Echocardiographic probability of pulmonary hypertension: a validation study

Michele D'Alto[1], Marco Di Maio[2], Emanuele Romeo[1], Paola Argiento[1], Ettore Blasi[1], Alessandro Di Vilio[1], Gaetano Rea[3], Antonello D'Andrea[4], Paolo Golino[1] and Robert Naeije[5]

[1]Dept of Cardiology, University "L. Vanvitelli" – Monaldi Hospital, Naples, Italy. [2]Dept of Medicine, Surgery and Dentistry, University of Salerno, Baronissi, Italy. [3]Radiology Unit, Monaldi Hospital, Naples, Italy. [4]Unit of Cardiology and Intensive Coronary Care, "Umberto I" Hospital, Nocera Inferiore, Italy. [5]Dept of Pathophysiology, Free University of Brussels, Brussels, Belgium.

Corresponding author: Michele D'Alto (mic.dalto@tin.it)

Shareable abstract (@ERSpublications)
Echocardiography with measurement of direct and indirect signs as suggested by the 2015 ESC/ERS guidelines can still be used to assess the probability of pulmonary hypertension and pulmonary vascular disease according to renewed definitions https://bit.ly/3m9w45k

Cite this article as: D'Alto M, Di Maio M, Romeo E, *et al*. Echocardiographic probability of pulmonary hypertension: a validation study. *Eur Respir J* 2022; 60: 2102548 [DOI: 10.1183/13993003.02548-2021].

This article has an editorial commentary: https://doi.org/10.1183/13993003.00481-2022

Received: 22 Sept 2021
Accepted: 10 Dec 2021

Abstract

Background According to current guidelines, the diagnosis of pulmonary hypertension (PH) relies on echocardiographic probability followed by right heart catheterisation (RHC). How echocardiography predicts PH recently redefined by mean pulmonary arterial pressure (mPAP) >20 mmHg instead of ⩾25 mmHg and pulmonary vascular disease defined by pulmonary vascular resistance (PVR) ⩾3 or >2 WU has not been established.

Methods A total of 278 patients referred for PH underwent comprehensive echocardiography followed by RHC. 15 patients (5.4%) were excluded because of insufficient quality echocardiography.

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

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

Introduction

The diagnosis of pulmonary hypertension (PH) rests on a step-by-step approach to define a clinical probability and is eventually confirmed by right heart catheterisation (RHC) [1]. Doppler echocardiography is an important component of this strategy. This procedure allows for the estimation of mean pulmonary arterial pressure (mPAP) from maximum tricuspid regurgitation velocity (TRV), acceleration time (AT) of right ventricular outflow tract (RVOT) flow velocity and early pulmonary regurgitation velocity, and offers indirect PH assessment by two-dimensional vascular and cardiac measurements [2]. The 2015 European Society of Cardiology (ESC)/European Respiratory Society (ERS) guidelines for the diagnosis and treatment of PH stated that TRV ⩽2.8 $m \cdot s^{-1}$ or undetectable would be associated with a low probability of PH, TRV 2.9–3.4 $m \cdot s^{-1}$ with an intermediate probability of PH and TRV >3.4 $m \cdot s^{-1}$ with a high probability of PH [3, 4]. The 2015 ESC/ERS 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, 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 two indirect signs [3, 4].

PH used to be defined by mPAP ⩾25 mmHg and pulmonary vascular disease by pulmonary vascular resistance (PVR) ⩾3 WU [3, 4]. There was a proposal at the 6th World Symposium on Pulmonary Hypertension (WSPH) held in Nice, France, in 2018 to redefine PH by mPAP >20 mmHg and pulmonary vascular disease by PVR ⩾3 WU [5]. mPAP 20 mmHg is the upper limit of normal [6] and population studies have shown that higher than normal values are associated with decreased survival [7]. A lower cut-off could also be considered for PVR. PVR ∼2 WU is the upper limit of normal [8] and higher values are also associated with 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 TRV 3.4 $m \cdot s^{-1}$ (RV–RA pressure gradient 46 mmHg) remained a valid cut-off value for the prediction of PH defined by mPAP >20 mmHg, but that lowering the threshold of TRV to 2.9 $m \cdot s^{-1}$ (RV–RA pressure gradient 31 mmHg) reduced its positive predictive value to <89% [10]. The authors also showed that prediction of pulmonary vascular disease by mPAP >20 mmHg combined with PVR ⩾3 WU by TRV was improved when combined with tricuspid annular plane excursion or RVOT-AT [10].

The purpose of the present study on patients referred for PH who underwent quasi-simultaneous noninvasive and invasive assessments was to assess the echocardiographic measurements listed in the current ESC/ERS guidelines for the prediction of PH and pulmonary vascular disease defined by either mPAP >20 mmHg, mPAP ⩾25 mmHg, PVR >2 WU or PVR ⩾3 WU.

Methods

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

RHC 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 arterial wedge pressure (PAWP) were taken at end-expiration. Cardiac output was measured by thermodilution using an average of at least three measurements. Cardiac index was calculated as cardiac output divided by body surface area. Pulmonary vascular resistance (PVR) was calculated as mPAP minus PAWP divided by cardiac output. PH was diagnosed by mPAP ⩾25 mmHg, post-capillary PH by PAWP >15 mmHg, and combined pre- and post-capillary PH by PAWP >15 mmHg and PVR ⩾3 WU, in agreement with the 2015 ESC/ERS guidelines [3, 4].

A comprehensive transthoracic echocardiographic examination was performed quasi-simultaneously (within 1 h) of RHC following international recommendations [11] by experienced dedicated cardiologists (P.A. and A.D.) using commercially available equipment, as described previously [12, 13].

Categorical data were expressed as counts and proportions; between-group comparisons were made using the Chi-squared test or Fisher's exact. The normality of each continuous variable was tested with the Shapiro–Wilk test. Nonnormal variables were expressed as median (interquartile range (IQR)); differences between medians were tested with the Kruskal–Wallis test. Normally distributed variables were expressed as mean with standard deviation; differences between means were tested with the t-test or ANOVA. No correction for multiple comparisons was applied. 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 mPAP >20 mmHg, mPAP ⩾25 mmHg, PVR ⩾3 WU or PVR >2 WU. Multivariate analysis was performed to identify independent echocardiographic predictors of each of these cut-off values. False positives and negatives, areas under receiver operating characteristic (ROC) curves (AUCs), sensitivities and specificities, and positive and negative predictive 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 Bland–Altman analysis [14].

Results

The anthropomorphic, functional, haemodynamic and echocardiographic data of the 263 patients included in the study are shown in tables 1 and 2. Of note, in tables 1 and 2 the distribution of data relies on the 2015 ESC/ERS guidelines cut-off values for the diagnosis of PH, *i.e.* mPAP ⩾25 mmHg and PVR ⩾3 WU [3, 4].

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

As shown in table 1, PH patients had worse New York Heart Association Functional Class and lower cardiac output, and by definition increased mPAP and PVR, compared with non-PH patients. The post-capillary PH patients showed lower mPAP and lower PVR, and by definition increased PAWP, compared with pre-capillary PH patients.

As shown in table 2, almost all echocardiographic features were altered in PH patients, with small differences between echocardiographic and catheterisation 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 the E/e' ratio was increased in the post-capillary PH group, in keeping with predominantly HFpEF and HFmrEF diagnoses.

The redefinition of PH by mPAP >20 mmHg decreased the non-PH group to 23 patients 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, haemodynamic and echocardiographic data remained similar.

The univariable and multivariable logistic regression testing of echocardiographic predictors of mPAP >20 mmHg is shown in table 3. All patients with TRV >3.4 $m \cdot s^{-1}$ had PH. At univariate analysis, TRV 2.9–3.4 $m \cdot s^{-1}$, RV/LV basal diameter >1.0, LV eccentricity index >1.1 and RVOT-AT <105 ms or notching and PA diameter >25 mm were significantly associated with PH, while early diastolic PA regurgitation velocity >2.2 $m \cdot s^{-1}$, IVC diameter >21 mm or no inspiratory collapse and RA area >18 cm^2 were not. At multivariable analysis, only TRV ⩾2.9 $m \cdot s^{-1}$ predicted mPAP >20 mmHg.

The univariable and multivariable logistic regression testing of echocardiographic predictors of PH defined by mPAP ⩾25 mmHg is shown in table 4. All patients with TRV >3.4 $m \cdot s^{-1}$ had PH. At univariate analysis, the same echocardiographic measurements were significantly associated with PH, but with in addition early PA regurgitation velocity >2.2 $m \cdot s^{-1}$. At multivariable analysis, TRV 2.9–3.4 $m \cdot s^{-1}$, LV eccentricity index >1.1 and PA diameter >25 mm independently predicted PH.

The univariable and multivariable logistic regression testing of echocardiographic predictors of mPAP >20 mmHg and PVR >2 WU is shown in table 5. At univariate analysis, TRV 2.9–3.4 or >3.4 $m \cdot s^{-1}$, LV eccentricity index >1.1, early PA diastolic regurgitation velocity >2.2 $m \cdot s^{-1}$, 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 mPAP >20 mmHg and PVR >2 WU. At multivariable analysis, TRV 2.9–3.4 or >3.4 $m \cdot s^{-1}$, 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 WU.

The univariable and multivariable logistic regression testing of echocardiographic predictors of mPAP ⩾25 mmHg and PVR ⩾3 WU is shown in table 6. At univariate analysis, all echocardiographic measurements were significantly associated with mPAP ⩾25 mmHg and PVR ⩾3 WU. At multivariable analysis, TRV 2.9–3.4 or >3.4 $m \cdot s^{-1}$, LV eccentricity index >1.1 and RVOT-AT <105 ms or notching independently predicted mPAP ⩾25 mmHg and PVR ⩾3 WU.

TABLE 1 Demographic, functional and invasive haemodynamic data of the overall population and differences between patients with and without pulmonary hypertension (PH) defined by mean pulmonary arterial pressure (mPAP) ⩾25 mmHg

	Overall	No PH (mPAP <25 mmHg)	PH (mPAP ⩾25 mmHg)	Pre-capillary PH (mPAP ⩾25 mmHg and PAWP >15 mmHg)	Post-capillary PH (mPAP ⩾25 mmHg and PAWP >15 mmHg)	p-value[#]	p-value[¶]
Patients	263	40	223	129	94		
Male	94 (35.7)	7 (17.5)	87 (39.0)	42 (32.6)	45 (47.9)	0.015	0.030
Weight (kg)	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)	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 (m^2)	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)	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 FC						<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 ($L{\cdot}min^{-1}{\cdot}m^{-2}$)	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 ($L{\cdot}min^{-1}$)	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)	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)	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 ($WU{\cdot}m^2$)	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)	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)	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
Heart rate ($beats{\cdot}min^{-1}$)	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

Data are presented as n, n (%), mean±SD or median (interquartile range), unless otherwise stated. PAWP: pulmonary arterial wedge pressure; BSA: body surface area; NYHA FC: New York Heart Association Functional Class; RAP: right atrial pressure; PVR: pulmonary vascular resistance; PVRi: pulmonary vascular resistance index. [#]: no PH *versus* PH; [¶]: pre-capillary *versus* post-capillary PH.

https://doi.org/10.1183/13993003.02548-2021

TABLE 2 Echocardiographic data of the overall population and differences between patients with and without pulmonary hypertension (PH) defined by mean pulmonary arterial pressure (mPAP) ⩾25 mmHg

	Overall	No PH (mPAP <25 mmHg)	PH (mPAP ⩾25 mmHg)	Pre-capillary PH (mPAP ⩾25 mmHg and PAWP ⩽15 mmHg)	Post-capillary PH (mPAP ⩾25 mmHg and PAWP >15 mmHg)	p-value[#]	p-value[¶]
Patients	263	40	223	129	94		
RV diastolic area (cm^2)	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 (cm^2)	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 (%)	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 (cm^2)	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)	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′	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 ($m{\cdot}s^{-1}$)	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)	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)	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)	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
LVEF (%)	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 diameter (mm)	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)	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

Data are presented as n or median (interquartile range), unless otherwise stated. PAWP: pulmonary arterial wedge pressure; RV: right ventricle; FAC: fractional area change; RA: right atrium; TAPSE: tricuspid annular plane systolic excursion; *E*/*e′*: ratio between early mitral inflow velocity and mitral annular early diastolic velocity; TRV: tricuspid regurgitation velocity; LVTD: left ventricular transverse diameter in diastole; LVTS: left ventricular transverse diameter in systole; IVS: interventricular septum; LVEF: left ventricular ejection fraction; PA: pulmonary artery; RVOT-AT: right ventricular outflow tract acceleration time. [#]: no PH *versus* PH; [¶]: pre-capillary *versus* post-capillary PH.

https://doi.org/10.1183/13993003.02548-2021

TABLE 3 Univariable and multivariable logistic regression testing of all direct and indirect echocardiographic signs of pulmonary hypertension (PH) as predictors of mean pulmonary arterial pressure (mPAP) >20 mmHg

Signs of PH and level	mPAP ⩽20 mmHg	mPAP >20 mmHg	Univariable OR (95% CI)	Multivariable OR (95% CI)
Patients	23	240		
Peak TRV ($m \cdot s^{-1}$)				
⩽2.8	21 (33.3)	42 (66.7)		
2.9–3.4	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
RVOT-AT (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 PA regurgitation velocity ($m \cdot s^{-1}$)				
⩽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
PA 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
IVC 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
RA area (end-systole) (cm^2)				
⩽18	18 (10.1)	160 (89.9)		
>18	5 (5.9)	80 (94.1)	1.80 (0.69–5.61); p=0.262	NS

Data are presented as n or n (%), unless otherwise stated. TRV: tricuspid regurgitation velocity; RV: right ventricle; LV: left ventricle; RVOT-AT: right ventricular outflow tract acceleration time; PA: pulmonary artery; IVC: inferior vena cava; RA: right atrium; NA: not applicable; NS: nonsignificant. Multivariable model metrics: Akaike Information Criterion 103.5, C-statistic 0.89, Hosmer–Lemeshow test p=1.00.

The number of false negatives and positives, true negatives and positives, AUC values, sensitivity, specificity, and 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 WU or mPAP ⩾25 mmHg and PVR ⩾3 WU are shown in table 7. The best AUC was always obtained with TRV ⩾2.9 $m \cdot s^{-1}$.

The incremental predictive values of one or more indirect signs in addition to peak TRV >3.4 or ⩾2.9 $m \cdot s^{-1}$ to predict PH defined by either mPAP >20 mmHg, mPAP ⩾25, mPAP >20 mmHg and PVR >2 WU or mPAP ⩾25 mmHg and PVR ⩾3 WU are shown in table 8. In particular, for the prediction of mPAP ⩾20 mmHg and PVR >2 WU, using 2.9 $m \cdot s^{-1}$ as cut-off for TRV, the best AUC was observed with the addition of one or more indirect echocardiographic sign and the positive predictive value was 100% with the presence of two or more indirect echocardiographic signs. Using 3.4 $m \cdot s^{-1}$ as cut-off for TRV, the best AUC was not improved by the addition of indirect signs and the positive predictive value was near 100%.

The AUCs for different cut-off values of TRV for the prediction of either mPAP >20 mmHg, mPAP ⩾25 mmHg, mPAP >20 mmHg and PVR >2 WU or mPAP ⩾25 mmHg and PVR ⩾3 WU 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 $m \cdot s^{-1}$.

A Bland–Altman analysis comparing mPAP measured at RHC 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.

TABLE 4 Univariable and multivariable logistic regression testing of all direct and indirect echocardiographic signs of pulmonary hypertension (PH) as predictors of mean pulmonary arterial pressure (mPAP) ⩾25 mmHg

Signs of PH and level	mPAP <25 mmHg	mPAP ⩾25 mmHg	Univariable OR (95% CI)	Multivariable OR (95% CI)
Patients	40	223		
Peak TRV ($m \cdot s^{-1}$)				
⩽2.8	33 (52.4)	30 (47.6)		
2.9–3.4	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				
⩽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				
⩾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 PA regurgitation velocity ($m \cdot s^{-1}$)				
⩽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)				
⩽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
IVC diameter (mm)/inspiratory collapse				
⩽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) (cm^2)				
⩽18	31 (17.4)	147 (82.6)		
>18	9 (10.6)	76 (89.4)	1.78 (0.84–4.15); p=0.153	NS

Data are presented as n or n (%), unless otherwise stated. TRV: tricuspid regurgitation velocity; RV: right ventricle; LV: left ventricle; RVOT-AT: right ventricular outflow tract acceleration time; PA: pulmonary artery; IVC: inferior vena cava; RA: right atrium; NA: not applicable; NS: nonsignificant. Multivariable model metrics: Akaike Information Criterion 125.2, C-statistic 0.93, Hosmer–Lemeshow test p=0.825.

A Bland–Altman analysis comparing PAWP measured at RHC or calculated from the *E*/*e*′ ratio at echocardiography also showed a small bias of 0.02 mmHg, suggesting good accuracy, but limits of agreement of 10 mmHg, suggesting limited precision.

Discussion

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

PH redefined by mPAP >20 mmHg was independently predicted either by TRV >3.4 or 2.9–3.4 $m \cdot s^{-1}$ alone. Pulmonary vascular disease was independently predicted by TRV >3.4 $m \cdot s^{-1}$ or by TRV 2.9–3.4 $m \cdot s^{-1}$ with the addition of three indirect signs to predict PVR ⩾3 WU or three indirect signs to predict PVR >2 WU. 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.

PH used to be defined by 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 mPAP >20 mmHg is higher than normal [6] and associated with decreased life expectancy [7]. The renewed PH definition by mPAP >20 mmHg has already entered clinical practice [15]. Interestingly, PVR ⩾3 WU remained requested for the diagnosis of pre-capillary PH (or pulmonary vascular disease) [3–5], while it has been shown that PVR ∼2 WU 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 four 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.

TABLE 5 Univariable and multivariable logistic regression testing of all direct and indirect echocardiographic signs of pulmonary hypertension (PH) as predictors of mean pulmonary arterial pressure (mPAP) >20 mmHg and pulmonary vascular resistance (PVR) >2 WU

Signs of PH and level	mPAP ⩽20 mmHg and/or PVR ⩽2 WU	mPAP >20 mmHg and PVR >2 WU	Univariable OR (95% CI)	Multivariable OR (95% CI)
Patients	38	225		
Peak TRV ($m \cdot s^{-1}$)				
⩽2.8	30 (47.6)	33 (52.4)		
2.9–3.4	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 PA regurgitation velocity ($m \cdot s^{-1}$)				
⩽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
IVC 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) (cm^2)				
⩽18	33 (18.5)	145 (81.5)		
>18	5 (5.9)	80 (94.1)	3.6 (1.5–11.0); p=0.010	NS

Data are presented as n or n (%), unless otherwise stated. TRV: tricuspid regurgitation velocity; RV: right ventricle; LV: left ventricle; RVOT-AT: right ventricular outflow tract acceleration time; PA: pulmonary artery; IVC: inferior vena cava; RA: right atrium; NA: not applicable; NS: nonsignificant. Multivariable model metrics: Akaike Information Criterion 70.5, C-statistic 0.90, Hosmer–Lemeshow test p=1.00.

Echocardiography allows for the estimation of mPAP based on either TRV, RVOT flow velocity pattern or early PA 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 values calculated from TRV or invasively measured are well correlated but with a dispersion resulting in an excessive proportion of false positive or negative diagnoses of PH [6, 12, 16, 17]. In fact, Bland–Altman analysis in these studies invariably shows only a 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 ESC/ERS guidelines to implement alternative assessments of PAPs as supportive measurements or internal controls. It is interesting that the added value of these supporting measurements was not significant for TRV >3.4 $m \cdot s^{-1}$ or significant but small for TRV 2.9–3.4 $m \cdot s^{-1}$ in the present patient population, and only to identify increased PVR especially when the diagnostic cut-off was brought down to 2 WU. This may be explained by the fact that PVR is better than PAP to estimate RV afterload and its effects on right heart remodelling [18, 19].

The cut-off values of echocardiographic measurements to predict PH as defined in the 2015 ESC/ERS 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 $m \cdot s^{-1}$ corresponds to sPAP 34 mmHg and mPAP 22 mmHg recalculated, respectively, using the Bernoulli equation and estimate of RAP [20] and an equation based on the known proportionality between

TABLE 6 Univariable and multivariable logistic regression testing of all direct and indirect echocardiographic signs of pulmonary hypertension (PH) as predictors of mean pulmonary arterial pressure (mPAP) ⩾25 mmHg and pulmonary vascular resistance (PVR) ⩾3 WU

Signs of PH and level	mPAP <25 mmHg and/or PVR <3 WU	mPAP ⩾25 mmHg and PVR ⩾3 WU	Univariable OR (95% CI)	Multivariable OR (95% CI)
Patients	84	179		
Peak TRV ($m \cdot s^{-1}$)				
⩽2.8	53 (84.1)	10 (15.9)		
2.9–3.4	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				
⩽1.1	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				
⩾105 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 PA regurgitation velocity ($m \cdot s^{-1}$)				
⩽2.2	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)				
⩽25	54 (38.8)	85 (61.2)		
>25	30 (24.2)	94 (75.8)	1.99 (1.17–3.42); p=0.012	NS
IVC diameter (mm)/inspiratory collapse				
⩽21 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) (cm^2)				
⩽18	72 (40.4)	106 (59.6)		
>18	12 (14.1)	73 (85.9)	4.13 (2.16–8.50); p<0.001	NS

Data are presented as n or n (%), unless otherwise stated. TRV: tricuspid regurgitation velocity; RV: right ventricle; LV: left ventricle; RVOT-AT: right ventricular outflow tract acceleration time; PA: pulmonary artery; IVC: inferior vena cava; RA: right atrium; NA: not applicable; NS: nonsignificant. Multivariable model metrics: Akaike Information Criterion 202.8, C-statistic 0.898, Hosmer–Lemeshow test p=0.999.

sPAP and mPAP [21]. A TRV threshold of 2.9 $m \cdot s^{-1}$ can be considered as the upper limit of normal as defined in large population studies [22, 23]. TRV 3.4 $m \cdot s^{-1}$ corresponds to sPAP 46 mmHg and mPAP ~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 $m \cdot s^{-1}$. 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 centre with the request to perform RHC for 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 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 study's 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 [24]. However, our study is representative of a "real-life" expert PH centre as required for diagnosis and treatment of pulmonary vascular diseases and considered in the ESC/ERS guidelines [2–4]. The fourth is that echocardiographic prediction of PH is not possible in every patient with a suspicion of PH. If needed, an alternative imaging modality such as cardiac magnetic resonance may have to be implemented in these patients. Finally, the study assessed echocardiographic cut-off values to estimate low

TABLE 7 Diagnostic accuracy of independent pulmonary hypertension predictors

Direct and indirect echocardiographic signs	False negative (n)	False positive (n)	True negative (n)	True positive (n)	AUC	Sensitivity	Specificity	Positive predictive value	Negative predictive value
To predict mPAP >20 mmHg									
Peak TRV ⩾2.9 m·s^{-1}	42	2	21	198	0.87	0.83	0.91	0.99	0.33
Peak TRV >3.4 m·s^{-1}	97	0	23	143	0.8	0.6	1	1	0.19
To predict mPAP ⩾25 mmHg									
Peak TRV ⩾2.9 m·s^{-1}	30	7	33	193	0.85	0.87	0.83	0.97	0.52
Peak TRV >3.4 m·s^{-1}	80	0	40	143	0.82	0.64	1	1	0.33
LV 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^{-1}	33	8	30	192	0.82	0.85	0.79	0.96	0.48
Peak TRV >3.4 m·s^{-1}	83	1	37	142	0.8	0.63	0.97	0.99	0.31
LV eccentricity index >1.1	93	13	25	132	0.62	0.59	0.66	0.91	0.21
RVOT-AT <105 ms and/or midsystolic notching	35	15	23	190	0.73	0.84	0.61	0.93	0.4
IVC 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^{-1}	10	31	53	169	0.79	0.94	0.63	0.85	0.84
Peak TRV >3.4 m·s^{-1}	50	14	70	129	0.78	0.72	0.83	0.9	0.58
LV eccentricity index >1.1	63	29	55	116	0.65	0.65	0.66	0.8	0.47
RVOT-AT <105 ms and/or midsystolic notching	16	42	42	163	0.71	0.91	0.5	0.8	0.72

AUC: area under the curve; mPAP: mean pulmonary arterial pressure; TRV: tricuspid regurgitation velocity; LV: left ventricle; RVOT-AT: right ventricular outflow tract acceleration time; IVC: inferior vena cava; PVR: pulmonary vascular resistance.

https://doi.org/10.1183/13993003.02548-2021

TABLE 8 Incremental diagnostic accuracy of the association of one or more independent predictors among indirect echocardiographic signs to tricuspid regurgitation velocity (TRV) as cut-off to predict pulmonary hypertension

Direct and indirect echocardiographic signs	False negative (n)	False positive (n)	True negative (n)	True positive (n)	AUC	Sensitivity	Specificity	Positive predictive value	Negative predictive value
To predict mPAP >20 mmHg									
Peak TRV ⩾2.9 m·s^{-1}	42	2	21	198	0.87	0.83	0.91	0.99	0.33
Peak TRV >3.4 m·s^{-1}	97	0	23	143	0.8	0.6	1	1	0.19
To predict mPAP ⩾25 mmHg									
Peak TRV ⩾2.9 m·s^{-1}	30	7	33	193	0.85	0.87	0.83	0.97	0.52
Peak TRV ⩾2.9 m·s^{-1} and ⩾1 indirect signs	62	2	38	161	0.84	0.72	0.95	0.99	0.38
Peak TRV ⩾2.9 m·s^{-1} and ⩾2 indirect signs	163	1	39	60	0.62	0.27	0.98	0.98	0.19
Peak TRV >3.4 m·s^{-1}	80	0	40	143	0.82	0.64	1	1	0.33
Peak TRV >3.4 m·s^{-1} and ⩾1 indirect signs	103	0	40	120	0.77	0.54	1	1	0.28
Peak TRV >3.4 m·s^{-1} and ⩾2 indirect signs	175	0	40	48	0.61	0.22	1	1	0.19
To predict mPAP >20 mmHg and PVR >2 WU									
Peak TRV ⩾2.9 m·s^{-1}	33	8	30	192	0.82	0.85	0.79	0.96	0.48
Peak TRV ⩾2.9 m·s^{-1} and ⩾1 indirect signs	39	6	32	186	0.83	0.83	0.84	0.97	0.45
Peak TRV ⩾2.9 m·s^{-1} and ⩾2 indirect signs	98	0	38	127	0.78	0.56	1	1	0.28
Peak TRV ⩾2.9 m·s^{-1} and ⩾3 indirect signs	188	0	38	37	0.58	0.16	1	1	0.17
Peak TRV >3.4 m·s^{-1}	83	1	37	142	0.8	0.63	0.97	0.99	0.31
Peak TRV >3.4 m·s^{-1} and ⩾1 indirect signs	85	1	37	140	0.8	0.62	0.97	0.99	0.3
Peak TRV >3.4 m·s^{-1} and ⩾2 indirect signs	124	0	38	101	0.72	0.45	1	1	0.24
Peak TRV >3.4 m·s^{-1} and ⩾3 indirect signs	191	0	38	34	0.58	0.15	1	1	0.17
To predict mPAP ⩾25 mmHg and PVR ⩾3 WU									
Peak TRV ⩾2.9 m·s^{-1}	10	31	53	169	0.79	0.94	0.63	0.85	0.84
Peak TRV ⩾2.9 m·s^{-1} and ⩾1 indirect signs	14	23	61	165	0.82	0.92	0.73	0.88	0.81
Peak TRV ⩾2.9 m·s^{-1} and ⩾2 indirect signs	75	5	79	104	0.76	0.58	0.94	0.95	0.51
Peak TRV >3.4 m·s^{-1}	50	14	70	129	0.78	0.72	0.83	0.9	0.58
Peak TRV >3.4 m·s^{-1} and ⩾1 indirect signs	51	11	73	128	0.79	0.72	0.87	0.92	0.59
Peak TRV >3.4 m·s^{-1} and ⩾2 indirect signs	93	3	81	86	0.72	0.48	0.96	0.97	0.47

AUC: area under the curve; mPAP: mean pulmonary arterial pressure; PVR: pulmonary vascular resistance.

https://doi.org/10.1183/13993003.02548-2021

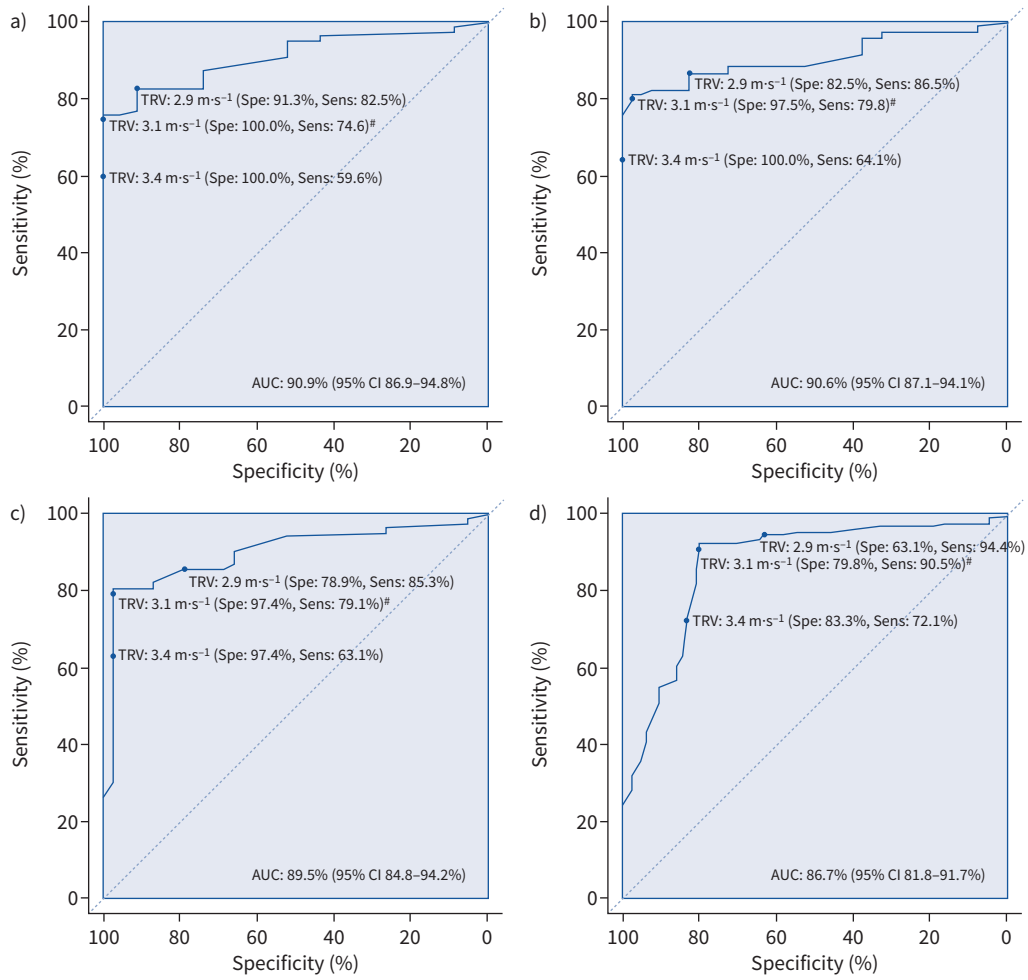

FIGURE 1 Receiver operator characteristic curves for the prediction of a) mean pulmonary arterial pressure (mPAP) >20 mmHg, b) mPAP ⩾25 mmHg, c) mPAP >20 mmHg and pulmonary vascular resistance (PVR) >2 WU and d) mPAP ⩾25 mmHg and PVR ⩾3 WU by increasing cut-off values for maximum tricuspid regurgitation velocity (TRV). Increasing the TRV cut-off increased the sensitivity ("Sens") but decreased the specificity ("Spe") of the predictions. In all cases the area under the curve (AUC) exceeded 80%. #: best cut-off value.

versus intermediate or high probability of PH as stated in the 2015 ESC/ERS guidelines, although without a re-evaluation of these probability categories [3, 4].

In conclusion, the echocardiographic prediction strategy of PH as defined in the 2015 ESC/ERS guidelines is valid for the new definition of PH based on mPAP >20 mmHg. The clinical probability of pulmonary vascular disease by either PVR ⩾3 or >2 WU can adequately be assessed by the same combination of measurements, although with more indirect signs when a cut-off value for PVR of 2 WU is to be taken into consideration.

Conflict of interest: M. D'Alto reports participation on a monitoring board for Actelion-Janssen, MSD, Dompè and Ferrer, outside the submitted work. R. Naeije reports lecture honoraria from AOP Pharmaceuticals; participation on a monitoring board for Johnson & Johnson, Actelion, Lung Biotechnology Corp and United Therapeutics, outside the submitted work. All other authors have nothing to disclose.

References

1 Frost A, Badesch D, Gibbs JSR, *et al.* Diagnosis of pulmonary hypertension. *Eur Respir J* 2019; 53: 1801904.
2 Rudski LG, Lai WW, Afilalo J, *et al.* Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American Society of Echocardiography endorsed by the European Association of

Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography. *J Am Soc Echocardiogr* 2010; 23: 685–713.

3 Galiè N, Humbert M, Vachiery JL, *et al.* 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS). Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). *Eur Heart J* 2016; 37: 67–119.

4 Galiè N, Humbert M, Vachiery JL, *et al.* 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS). Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). *Eur Respir J* 2015; 46: 903–975.

5 Simonneau G, Montani D, Celermajer DS, *et al.* Hemodynamic definitions and updated clinical classification of pulmonary hypertension. *Eur Respir J* 2019; 53: 1801913.

6 Gall H, Yogeswaran A, Fuge J, *et al.* Validity of echocardiographic tricuspid regurgitation gradient to screen for new definition of pulmonary hypertension. *EClinicalMedecine* 2021; 34: 100822.

7 Kovacs G, Berghold A, Scheid S, *et al.* Pulmonary artery pressure during rest and exercise in healthy subjects: a systematic review. *Eur Respir J* 2009; 34: 888–894.

8 Maron BA, Hess E, Maddox TM, *et al.* Association of borderline pulmonary hypertension with mortality and hospitalization in a large patient cohort: insights from the veterans affairs clinical assessment, reporting, and tracking program. *Circulation* 2016; 133: 1240–1248.

9 Kovacs G, Olschewski A, Berghold A, *et al.* Pulmonary vascular resistance during exercise: a systematic review. *Eur Respir J* 2012; 39: 319–328.

10 Maron BA, Brittain EL, Hess E, *et al.* Pulmonary vascular resistance and clinical outcomes in patients with pulmonary hypertension: a retrospective cohort study. *Lancet Respir Med* 2020; 8: 873–884.

11 Lang RM, Badano LP, Mor-Avi V, *et al.* Recommendation for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging* 2015; 16: 233–270.

12 D'Alto M, Romeo E, Argiento P, *et al.* Accuracy and precision of echocardiography *versus* right heart catheterization for the assessment of pulmonary hypertension. *Int J Cardiol* 2013; 168: 4058–3062.

13 D'Alto M, Romeo E, Argiento P, *et al.* Echocardiographic prediction of pre- *versus* post-capillary pulmonary hypertension. *J Am Soc Echocardiogr* 2015; 28: 108–115.

14 Bland JM, Altman DG. Statistical methods for assessing agreement between two different methods of clinical measurement. *Lancet* 1986; 1: 307–310.

15 Maron BA, Kovacs G, Vaidya A. Cardiopulmonary hemodynamics in pulmonary hypertension and heart failure: JACC review topic of the week. *J Am Coll Cardiol* 2020; 76: 2671–2681.

16 Fisher MR, Forfia PR, Chamera E, *et al.* Accuracy of Doppler echocardiography in the hemodynamic assessment of pulmonary hypertension. *Am J Respir Crit Care Med* 2009; 179: 615–621.

17 Rich JD, Shah SJ, Swamy RS, *et al.* Inaccuracy of Doppler echocardiographic estimates of pulmonary artery pressures in patients with pulmonary hypertension. *Chest* 2011; 139: 988–993.

18 Vonk-Noordegraaf A, Haddad F, Chin KM, *et al.* Right heart adaptation to pulmonary arterial hypertension: physiology and pathobiology. *J Am Coll Cardiol* 2013; 62: D22–D33.

19 Vonk Noordegraaf A, Chin KM, Haddad F, *et al.* Pathophysiology of the right ventricle and of the pulmonary circulation in pulmonary hypertension: an update. *Eur Respir J* 2019; 53: 1801900.

20 Yock P, Popp R. Noninvasive estimation of right ventricular systolic pressure by Doppler ultrasound in patients with tricuspid regurgitation. *Circulation* 1984; 70: 657–662.

21 Chemla D, Castelain V, Humbert M, *et al.* New formula for predicting mean pulmonary artery pressure using systolic pulmonary artery pressure. *Chest* 2004; 126: 1313–1317.

22 McQuillan BM, Picard MH, Leavitt M, *et al.* Clinical correlates and reference intervals for pulmonary artery systolic pressure among echocardiographically normal subjects. *Circulation* 2001; 104: 2797–2802.

23 Marra AM, Naeije R, Ferrara F, *et al.* Reference ranges and determinants of tricuspid regurgitation velocity in healthy adults assessed by two-dimensional Doppler echocardiography. *Respiration* 2018; 96: 425–433.

24 Naeije R, D'Alto M, Forfia PR. Clinical and research measurement techniques of the pulmonary circulation: the present and the future. *Progr Cardiovasc Dis* 2015; 57: 463–472.