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Early View

Original article

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A comprehensive echocardiographic method for risk stratification in pulmonary arterial hypertension.

Short title: echocardiography-based risk stratification in PAH

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Take home message:

The proposed comprehensive echocardiographic approach reflecting both RV pump function and systemic venous congestion is highly effective in risk stratification of PAH patients, outperforming the prognostic parameters suggested by current guidelines.

ABSTRACT

Question addressed. Echocardiography is not currently considered as providing sufficient prognostic information to serve as an integral part of treatment goals in pulmonary arterial hypertension (PAH). We tested the hypothesis that incorporation of multiple parameters reflecting right heart function would improve the prognostic value of this imaging modality.

Methods and Main Results. We pooled individual patient data from a total of 517 patients (mean age 52 ± 15 years, 64.8% females) included in seven observational studies conducted at five European and United States academic centers. Patients were subdivided into three groups representing progressive degrees of RV dysfunction based on a combination of echocardiographic measurements: group 1 (low-risk): normal tricuspid annular plane systolic excursion (TAPSE) and non-significant tricuspid regurgitation (TR) (n=129); group 2 (intermediate-risk): normal TAPSE and significant TR or impaired TAPSE and non-dilated inferior vena cava (IVC) (n=256); group 3 (high-risk): impaired TAPSE and dilated IVC (n=132). The 5-year cumulative survival rate was 82% in group 1, 63% in group 2, and 43% in group 3. Low-risk patients had better survival rates than intermediate-risk patients (log-rank χ^2: 12.25 $p<0.001$) and intermediate-risk patients had better survival rates than high-risk patients (log-rank χ^2: 26.25 $p<0.001$). Inclusion of other parameters such as right atrial area and pericardial effusion did not provide added prognostic value.

Answer to the question. The proposed echocardiographic approach integrating the evaluation of TAPSE, TR grade and IVC is effective in stratifying the risk for all-cause mortality in PAH patients, outperforming the prognostic parameters suggested by current guidelines.

Key words: Pulmonary arterial hypertension; risk stratification; echocardiography

Introduction

The importance of risk stratification has gained significant momentum in the field of pulmonary arterial hypertension (PAH). In 2015, the European Society of Cardiology/European Respiratory Society (ESC/ERS) guidelines recommended the use of a broad range of invasive and non-invasive parameters to assess the mortality risk of PAH patients (1). In 2017, abbreviated versions of this model were evaluated retrospectively in newly diagnosed PAH cohorts, and further validated in systemic sclerosis-associated PAH, demonstrating that stratifying patients into low, intermediate and high-risk groups based upon select measurements predicted mortality (2-6). As suggested in the most recent recommendations from the 6th World Symposium on Pulmonary Hypertension, currently approved PAH therapies should be initiated based on risk stratification. Furthermore, achievement of a low-risk status should be the goal of therapy during follow-up assessment (7).

The National Institutes of Health (NIH) Registry on Primary Pulmonary Hypertension first demonstrated that mortality best correlates with hemodynamic indices of right ventricular (RV) function, specifically right atrial pressure (RAP) and cardiac index (CI) (8). Since then, two hemodynamic variables, i.e. one indicator of pump function (CI or stroke volume index) and one of systemic congestion (RAP), proved to have pivotal roles in the multidimensional assessment of prognosis and treatment response in PAH, in association with demographic, clinical, functional, and biochemical variables (2-6, 9-12).

However, despite extensive literature reporting that a number of echocardiographic variables may provide significant prognostic information, this imaging modality remains of limited application in risk stratification and guidance of treatment goals as it is felt to provide insufficient prognostic information (1). It is noteworthy that a recent statement of the American Thoracic Society recommends that deriving and validating imaging biomarkers for an accurate evaluation of right

ventricular (RV) function is a major research priority to be addressed in the next 5 years (13). We surmised that the present limited role of echocardiography might be, at least in part, related to the use of single best prognostic indicators rather than on the identification of a combination of parameters which could provide a comprehensive assessment of right heart pump function and of systemic venous congestion, similar to the established hemodynamic approach.

Accordingly, to test the hypothesis that a comprehensive echocardiographic assessment of RV function would be highly valuable in the risk stratification of PAH patients, we performed a patient-level pooled analysis of published studies conducted at our centers, focusing on RV systolic function, the degree of tricuspid regurgitation and the presence or absence of systemic venous congestion.

Methods

Study selection

We pooled individual patient data (IPD) from observational studies conducted at our centers that assessed the prognostic value of echocardiography in patients with PAH. To be eligible for inclusion, patients had to be characterized with the following echocardiographic parameters: an index of RV systolic function represented by the tricuspid annular plane systolic excursion (TAPSE), the degree of tricuspid regurgitation (TR) and a marker of systemic venous congestion represented by inferior vena cava (IVC) diameter (14-20). The primary outcome of the study was all-cause mortality. This analysis is part of a study that was registered on PROSPERO (registration number: CRD42019141216). Two authors (FF, VM) extracted IPD from the selected studies including: study design, sample size, patient characteristics, World Health Organization/New York Heart Association (WHO/NYHA) functional class, functional capacity expressed as 6-minute walking

distance, PAH etiology, PAH specific therapy, echocardiographic assessment, follow-up and all-cause mortality. Data on scheduled lung transplantation were reported only in one study (15) where 2 patients underwent lung transplantation and their follow-up was censored at the time of surgery. Data on overlapping population between the studies were excluded.

Statistical analysis

Continuous variables are presented as mean ± standard deviation in case of Gaussian distribution, and as median (interquartile range) if not normally distributed. Categorical variables are presented as frequencies and percentages. To assess the hazard ratio (HR) change for all-cause mortality across a range of TAPSE at baseline, a spline curve analysis was performed. The cut-off value of TAPSE associated with excess mortality according to the literature was used to define RV systolic dysfunction (21). According to the pathophysiological aim of the study, three echocardiographic variables were "a priori" selected: TAPSE, defined as abnormal when ≤17 mm; TR, defined as significant if moderate or severe (22); IVC diameter, defined as dilated when >20 mm (21). Based on the combination of these variables, four echocardiographic risk groups of patients were identified representing progressive degrees of right heart dysfunction based upon the presence/absence of RV dysfunction by TAPSE and degree of TR, and presence/absence of systemic venous congestion by IVC dilatation:

- group 1: normal TAPSE and non-significant TR,
- group 2: normal TAPSE in the presence of significant TR,
- group 3: impaired TAPSE without systemic congestion,
- group 4: impaired TAPSE associated with systemic congestion.

Differences among the groups were analyzed using the one-way analysis of variance (ANOVA) for continuous variables with Gaussian distribution, the Kruskal-Wallis test for non-normally

distributed continuous variables and the Pearson's chi-square test for categorical variables. The Kaplan-Meier curves were used to estimate the 1-, 3- and 5-year survival rates and differences between groups were analyzed using the Mantel-Cox log-rank test. A multivariable Cox proportional hazards regression analysis was performed to assess the clinical and echocardiographic factors that were independently associated with all-cause mortality. Possible confounders with a significant p-value ($p<0.05$) in the univariable analysis were selected (taking into account data availability and collinearity between variables) and included in the multivariable regression analysis. The proportional-hazards assumption was confirmed using statistics and graphs on the basis of the Schoenfeld residuals. P values <0.05 were considered significant. All data were analyzed with SPSS for Windows, version 21 (SPSS Inc, Armonk, NY:IBM Corp) and R environment 3.4.3 (R Foundation for Statistical Computing) using the "stats" and "survival" packages.

Results

Studies' characteristics

Data from 7 original articles were included in this study. Characteristics of the publications included in the analysis are presented in Table 1. With the exception of two retrospective studies, all other studies had a prospective design. The median follow-up ranged from 15 to 95 months. The outcome measure defined as all-cause mortality was available in all studies.

Patient population

After excluding overlapping patients between studies, patients with no PAH, and with incomplete echocardiographic data to be classified in one of the 4 echocardiographic groups, a total of 517 patients (mean age 52 ± 15 years, 64.8% females) was included in the analysis (Figure 1): 253

patients from Giessen University, Germany (20); 123 from IRCCS Policlinico San Matteo, Pavia, Italy (15-16); 71 from the Johns Hopkins Hospital, Baltimore, USA (14,17,19); 70 from the University of Pennsylvania Hospital and Temple University Hospital, Philadelphia, USA (18). The main characteristics of the patients included in the study were similar to those excluded due to missing echocardiographic data (Supplementary Table 1). Clinical and demographic characteristics of the study population are reported in Table 1. Concerning the aetiology, 64.8% had idiopathic PAH, 8.9% had scleroderma-associated PAH, and 8.4% had congenital heart disease-associated PAH. 375 patients (72.5%) were on treatment with PAH-specific drugs (42.7% on monotherapy and 57.3% on combination therapy) at the time of echocardiographic assessment. Most patients (66.1%) were in WHO/NYHA functional class III-IV. To investigate the association between TAPSE and all-cause mortality, a spline curve analysis was performed. The assumption of linearity for all-cause mortality, predicted from the baseline TAPSE, was not violated (χ^2=2.56, P=0.29), i.e. demonstrating a nonlinear relation of TAPSE vs. all-cause mortality. The spline curve analysis showed, after a slow rise in HR, a steady increase in the hazard ratio for all-cause mortality for a TAPSE of 17 mm and lower (Figure 2). Therefore, based on previous (21) and current findings, we considered appropriate to identify RV systolic dysfunction as TAPSE ≤17 mm. A total of 129 patients (25%) were in the echocardiographic group 1, 155 patients (30%) in group 2, 101 patients (19.5%) in group 3, and 132 patients (25.5%) in group 4. There was a statistically significant difference in WHO functional class and in 6MWD across groups, with the highest percentage of patients in WHO/NYHA functional class III-IV (p<0.001) as well as the lowest values of 6MWD in group 4 (p=0.007). Heart rate was the lowest in patients in group 1 (p=0.004).

Echocardiographic data

Clinical and echocardiographic characteristics are presented in Table 2. Overall, the study population had normal left ventricular size and function, while right heart chambers were increased in dimensions, with a median right atrial area of 21 cm^2 (17-26) and a RV end-diastolic diameter of 38 mm (30-45). TAPSE was impaired (≤17 mm) in 45.1% of patients, with an overall mean value of 18 ± 5 mm for the entire cohort. Fractional area change was also impaired (≤35%) in 76.6% of patients, with an overall mean value of 27.1 ± 12.2.%. 333 patients (65%) had a significant TR (TR grade ≥ moderate). Estimated pulmonary artery systolic pressure was 68 ± 26 mmHg, and pulmonary flow acceleration time was 78 ± 22 msec; pericardial effusion was only present in 27.6% of patients. Clinical and echocardiographic characteristics of the four echocardiographic risk groups are shown in Table 2. All indices of right heart function and morphology were increasingly worse from group 1 to group 4.

Outcome data

During a median follow-up of 46 (21-99) months, 206 (39.8%) patients died. The Kaplan-Meier analysis showed lower survival rates in patients with more impaired RV systolic function and with systemic congestion (group 4) (log-rank χ^2 :58.12; p<0.001; Figure 3 - left panel). The survival rates between groups 2 and 3 did not differ significantly (log-rank chi-square 1.68 p=0.195). Therefore, we considered appropriate to merge patients belonging to these two groups into one, thus identifying three echo-derived risk categories which had significantly different survival rates at follow-up (Figure 3 right panel): low-risk (group 1), intermediate-risk (group 2 and 3) and high-risk (group 4). The cumulative 1-, 3-, and 5-year survival were: 92%, 87%, and 82% for low-risk; 85%, 73%, and 63% for intermediate-risk; and 68%, 57%, and 43% for high-risk patients. Low-risk patients had better survival rates than intermediate-risk patients (log-rank χ^2: 12.25 p<0.001) and the latter had better survival rates than high-risk patients (log-rank χ^2: 26.25 p<0.001).

At univariable Cox regression analysis the following parameters were associated with all-cause mortality: older age, male sex, higher heart rate, PAH associated with pulmonary veno-occlusive disease, connective tissue disease etiology, being an incident patient, being treated before 2011, WHO/NYHA functional class III/IV, lower 6MWD, impaired RV systolic function, RV dilation, shorter pulmonary flow acceleration time, higher pulmonary systolic pressure, greater right atrial (RA) area, systemic congestion, significant TR, and lower left ventricular volume and ejection fraction (Table 3). In the multivariable analysis after adjusting for potential confounders, intermediate- and high-risk categories were independently associated with 2.5- and 4.4- fold increased risk of all-cause mortality compared with low-risk patients. Moreover, these echocardiographically defined risk categories retained an independent association with all-cause mortality in several multivariable Cox regression models (Supplementary Table 2S). As shown in Supplementary Figure 1S, the chi-squared of a Cox regression model including a single echocardiographic parameter of RV systolic dysfunction (TAPSE≤17 mm), systemic congestion (dilated IVC), or significant TR (TR grade 2-3), significantly increased when these parameters were combined (χ^2 change: 15.54 [p<0.001], 41.06 [p<0.001], and 47.96 [p<0.001], respectively). This analysis thus supports the echocardiographic-group risk stratification based on the combination of these three variables. Importantly, the presence of pericardial effusion was not associated with all-cause mortality at univariate analysis; in addition, although RA area showed an independent association with the primary outcome (Supplementary Table 3S), its additive value was outperformed by the proposed echocardiographic risk stratification model (Supplementary Figure 2S).

Discussion

The main finding of the present study is the demonstration that a comprehensive assessment of right heart function, easily obtainable through the combination of an echocardiographic indicator of the systolic function of the right ventricle associated with the degree of tricuspid regurgitation and an estimate of systemic venous congestion, can provide an accurate prognostic stratification of PAH patients, outperforming the prognostic value of the parameters suggested by current guidelines.

There is a sound physiological rationale for the proposed combination of echocardiographic parameters. First, it is important to acknowledge that the assessment of ventricular function using imaging methodologies is limited by the load-dependency of all parameters assessing cardiac motion, whether they are volume-based as in ejection fraction, or area-based as in fractional area change, or single plane-based such as TAPSE. Indeed, the presence of significant atrio-ventricular valve regurgitation inevitably leads to an overestimation of the systolic function of the left/right ventricle if this is based only on the analysis of ventricular motion. As a matter of fact, patients with normal TAPSE with absent or trivial TR had a significantly better prognosis than those with normal TAPSE associated with moderate to severe TR.

Patients with reduced TAPSE were further sub-grouped according to the absence or presence of dilated IVC. The rationale for this subdivision is simply based on the fact that the presence of reduced TAPSE and dilated IVC identifies PAH patients having impaired RV systolic function associated with systemic venous congestion. This is consistent with the observation in heart failure from left heart disease where patients with severe left ventricular dysfunction have a better exercise tolerance and improved prognosis if their pulmonary artery wedge pressure is normal (i.e. if there is no pulmonary congestion) (23). Our results clearly indicate that patients

with reduced TAPSE without dilated IVC had a significantly better prognosis compared to patients with reduced TAPSE and dilated IVC.

The major strength of the present study is that the proposed methodology uses a combination of simply and widely available echocardiographic parameters that reflect a comprehensive assessment of right heart function, thus conforming with the results of multiple seminal invasive hemodynamic studies that have demonstrated the association of an indicator of pump function and one of systemic venous congestion is the best prognostic predictor in PAH (2-4, 7-12). Importantly, the results of this study might pave the way for testing future, potentially more sensitive, parameters mirroring RV systolic function or the degree of TR or systemic venous congestion. In particular, three-dimensional analysis of RV volumes and ejection fraction, or two- or three-dimensional assessment of RV strain or indices of ventriculo-arterial coupling might be tested to replace TAPSE (24). The quantification of TR regurgitation is known to be a challenging task for echocardiographists, and a most recent position statement specifies that new parameters should be identified and validated in prospective outcome studies (25). Finally, the best modality to assess the prognostic relevance of right atrial function needs to be further clarified (26).

Importantly, this proposed comprehensive risk stratification model was superior to single echocardiographic parameters recommended by current PAH Guidelines. Pericardial effusion was not associated with all-cause mortality in our study. In addition, while RA area was associated with all-cause mortality, this finding provided no added value to the comprehensive echocardiographic assessment.

Limitations

A major limitation of the present study is its retrospective nature with the inclusion of a limited amount of studies on the topic. As a matter of fact, this is a pooled analysis of 7 studies conducted

at 5 institutions which may represent a source of selection bias. However, this limitation is partially overcome by the large number of patients enrolled in referral centers with great expertise in the echocardiographic evaluation of PAH, including prevalent and incident patients with different forms of PAH. In addition, we have included several variables in Cox regression analysis (i.e. study design, year of publication, incident/prevalent patients, site of enrollment) that partially allow taking into account between-studies heterogeneity. Another important limitation of the present study is the lack of integration of the proposed echocardiographic assessment, in a multidimensional tool including all the hemodynamic, clinical, functional, and biochemical variables suggested by international guidelines. This should be addressed in future prospective studies. Similarly, since some studies suggest that treatment with PAH-specific drugs have beneficial effects on various echocardiographic parameters of RV morphology and function (24), the relevance of follow-up assessment using the proposed echocardiographic approach should be further explored. Echocardiographic variables are clearly preferable for serial evaluations compared to risk assessment tools incorporating invasive hemodynamic variables. They are also more practical and less costly, albeit less accurate, compared to other imaging techniques, such as cardiac magnetic resonance, that recently demonstrated to be useful in improving risk stratification of PAH patients (27).

Conclusion

Our study underlines the prognostic importance in PAH patients of combining individual echocardiographic parameters into a comprehensive physiological approach reflecting both RV pump function and systemic venous congestion. If validated in prospective studies and in cohorts of patients with different types of PAH, this approach could refine the current guideline

recommendations related to echocardiography in assessing prognosis and stratification of PAH, which are currently limited to the assessment of the right atrial area and the presence of pericardial effusion.

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Disclosures

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Tables

Table 1. General characteristics of publications included in the analysis.

Publication	Retrospective or prospective design	Incident/ prevalent PAH patients, N *	Median follow-up	Outcome measurement
Forfia P et al. 2006	prospective	15/32	19.3 months	All-cause mortality
Ghio S et al. 2010	prospective	45/5	52 months	All-cause mortality and lung transplantation
Mathai S et al. 2011	prospective	6/7	15.7 months	All-cause mortality and lung transplantation
Ghio S et al. 2016	retrospective	33/48	36 months	All-cause mortality and lung transplantation
Mazurek J et al. 2017	prospective	0/70	456 days	All-cause mortality
Mukherjee M et al. 2017	prospective	17/38	95 months	All-cause mortality
Tello K et al. 2018	retrospective	0/290	72.5 months	All-cause mortality

* overlapping cases were not considered

Table 2. Characteristic of the overall population and of the four pathophysiologically defined echocardiographic risk groups.

	Overall population N=517	Group 1 N=129	Group 2 N=155	Group 3 N=101	Group 4 N=132	P value
Age, y	52 ± 15	52 ± 14	53 ± 14	51 ± 17	51 ± 17	0.598
Female sex, N (%)	316 (64.8)	67 (57)	102 (70)	68 (68)	79 (64)	0.140
HR, bpm	78 ± 14	74 ± 13	76 ± 14	80 ± 15	80 ± 13	0.004
SBP, mmHg	123 ± 19	124 ± 17	121 ± 15	123 ± 26	125 ± 18	0.832
DBP, mmHg	72 ± 11	74 ± 11	68 ± 9	71 ± 11	74 ± 13	0.109
PAH etiology:						
- Idiopathic, N (%)	285 (64.8)	75 (65)	85 (59)	50 (70)	75 (68)	0.057
- Congenital heart disease, N (%)	37 (8.4)	7 (6)	12 (8)	10 (14)	8 (7)	
- Portal hypertension, N (%)	22 (5.0)	9 (8)	10 (7)	1 (1)	2 (2)	
- HIV, N (%)	12 (2.7)	3 (3)	7 (5)	1 (1)	1 (1)	
- PVOD, N (%)	11 (2.5)	2 (2)	4 (3)	3 (4)	2 (2)	
- Scleroderma, N (%)	39 (8.9)	5 (4)	18 (13)	5 (7)	11 (10)	
- Connective tissue disease, N (%)	23 (5.2)	10 (9)	4 (3)	1 (2)	8 (7)	
- Other, N (%)	11 (2.5)	4 (4)	4 (3)	0 (0)	3 (3)	
Prevalent patients, N (%)	421 (81.4)	118 (92)	137 (88)	75 (74)	91 (69)	<0.001
WHO FC III-IV, N (%)	339 (66.1)	63 (49)	103 (67)	66 (66)	107 (81)	<0.001
6MWD, m	358 ± 131	405 ± 107	353 ± 128	351 ± 137	317 ± 144	0.007
Vasoactive therapy						
- PDE5i, N (%)	287 (58.2)	74 (58)	91 (61)	51 (56)	71(57)	0.896
- sGC, N (%)	10 (2.7)	3 (4)	2 (2)	5 (5)	0 (0)	0.121
- ERA, N (%)	240 (48.7)	64 (50)	83 (55)	36 (40)	47 (46)	0.105
- Prostanoids, N (%)	122 (23.6)	31 (24)	41 (27)	20 (20)	30 (23)	0.670
Monotherapy N (%)	160 (32.4)	45 (35)	52 (34)	32 (35)	31 (25)	0.246

Combination therapy N (%)	215 (43.5)	55 (43)	71 (47)	34 (37)	55 (44)	0.531
Center location:						
- Europe, N (%)	375 (72.7)	86 (67)	100 (64)	92 (91)	98 (74)	<0.001
- USA, N (%)	141 (27.3)	43 (33)	55 (36)	9 (9)	34 (26)	
Echocardiographic data:						
- RVEDD, mm	38 (30-45)	32 (5-40)	37 (28-47)	38 (34-46)	42 (34-49)	<0.001
- RVEDA, cm^2	29 ± 9	25 ± 7	28 ± 10	28 ± 9	33 ± 8	<0.001
- FAC, %	27.1 ± 12.2	30 ± 10	30 ± 12	26 ± 10	23 ± 14	0.001
- TAPSE, mm	18 ± 5	22 ± 4	22 ± 4	14 ± 2	13 ± 3	<0.001
- TR moderate to severe, N (%)	333 (65.0)	0 (0)	155 (100)	66 (67)	112 (87)	<0.001
- Dilated IVC, N (%)	196 (44.0)	25 (26)	39 (34)	0 (0)	132 (100)	<0.001
- PASP, mmHg	68 ± 26	50 ± 22	71 ± 28	73 ± 23	77 ± 21	<0.001
- AcT, msec	78 ± 22	88 ± 23	81 ± 20	71 ± 19	69 ± 18	<0.001
- RA area*, cm^2	21 (17-26)	19 (15-23)	20 (17-24)	20 (16-25)	29 (24-36)	<0.001
- Pericardial effusion§ (%)	32 (27.6)	7 (35)	9 (24)	4 (25)	12 (29)	0.822
- LVEDV, ml	65 (50-81)	80 (63-95)	70 (62-90)	64 (47-80)	54 (43-67)	<0.001
- LV EF, %	68 ± 12	69 ± 12	68 ± 11	68 ± 13	65 ± 12	0.016
Year of study publication:						
2006-2011 (%)	71 (13.7)	18 (14)	19 (12)	9 (9)	25 (19)	0.152
2016-2018 (%)	446 (86.3)	111 (86)	136 (88)	92 (91)	107 (81)	
Patient enrollment:						
Prospective (%)	187 (36.2)	50 (39)	60 (39)	18 (18)	59 (45)	<0.001
Retrospective (%)	330 (63.8)	79 (61)	95 (61)	83 (82)	73 (55)	

* data available for 314 patients.

§ data available for 116 patients.

All percentages are calculated based on data availability for each parameter.

List of abbreviations: HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; PAH, pulmonary arterial hypertension; HIV, human immunodeficiency virus; PVOD, pulmonary veno-occlusive disease; WHO FC, world health organization functional class; 6MWD, 6-minute walking distance; PDE5i, phosphodiesterase 5 inhibitor; sGC, soluble guanylate cyclase stimulator; ERA, endothelin receptor antagonist; RVEDD, right ventricular end diastolic diameter; RVEDA, right ventricular end diastolic area; FAC, fractional area change; TAPSE, tricuspid annular plane systolic excursion; TR, tricuspid regurgitation; PASP, pulmonary arterial systolic pressure; AcT, acceleration time; RA, right atrial; LVEDV, left ventricular end diastolic volume; LV EF, left ventricular ejection fraction.

Table 3. Univariable and multivariable Cox regression analysis

	Univariate Analysis HR (95% CI)	*P* value	Multivariate Analysis HR (95% CI)	*P* value
Age	1.02 (1.01-1.03)	<0.001	1.02 (1.01-1.03)	<0.001
Female sex	0.71 (0.53-0.94)	0.017	0.69 (0.51-0.94)	0.019
Heart rate	1.02 (1.01-1.03)	0.002		
PVOD*	5.00 (2.50-10.00)	<0.001		
Scleroderma PAH*	1.50 (0.90-2.50)	0.121		
Connective tissue disease PAH*	2.80 (1.49-5.26)	0.001		
Incident PAH§	1.67 (1.16-2.41)	0.006	1.06 (0.61-1.84)	0.831
Combination therapy °	1.16 (0.88-1.54)	0.293		
Study published in 2016-18Δ	0.55 (0.36-0.83)	0.005	0.53 (0.27-1.03)	0.060
Data from retrospective study £	0.90 (0.66-1.21)	0.484		
WHO FC III-IV	2.96 (2.02-4.34)	<0.001	2.46 (1.61-3.75)	<0.001
6MWD, per 10 m increase	0.96 (0.94-0.98)	<0.001		
Center location in USA	0.83 (0.60-1.18)	0.301		
TAPSE#	0.92 (0.89-0.94)	<0.001		
TAPSE ≤17 mm	2.37 (1.78-3.14)	<0.001		
RVEDD	1.01 (1.00-1.02)	0.076		
RVEDA	1.05 (1.02-1.07)	<0.001		
FAC	0.97 (0.95-0.99)	0.008		
AcT	0.98 (0.97-0.99)	<0.001		
PASP	1.01 (1.00-1.01)	0.006		
RA area	1.04 (1.02-1.06)	<0.001		
Pericardial effusion	1.33 (0.69-2.59)	0.396		
Dilated IVC	2.12 (1.57-2.86)	<0.001		
TR moderate to severe	2.00 (1.43-2.79)	<0.001		
LVEDV	0.99 (0.97-0.99)	0.005		
LVEF	0.98 (0.97-0.99)	0.002	0.99 (0.98-1.01)	0.230
Intermediate-† vs low-risk¤	2.15 (1.38-3.37)	0.001	2.51 (1.46-4.29)	0.001
High-¥ vs low-risk¤	4.54 (2.88-7.15)	<0.001	4.37 (2.52-7.59)	<0.001

*versus idiopathic PAH

*versus idiopathic PAH
§versus prevalent PAH
°versus monotherapy or no specific therapy
Δ versus 2006-2011
£ versus prospective study
as a continuous variable
† Group 2 and 3
¤ Group 1

[¥] Group 4

List of abbreviations: HR, hazard ratio; CI, confidence interval; PAH, pulmonary arterial hypertension; WHO FC, world health organization functional class; 6MWD, six-minute walking distance; TAPSE, tricuspid annular plane systolic excursion; RVEDD, right ventricular end diastolic diameter; RVEDA, right ventricular end diastolic area; FAC, fractional area change; AcT, acceleration time; PASP, pulmonary arterial systolic pressure; RA, right atrial; ICV, inferior vena cava; TR, tricuspid regurgitation; LVEDV, left ventricular end diastolic volume; LV EF, left ventricular ejection fraction.

Figures Legends

Figure 1. Title: Patients selection.

§ Patients excluded due to overlap between studies: 37 from Mathai S et al (25 overlapping cases with Forfia P et al and 12 overlapping cases with Mukherjee M et al), 9 from Ghio S et al 2010 which overlapped with Ghio S et al 2016.

°form Forfia P et al.

*Patients excluded due to incomplete echocardiographic data to be classified according to the 4 groups: 74 with unavailable data on inferior vena cava, 12 with unavailable TAPSE, 3 with unavailable tricuspid regurgitation grade.

PAH = pulmonary arterial Hypertension; PH = pulmonary hypertension; WHO = world health organization

Figure 2. Title: Spline curve for TAPSE vs. hazard ratio of all-cause mortality.

Changes in hazard ratio for all-cause mortality across the baseline TAPSE.

TAPSE = tricuspid annular plane systolic excursion

Figure 3. Title: Kaplan-Meir curves for survival according to 4 (left) and 3 (right) echocardiographic-based risk Groups in patients with pulmonary arterial hypertension.

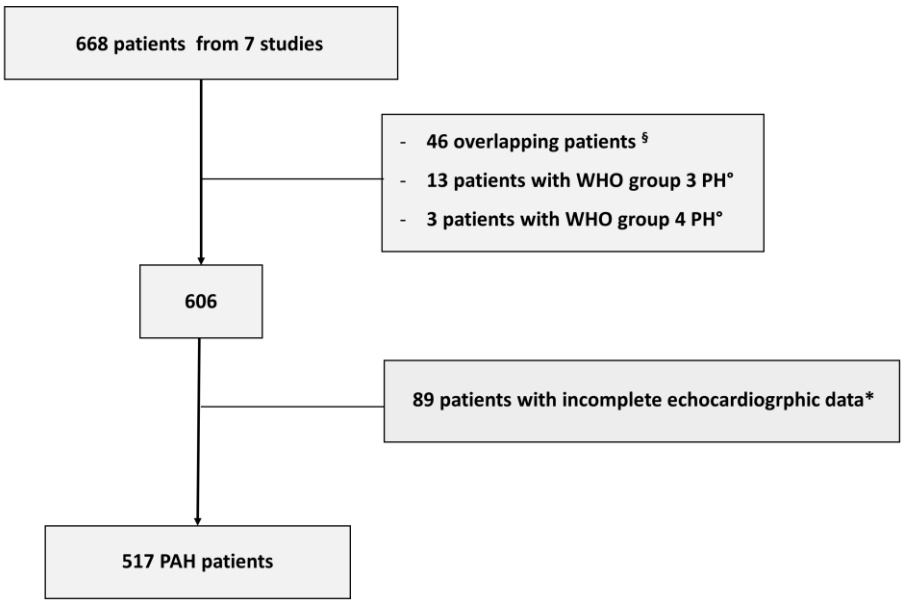
The Kaplan-Meier curves show significantly lower 5-year survival rates for high-risk patients (Group 4 – red line) compared to both intermediate-risk (Group 2 and 3 – grey and blue line on the left panel and orange line on the right panel) [43% vs 63%, respectively; $p<0.001$] and low-risk (Group 1 – green line) [43% vs 82%, respectively; $p<0.001$).

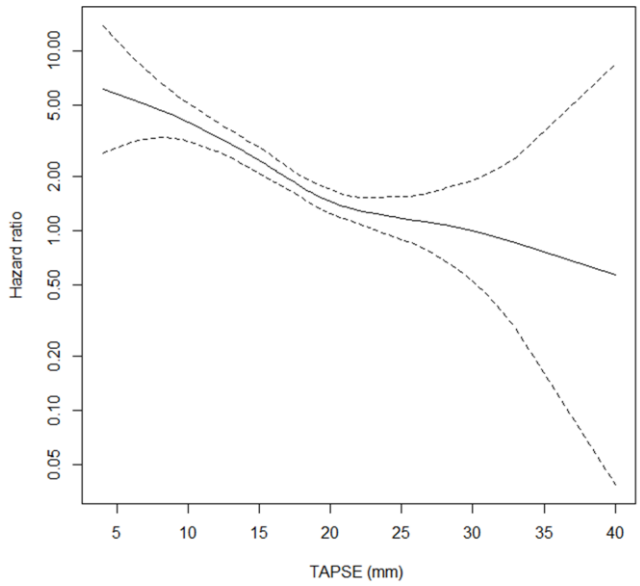
IVC = inferior vena cava; TAPSE = tricuspid annular plane systolic excursion; TR = tricuspid regurgitation.

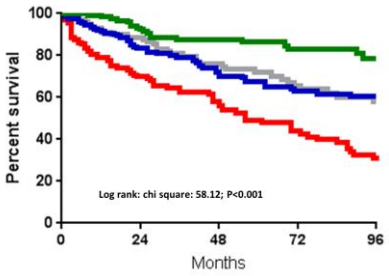
Figure 4. Title: Echocardiographic risk stratification in patients with pulmonary arterial hypertension.

Three risk categories were identified (right panel) from 4 groups (left panel) representing progressively increasing degrees of right heart dysfunction based upon presence/absence of RV dysfunction and of systemic venous congestion: 1) low-risk (green box): preserved TAPSE and non-significant TR (Group 1); 2) intermediate-risk (orange box): either preserved TAPSE and significant TR (Group 2) or impaired TAPSE and non-dilated IVC (Group 3); 4) high-risk (red box): impaired TAPSE and dilated IVC (Group 4).

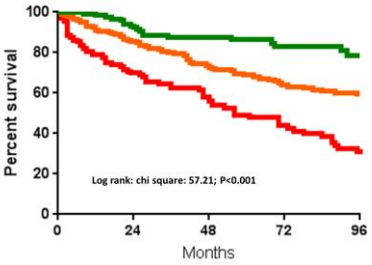
IVC = inferior vena cava; TAPSE = tricuspid annular plane systolic excursion; TR = tricuspid regurgitation.


668 patients from 7 studies
- 46 overlapping patients §
- 13 patients with WHO group 3 PH°
- 3 patients with WHO group 4 PH°
606
89 patients with incomplete echocardiogrphic data*
517 PAH patients

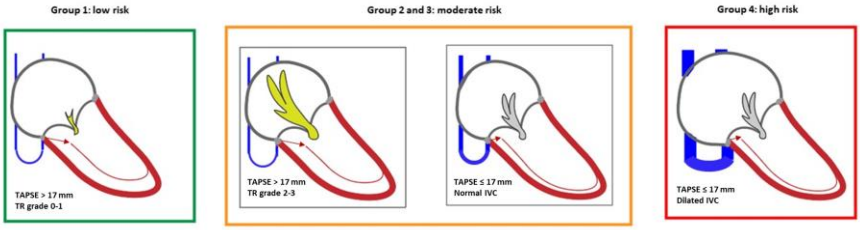

Hazard ratio
0.05
0.10
0.20
0.50
1.00
2.00
5.00
10.00
5
10
15
20
25
30
35
40
TAPSE (mm)



N. at risk					
TAPSE>17mm, TR 0-1	129	104	63	50	36
TAPSE>17mm, TR 3-4	155	105	79	54	46
TAPSE≤17mm, normal IVC	101	81	59	40	29
TAPSE≤17mm, dilated IVC	132	79	54	33	21



N. at risk					
TAPSE>17mm, TR 0-1	129	104	63	50	36
TAPSE>17mm, TR 2-3 or TAPSE≤17mm, normal IVC	256	186	138	94	75
TAPSE≤17mm, dilated IVC	132	79	54	33	21


Group 1: low risk
TAPSE > 17 mm
TR grade 0-1
Group 2 and 3: moderate risk
TAPSE > 17 mm
TR grade 2-3
TAPSE ≤ 17 mm
Normal IVC
Group 4: high risk
TAPSE ≤ 17 mm
Dilated IVC

Fortuni F ©

Supplementary Table 1S: Comparison between included and excluded patients due to missing echocardiographic data

Variable	Study population N = 517	Excluded patients N = 89	P value
Age, years	52 ± 15	55 ± 17	0.132
Female (%)	316 (64.8)	70 (78.7)	0.010
WHO FC III-IV (%)	339 (66.1)	64 (71.9)	0.281
Monotherapy, %	160 (32.4)	29 (33.3)	0.862
Combination therapy, %	215 (43.5)	32 (36.8)	0.241

List of abbreviations: WHO FC, World Health Organization functional class

Supplementary Table 2S: Adjusted HRs for all-cause mortality per 1 increase in echocardiographic risk category

Adjusted for	HR per 1 echocardiographic risk category increase (95% CI)	*P* value
1) Age, gender, incident/prevalent, year of publication, WHO FC, LVEF	1.96 (1.55-2.46)	<0.001
2) Age, gender, incident/prevalent, year of publication, WHO FC, heart rate, LVEF	1.86 (1.46-2.37)	<0.001
3) Age, gender, incident/prevalent, year of publication, WHO FC, LVEF, PAH etiology	2.11 (1.65-2.71)	<0.001
4) Age, gender, incident/prevalent, year of publication, 6MWD, LVEF	2.38 (1.45-3.91)	0.001
5) Age, gender, incident/prevalent, year of publication, WHO FC, LVEF, AcT	1.96 (1.50-2.55)	<0.001
6) Age, gender, incident/prevalent, year of publication, WHO FC, LVEF, RVEDA	2.01 (1.31-3.08)	0.001
7) Age, gender, incident/prevalent, year of publication, WHO FC, LVEF, RA area	1.92 (1.32-2.80)	0.001
8) Age, gender, incident/prevalent, year of publication, WHO FC, LVEF, PASP	1.94 (1.49-2.53)	<0.001

These analyses were conducted based on data availability, multivariable Cox regression model 1 included 444 patients, model 2 405 patients, model 3 367 patients, model 4 135 patients, model 5 385 patients, model 6 194 patients, model 7 277 patients, and model 8 352 patients.

List of abbreviations: AcT, acceleration time; HR, hazard ratio; LVEF, left ventricular ejection fraction; PAH, pulmonary arterial hypertension; RA, right atrial; RV EDA, right ventricular end diastolic area; 6MWD, 6-minute walking distance; WHO FC, World Health Organization functional class

Supplementary Table 3S. Univariable and multivariable Cox regression analysis with a multivariable Cox regression model including: age, gender, incident prevalent, WHO FC, RA area, and LVEF

	Univariate Analysis HR (95% CI)	*P* value	Multivariate Analysis HR (95% CI)	*P* value
Age	1.02 (1.01-1.03)	<0.001	1.03 (1.02-1.05)	<0.001
Female sex	0.71 (0.53-0.94)	0.017	0.87 (0.57-1.33)	0.521
Heart rate	1.02 (1.01-1.03)	0.002		
PVOD*	5.00 (2.50-10.00)	<0.001		
Scleroderma PAH*	1.50 (0.90-2.50)	0.121		
Connective tissue disease PAH*	2.80 (1.49-5.26)	0.001		
Incident PAH§	1.67 (1.16-2.41)	0.006	1.83 (0.78-4.33)	0.165
Combination therapy °	1.16 (0.88-1.54)	0.293		
Study published in 2016-18Δ	0.55 (0.36-0.83)	0.005	0.26 (0.03-2.01)	0.196
Data from retrospective study £	0.90 (0.66-1.21)	0.484		
WHO FC III-IV	2.96 (2.02-4.34)	<0.001	2.30 (1.36-2.89)	0.002
6MWD, per 10 m increase	0.96 (0.94-0.98)	<0.001		
Center location in USA	0.83 (0.60-1.18)	0.301		
TAPSE#	0.92 (0.89-0.94)	<0.001		
TAPSE ≤17 mm	2.37 (1.78-3.14)	<0.001		
RVEDD	1.01 (1.00-1.02)	0.076		
RVEDA	1.05 (1.02-1.07)	<0.001		
FAC	0.97 (0.95-0.99)	0.008		
AcT	0.98 (0.97-0.99)	<0.001		
PASP	1.01 (1.00-1.01)	0.006		
RA area	1.04 (1.02-1.06)	<0.001	1.04 (1.02-1.06)	<0.001
Pericardial effusion	1.33 (0.69-2.59)	0.396		
Dilated IVC	1.95 (1.46-2.64)	<0.001		
TR moderate to severe	2.00 (1.43-2.79)	<0.001		
LVEDV	0.99 (0.97-0.99)	0.005		
LVEF	0.98 (0.97-0.99)	0.002	1.01 (0.99-1.02)	0.509
Intermediate-† vs low-risk¤	2.15 (1.38-3.37)	0.001		
High-¥ vs low-risk¤	4.54 (2.88-7.15)	<0.001		

*versus idiopathic PAH

§versus prevalent PAH

°versus monotherapy or no specific therapy

Δ versus 2006-2011

£ versus prospective study

as a continuous variable

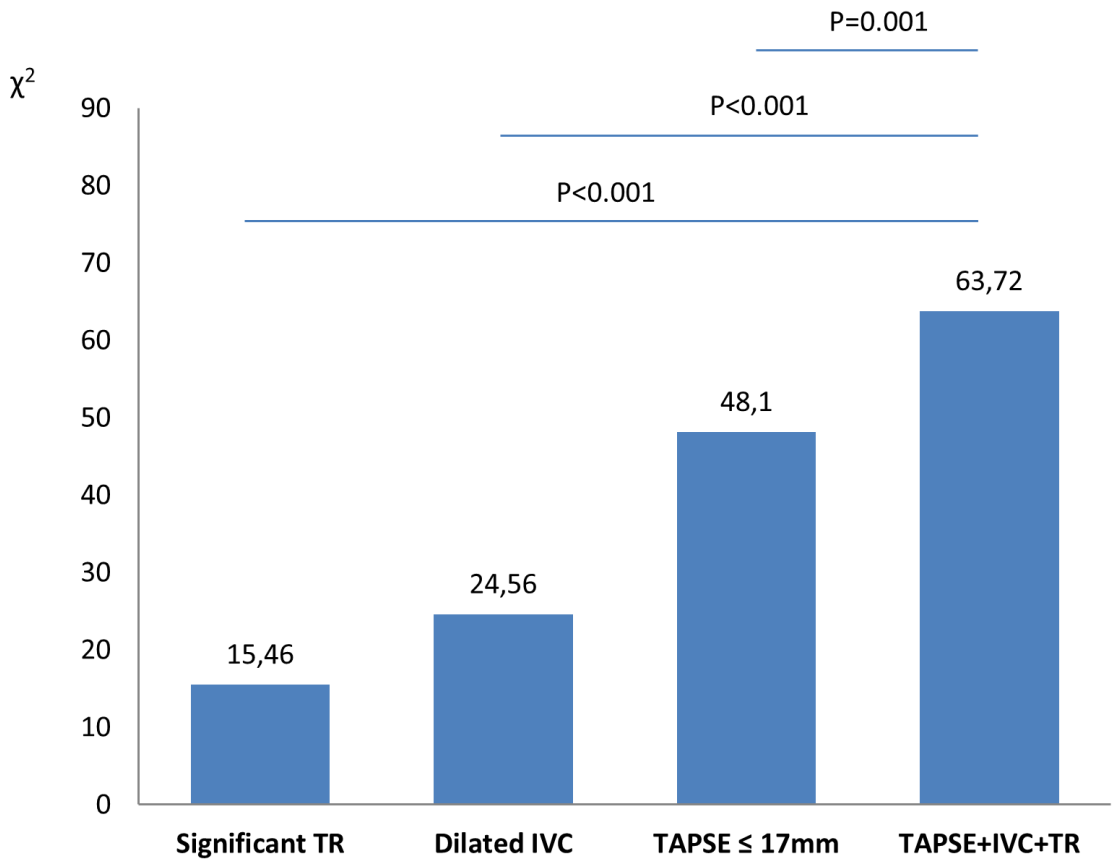
† Group 2 and 3

¤ Group 1

¥ Group 4

List of abbreviations: HR, hazard ratio; CI, confidence interval; PAH, pulmonary arterial hypertension; WHO FC, world health organization functional class; 6MWD, six-minute walking distance; TAPSE, tricuspid annular plane systolic excursion; RVEDD, right ventricular end diastolic diameter; RVEDA, right ventricular end diastolic area; FAC, fractional area change; AcT, acceleration time; PASP, pulmonary arterial systolic pressure; RA, right atrial; ICV, inferior vena cava; TR, tricuspid regurgitation; LVEDV, left ventricular end diastolic volume; LV EF, left ventricular ejection fraction.

Supplementary Figure 1S: Association between individual and combined echocardiographic parameters with all-cause mortality.

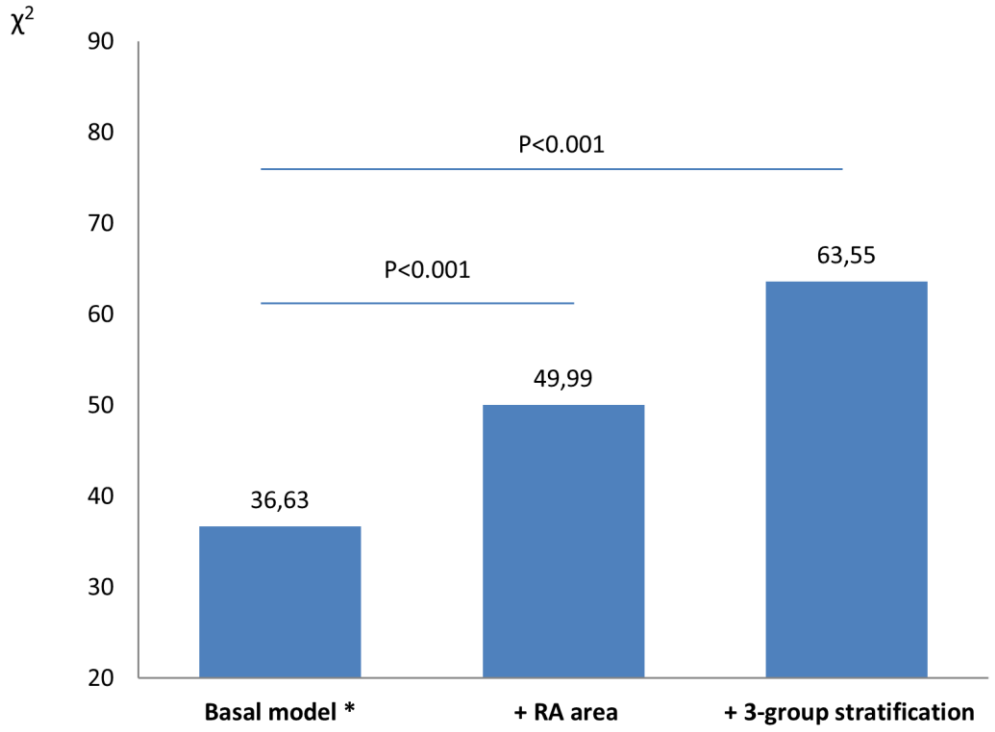


The model χ^2 values are presented for a series of Cox regression analysis model: the combination of significant TR, dilated IVC and decreased TAPSE is associated with a significant increase in χ^2 value compared with the use of these parameters individually.

This analysis was conducted on patients that had all the parameters included in the Cox regression models available (440).

IVC = inferior vena cava; TAPSE = tricuspid annular plane systolic excursion; TR = tricuspid regurgitation

Supplementary Figure 2S. Incremental prognostic value of the proposed stratification model compared with RA area



*The basal model includes age, gender, WHO class III-IV, year of study publication, incident/prevalent, and LVEF. This analysis was conducted based on data availability and included 277 patients.

The model χ^2 values are presented for a series of Cox regression analysis model: the proposed risk stratification into 3 groups based on TAPSE, IVC dilation and TR severity when added to the basal model is associated with a higher increase in the χ^2 value compared with the addition of RA area.

The first blue bar from the left shows the χ^2 of the basal model; the second one the χ^2 value of the basal model + RA area and the third the χ^2 value of the basal model + our 3-groups risk stratification.

IVC = inferior vena cava; RA = right atrial; TAPSE = tricuspid annular plane systolic excursion; TR = tricuspid regurgitation

Appendix 1

List of all contributors:

Pavia: Michela Coccia, Federico Fortuni, Stefano Ghio, Alessandra Greco, Arianna Grelli, Letizia Mannucci, Claudia Raineri, Laura Scelsi.

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