.4)	65 (95.6)	4.7 (1.6-20.1, p=0.012)	6.0 (1.5-32.4, p=0.020)
RA area (end-systole, cm²)	≤ 18	33 (18.5)	145 (81.5)	-	-
	> 18	5 (5.9)	80 (94.1)	3.6 (1.5-11.0, p=0.010)	NS

Multivariable model metrics: AIC =70.5, C-statistic =0.90, Hosmer-Lemeshow test: p= 1.00. LV: left ventricle; mPAP: mean pulmonary artery pressure; NA: not applicable; OR: odds ratio; PH: pulmonary hypertension; RV: right ventricle.

Table 6: Univariable and multivariable logistic regression testing of all echocardiographic signs of pre-capillary PH defined by mPAP \geq 25 mmHg and PVR $>$ 3 WU. Frequencies of these echocardiographic findings in patients with and without mPAP \geq 25 mmHg and PVR $>$ 3 WU are also shown.

Signs of PH	Level	mPAP <25 mmHg and/or PVR \leq 3 WU	mPAP \geq 25 mmHg and PVR $>$ 3 WU	OR univariable	OR multivariable
n		84	179		
Peak TRV (m/s)	<2.9	53 (84.1)	10 (15.9)	-	-
	\geq2.9 and \leq3.4	17 (29.8)	40 (70.2)	12.47 (5.34-31.52, p<0.001)	10.17 (4.08-27.37, p<0.001)
	>3.4	14 (9.8)	129 (90.2)	48.84 (21.31-123.12, p<0.001)	24.89 (10.24-65.69, p<0.001)
RV/LV basal diameter ratio	<1.0	63 (40.6)	92 (59.4)	-	-
	>1.0	21 (19.4)	87 (80.6)	2.84 (1.62-5.13, p<0.001)	NS
LV eccentricity index	\leq1.1	55 (46.6)	63 (53.4)	-	-
	>1.1	29 (20.0)	116 (80.0)	3.49 (2.04-6.08, p<0.001)	3.50 (1.66-7.65, p=0.001)
RVOT-AT (ms)/midsystolic notching	\geq105 and no notch	42 (72.4)	16 (27.6)	-	-
	<105 or notch	42 (20.5)	163 (79.5)	10.19 (5.32-20.37, p<0.001)	5.23 (2.25-12.50, p<0.001)
Early diastolic pulmonary regurgitation velocity (m/sec)	\leq2.2	77 (37.6)	128 (62.4)	-	-
	>2.2	7 (12.1)	51 (87.9)	4.38 (2.01-11.02, p=0.001)	NS
PA diameter (mm)	\leq25	54 (38.8)	85 (61.2)	-	-
	>25	30 (24.2)	94 (75.8)	1.99 (1.17-3.42, p=0.012)	NS
Inferior cava diameter (mm)/inspiratory collapse	\leq21 or no decreased collapse	69 (35.4)	126 (64.6)	-	-
	>21 and decreased collapse	15 (22.1)	53 (77.9)	1.93 (1.04-3.79, p=0.045)	NS
RA area (end-systole, cm²)	\leq18	72 (40.4)	106 (59.6)	-	-
	>18	12 (14.1)	73 (85.9)	4.13 (2.16-8.50, p<0.001)	NS

Multivariable model metrics: AIC =202.8, C-statistic =0.898, Hosmer-Lemeshow test: p =0.999. NA: not applicable; OR: odds ratio; PVR: pulmonary vascular resistance. other abbreviations see table 2.

Table 7: Diagnostic accuracy of independent PH predictors

Direct and indirect echocardiographic signs	FN	FP	TN	TP	AUC	Sen	Spe	PPV	NPV
• to predict a mPAP >20 mmHg:									
Peak TRV ≥ 2.9 m/s	42	2	21	198	0.87	0.83	0.91	0.99	0.33
Peak TRV >3.4 m/s	97	0	23	143	0.8	0.6	1	1	0.19
• to predict a mPAP ≥ 25 mmHg:									
Peak TRV ≥ 2.9 m/s	30	7	33	193	0.85	0.87	0.83	0.97	0.52
Peak TRV >3.4 m/s	80	0	40	143	0.82	0.64	1	1	0.33
Left ventricular eccentricity index >1.1	88	10	30	135	0.68	0.61	0.75	0.93	0.25
• to predict mPAP >20 mmHg and PVR >2 WU:									
Peak TRV ≥ 2.9 m/s	33	8	30	192	0.82	0.85	0.79	0.96	0.48
Peak TRV >3.4 m/s	83	1	37	142	0.8	0.63	0.97	0.99	0.31
Left ventricular eccentricity index >1.1	93	13	25	132	0.62	0.59	0.66	0.91	0.21
RV outflow Doppler acceleration time <105 msec and/or midsystolic notching	35	15	23	190	0.73	0.84	0.61	0.93	0.4
Inferior cava diameter >21 mm with decreased inspiratory collapse	160	3	35	65	0.61	0.29	0.92	0.96	0.18
• to predict mPAP ≥ 25 mmHg and PVR >3 WU:									
Peak TRV ≥ 2.9 m/s	10	31	53	169	0.79	0.94	0.63	0.85	0.84
Peak TRV >3.4 m/s	50	14	70	129	0.78	0.72	0.83	0.9	0.58
Left ventricular eccentricity index >1.1	63	29	55	116	0.65	0.65	0.66	0.8	0.47
RV outflow Doppler acceleration time <105 msec and/or	16	42	42	163	0.71	0.91	0.5	0.8	0.72

midsystolic notching									
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AUC: area under the curve; FN: false negative; FP: false positive; LV: left ventricle; mPAP: mean pulmonary artery pressure; RV: right ventricle; TN: true negative; Sen: sensibility; Spe: specificity; NPV: negative predictive value; PPV: positive predictive value.

<ul style="list-style-type: none"> to predict a mPAP >20 mmHg and PVR >2 WU 									
Peak TRV ≥ 2.9 m/s	33	8	30	192	0.82	0.85	0.79	0.96	0.48
Peak TRV ≥ 2.9 m/s + 1 or more indirect signs	39	6	32	186	0.83	0.83	0.84	0.97	0.45
Peak TRV ≥ 2.9 m/s + 2 or more indirect signs	98	0	38	127	0.78	0.56	1	1	0.28
Peak TRV ≥ 2.9 m/s + 3 or more indirect signs	188	0	38	37	0.58	0.16	1	1	0.17
Peak TRV >3.4 m/s	83	1	37	142	0.8	0.63	0.97	0.99	0.31
Peak TRV >3.4 m/s + 1 or more indirect signs	85	1	37	140	0.8	0.62	0.97	0.99	0.3
Peak TRV >3.4 m/s + 2 or more indirect signs	124	0	38	101	0.72	0.45	1	1	0.24
Peak TRV >3.4 m/s + 3 or more indirect signs	191	0	38	34	0.58	0.15	1	1	0.17
<ul style="list-style-type: none"> to predict a mPAP ≥ 25 mmHg and PVR >3 WU 									
Peak TRV ≥ 2.9 m/s	10	31	53	169	0.79	0.94	0.63	0.85	0.84

Peak TRV ≥ 2.9 m/s + 1 or more indirect signs	14	23	61	165	0.82	0.92	0.73	0.88	0.81
Peak TRV ≥ 2.9 m/s + 2 or more indirect signs	75	5	79	104	0.76	0.58	0.94	0.95	0.51
Peak TRV > 3.4 m/s	50	14	70	129	0.78	0.72	0.83	0.9	0.58
Peak TRV > 3.4 m/s + 1 or more indirect signs	51	11	73	128	0.79	0.72	0.87	0.92	0.59
Peak TRV > 3.4 m/s + 2 or more indirect signs	93	3	81	86	0.72	0.48	0.96	0.97	0.47

Abbreviations: see table 7. TRV: tricuspid regurgitation velocity.