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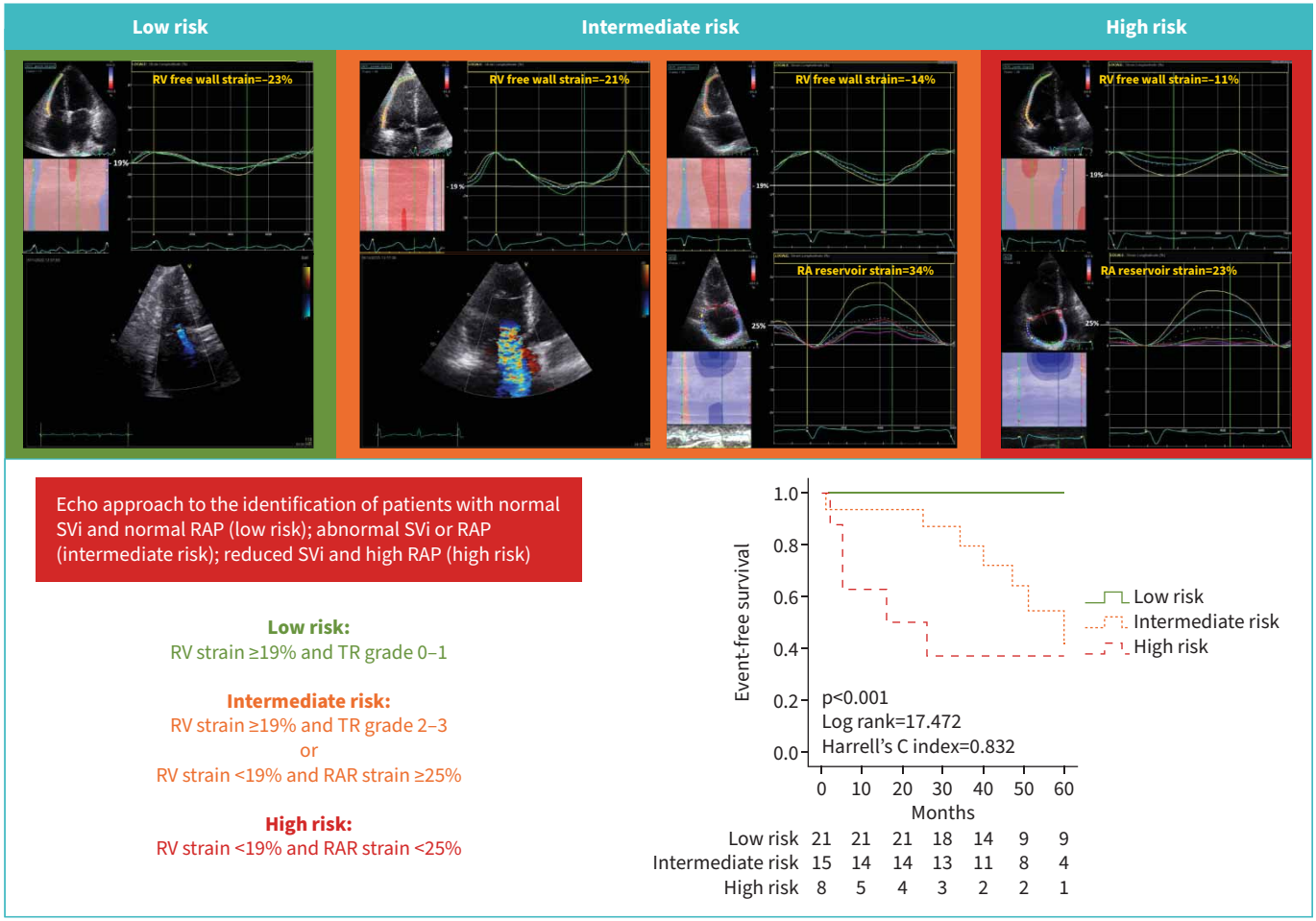

GRAPHICAL ABSTRACT Risk stratification based on advanced echocardiographic parameters. The illustration depicts the comprehensive assessment of right ventricular pump function and of systemic venous congestion based on strain imaging parameters and on the degree of tricuspid regurgitation at re-evaluation. This approach is conforming with the haemodynamic approach recommended by international guidelines to stratify prognosis in PAH patients, based on the association of an indicator of pump function and an indicator of systemic venous congestion. RV: right ventricular; RA: right atrial; SVi: stroke volume index; RAP: right atrium pump; TR: tricuspid regurgitation; RAR: right atrial reservoir.

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Comprehensive pathophysiology-based assessment of right ventricular pump function and systemic venous congestion using strain imaging parameters is associated with high accuracy in risk stratification of patients with PAH. https://bit.ly/40bWVRa

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Abstract

Background A novel approach to derive prognostic information from echocardiography in pulmonary arterial hypertension (PAH) is to define a phenotype of right heart function combining standard echocardiographic parameters which describe right ventricular pump function and systemic venous congestion. We tested the hypothesis that the combination of advanced strain imaging parameters could yield high prognostic accuracy.

Methods This was a prospective observational study with a single centre derivation cohort and a second centre validation cohort. The derivation cohort included 49 naive PAH patients who underwent right heart catheterisation and echocardiographic evaluation at baseline and 4–12 months after diagnosis. The validation cohort included 83 prevalent PAH patients who underwent the same examinations at 12 months after diagnosis. We stratified the risk of the derivation cohort according to three models: Model 1, based on haemodynamic parameters; Model 2, based on standard echocardiographic parameters; and Model 3, based on advanced echocardiographic parameters. The median follow-up period was 21 months; the end point of the analysis was clinical worsening.

Results In the derivation cohort, haemodynamic and echocardiographic parameters obtained at diagnosis were not associated with outcome, whereas a significant association was observed at first reassessment. Model 3 yielded a better predictive accuracy (Harrell's C index 0.832) as compared to Model 2 (Harrell's C index 0.667), and to Model 1 (Harrell's C index 0.713). The validation cohort confirmed the accuracy of Model 3.

Conclusions A comprehensive assessment of right heart function using right ventricular strain, right atrial reservoir strain and degree of tricuspid regurgitation provides accurate prognostic information in prevalent PAH patients.

Introduction

Pulmonary arterial hypertension (PAH) is a progressive disease with high mortality. During the past two decades, advances have been brought about with the introduction of therapies targeting the pulmonary circulation, and clinicians are now facing the difficulties in customising treatment in individual patients. The recommendation from the 2022 European Society of Cardiology (ESC)/European Respiratory Society (ERS) Guidelines for the diagnosis and treatment of pulmonary hypertension is to select PAH therapies according to individual risk, with the goal of achieving a low-risk status during follow-up assessment [1]. However, current risk stratification tools are characterised by moderate certainty of the evidence [2–5].

Direct imaging of the right ventricle has the potential to increase understanding of the disease and therefore to help obtain more refined prognostic assessments [6]. A recent meta-analysis of studies evaluating the prognostic role of standard echocardiography in PAH demonstrated that a more fruitful approach to deriving prognostic information from echocardiography is to combine parameters to obtain a comprehensive, pathophysiology-based assessment of right heart function [7]. This approach matches the way right heart haemodynamics has been successfully used for decades to predict prognosis in patients with PAH (that is, combining parameters of right ventricular pump function and of right heart congestion) [8, 9]. In recent years advanced echocardiographic techniques have been shown to be clinically feasible, despite an inherent greater complexity, to investigate right ventricular (RV) and right atrial (RA) function. Both RV free wall strain and RA reservoir strain have been shown to be individually associated with prognosis in PAH patients but have never been combined in a comprehensive approach [10–16].

We therefore designed a proof-of-concept study to test the hypothesis that the definition of a phenotype of right heart function based on advanced strain imaging parameters which describe RV pump function and right heart congestion (in order to resemble the gold standard haemodynamic approach) might improve the accuracy of echocardiography in stratifying the risk of PAH patients.

Methods

Study

The study was designed as a longitudinal, observational study, with a single centre derivation cohort of naive patients and a second centre validation cohort of prevalent patients.

Patients

Derivation cohort

The enrolment included a derivation cohort of patients who had undergone elective hospitalisation in the Cardiology Division of Fondazione IRCCS Policlinico San Matteo between 1 January 2012 and 1 January 2019 to perform the diagnostic examinations recommended by ESC/ERS guidelines in case of suspected PAH and were diagnosed as affected by PAH [17]. Living patients were hospitalised a median of 6 months after diagnosis to evaluate the effectiveness of treatment and underwent repeat echocardiography and right heart catheterisation (RHC). All patients signed an informed consent approved by the Institutional Review Board of Foundation IRCCS Policlinico San Matteo, Pavia, Italy for longitudinal, non-pharmacological, non-sponsored studies. The protocol was approved by the Institutional Review Board of the Policlinico San Matteo, Pavia (Protocol n. 20180054581, date 20 June 2019).

Validation cohort

Consecutive prevalent PAH patients were recruited in the same time period from the pulmonary hypertension centre of the Sapienza University of Rome. The validation cohort included prevalent PAH patients to validate the prognostic accuracy of the advanced echocardiographic model obtained in the derivation cohort at re-evaluation (supplementary figure S1 shows the timeline for both the derivation cohort and the validation cohort). The protocol was approved by the Institutional Review Board for human studies of the Policlinico Umberto I-Sapienza University of Rome (Protocol n. 4659). All patients underwent World Health Organization (WHO) functional class evaluation, brain natriuretic peptide (BNP) assessment, 6-min walk test (6MWT), RHC and a complete echocardiographic evaluation with data storage on a server.

Treatment

The treatment of PAH patients evolved during the enrolment period in parallel with the availabilities of new drugs. However, treatment strategies were always based on recommendations of current international guidelines.

Longitudinal monitoring

Survival and clinical data were obtained through patient follow-up visits or, in case of no visits, by telephone contact.

Right heart catheterisation

RHC was performed using a balloon-tipped catheter *via* jugular approach. The following haemodynamic parameters were measured or calculated: pulmonary capillary wedge pressure (PCWP); systolic, diastolic and mean pulmonary artery pressure (mPAP); cardiac output (calculated by thermodilution); cardiac index; stroke volume index (SVi); RA pressure; pulmonary vascular resistance (PVR), calculated as (mPAP − PCWP)/cardiac output.

Echocardiographic and Doppler study

A complete M-mode, two-dimensional and Doppler evaluation was performed using commercially available GE ultrasound equipment; images and clips were stored on a GE server (Image Vault, GE Healthcare, Chicago, IL, USA).

Strain analysis

Studies were uploaded to the workstation EchoPAC PC SW-only, version 202, revision 61.0. Two-dimensional RV and RA strain analysis was performed offline using high frame-rate acquisitions (>40 frames·s^{-1}) of apical focused views [17]. Inadequate quality was defined as poor visualisation or poor tracking of >1 atrial or ventricular segment. Operators from both centres are part of the core lab for echocardiography reading for the Italian Pulmonary Hypertension network (IPHNET). Interobserver bias, correlation and intra-class variability for RV strain and right atrial reservoir (RAR) strain were calculated [18].

Statistical analysis

Descriptive statistics were used to summarise data gathered in the study. Continuous variables were expressed as median and interquartile range (IQR). Categorical variables were displayed as count and percentages. Data at baseline and at follow-up were compared with the Wilcoxon signed rank test for paired data if continuous and ordinal and with McNemar test if dichotomous. Spearman's correlations were performed to analyse relationships between haemodynamic and echocardiographic variables. Normality was checked by Kolmogorov–Smirnov with Lilliefors significance correction.

End point of event-free survival analysis was the combination of all cause death, lung transplant and hospitalisation due to clinical worsening. Event-free survival estimates were calculated according to the Kaplan–Meier method, with all events or censoring times measured from time of first re-evaluation. Prognostic assessment was focused on follow-up evaluation management, which was based on the previous finding that the predictive value of haemodynamic variables at diagnosis is poor whereas SVi and right atrium pump (RAP) at first follow-up are strong independent prognostic variables [8]. The significance of differences in the primary end point between groups was assessed with the use of the log-rank test. Stratification for Kaplan–Meier graphs is provided for illustrative purposes. The Harrell's C index was used to compare risk stratification models. Two-sided significance testing was used for all statistical tests, with a p-value <0.05 considered statistically significant.

Risk stratification

1) Haemodynamic-based model 1. Haemodynamic parameters used for risk assessment were SVi and RAP. Three risk groups were defined: low-risk (RAP <8 mmHg, SVi ⩾31 mL·m^{-2}); intermediate risk (RAP <8 mmHg, SVi <31 mL·m^{-2} or RAP ⩾8 mmHg, SVi ⩾31 mL·m^{-2}) and high risk (RAP ⩾8 mmHg, SVi <31 mL·m^{-2}) [8].
2) Standard echocardiography-based model 2. Parameters used for risk assessment were TAPSE, degree of tricuspid regurgitation (TR) based on area of regurgitant jet and diameter of inferior vena cava (IVC). Three risk groups were defined: low-risk (TAPSE >17 mm and TR grade 0–1); intermediate risk (TAPSE >17 mm and TR grade 2–3 or TAPSE ⩽17 mm and IVC ⩽20 mm) and high risk (TAPSE ⩽17 mm and IVC >20 mm) [9].
3) Advanced echocardiography-based model 3. Parameters used for risk assessment were RV strain (dichotomised at its median value (−19%), given the slight disagreement in the literature about its best prognostic cut-off and corrected for the degree of TR) and RAR strain (dichotomised at cut-off value of 25%, according to literature data) [11, 12–16]. Three risk groups were defined: low-risk (RV strain ⩾19% and TR grade 0–1); intermediate risk (RV strain ⩾19% and TR grade 2–3 or RV strain <19% and RAR strain ⩾25%) and high risk (RV strain <19% and RAR strain <25%).

Results

Derivation cohort

Clinical characteristics at diagnosis and at first re-evaluation (table 1)

The derivation cohort included 49 patients who had, both at diagnosis and at a first re-evaluation within 1 year of diagnosis, WHO/New York Heart Association (NYHA) functional class evaluation, BNP assessment, 6MWT, RHC and complete echocardiographic recording stored on the server. The majority of patients were women, median age 56 years at diagnosis, the majority in WHO class II or III. Two-thirds were initially treated with monotherapy and one third with double combination therapy; a single patient received triple upfront therapy.

TABLE 1 Clinical characteristics (derivation cohort)

Patients n		49	
Age at baseline years, median (IQR)		56 (44–69)	
BSA m^2, median (IQR)		1.70 (1.54–1.85)	
Male sex, n (%)		16 (33)	
Time from diagnostic RHC/TTE to first RHC/TTE on PAH-specific therapy, months, median (IQR)		6 (4–12)	
Aetiology (IPAH/scleroderma-associated/drug induced), n (%)			
Idiopathic PAH		20 (41)	
Heritable PAH		6 (12)	
Connective tissue disease-associated PAH		16 (33)	
Others		7 (14)	
First-line PAH-specific therapy, n (%)			
Monotherapy		34 (69.4)	
Double therapy		13 (26.5)	
Prostanoids therapy		2 (4.1)	
	Baseline	**Control**	**p-value**
WHO class I/II/III/IV, n	3/22/22/2	12/30/6/1	<0.001
BNP pg·mL^{-1}, median (IQR)	229 (66–392)	174 (57–381)	0.542
6MWT m, median (IQR)	410 (322–491)	550 (400–630)	0.001

IQR: interquartile range; BSA: body surface area; RHC: right heart catheterisation; TTE: transthoracic echocardiography; PAH: pulmonary arterial hypertension; IPAH: idiopathic pulmonary arterial hypertension; WHO: World Health Organization; BNP: brain natriuretic peptide; 6MWT: 6-min walking test distance.

The most frequently used initial treatment strategy after diagnostic RHC was oral monotherapy (69.4%), followed by double oral combination therapy (26.5%). Upfront therapy with prostacyclin was used in 4.1% of patients. The first re-evaluation within the first year after diagnosis was performed after a median of 6 months after the beginning of PAH-specific treatment. At re-evaluation, WHO class and distance walked at 6MWT significantly improved; BNP numerically improved, but it did not reach statistical significance, most likely because of the small number and large standard deviation of the data.

Haemodynamic data at diagnosis and at first re-evaluation (table 2)

Haemodynamic data at diagnosis indicate severe pulmonary hypertension (median mPAP of 48 mmHg, PVR of 10.6 WU and cardiac index of 2.1 L·min^{-1}·m^{-2}) with normal RAP. At the first re-evaluation, all haemodynamic parameters were significantly improved, with the exception of RAP, which was substantially unchanged.

Echocardiographic data at baseline and at first re-evaluation (table 3)

Echocardiographic data at diagnosis confirmed the severity of pulmonary hypertension, with impaired indices of systolic RV function, severe compression of the left ventricle in end-diastole, TR of moderate to severe in most cases and dilated IVC. At the first re-evaluation after beginning of treatment, most echocardiographic parameters significantly improved.

TABLE 2 Haemodynamic data at diagnosis and at first re-evaluation (derivation cohort)

	Diagnosis	**First re-evaluation**	**p-value**
PAP systolic/diastolic/mean, mmHg (median)	79/32/48	61/24/41	<0.001[#]
RAP mmHg, median (IQR)	7 (5–10)	5 (4–8)	0.057
PVR WU, median (IQR)	10.6 (7.5–14.3)	7 (4.8–10.5)	<0.001
Cardiac index L min^{-1}·m^{-2}, median (IQR)	2.10 (1.82–2.71)	2.56 (2.14–2.94)	<0.001
SVi mL·m^{-2}, median (IQR)	29 (20–36)	35 (28–43)	<0.001
HR bpm, median (IQR)	80 (73–90)	74 (67–83)	<0.001

PAP: pulmonary arterial pressure; RAP: right atrial pressure; IQR: interquartile range; PVR: pulmonary vascular resistance; SVi: stroke volume index; HR: heart rate; bpm: beats per min. [#]: statistical significance was found for all three parameters.

TABLE 3 Echocardiographic data at diagnosis and at first re-evaluation (derivation cohort)

	Diagnosis	First re-evaluation	p-value
RVOT (Plax view) mm	34 (31–40)	32 (28–36)	0.001
RV-EDA cm^2	28 (23–33)	24 (20–29)	0.001
FAC %	26 (19–35)	31 (25–39)	0.001
TAPSE mm	17 (14–21)	19 (17–22)	0.001
RV free wall strain %	−14 (−18– −10)	−19 (−23– −15)	<0.001
End-diastolic eccentricity index (LV)	1.8 (1.54–2.12)	1.26 (0.99–1.44)	<0.001
IVC mm	16 (14–18)	15 (12–17)	0.326
IVC collapse <50%	13 (27)	10 (22)	0.629
RAR strain %	20 (16–28)	26 (20–31)	0.014
TR grade 0–1	24 (49)	41 (84)	<0.001
TR grade 2–3	25 (51)	8 (16)	
TR PISA radius mm[#]	6.5 (5–8)	4 (3.3–7)	0.003
TR EROA $cm^{2\#}$	0.24 (0.17–0.35)	0.16 (0.10–0.29)	0.111
TR R-Vol mL[#]	32 (21–51)	16 (10–29)	0.036

Data are presented as median (IQR) or n (%). RVOT: right ventricular outflow tract diameter; RV-EDA: Right ventricle end-diastolic area; FAC: fractional area change; TAPSE: tricuspid annular plane systolic excursion; RV: right ventricle; IVC: inferior vena cava; RAR: right atrium reservoir; TR: tricuspid regurgitation; PISA: proximal isovelocity surface area; EROA: effective regurgitant orifice area; R-Vol: regurgitant volume. [#]: quantitative analysis of TR was performed in 36 patients at baseline and in 20 patients at control.

RV strain showed a much better correlation with SVi (Spearman's $\rho = -0.519$, $p<0.001$) than TAPSE (Spearman's $\rho=0.383$, $p<0.001$) and fractional area change (FAC) (Spearman's $\rho=0.277$, $p=0.006$).

RAR strain showed a much better correlation with RAP (Spearman's $\rho = -0.463$, $p<0.001$) than IVC dilatation (Spearman's $\rho=0.085$, $p=0.415$) and left ventricular eccentricity index in end-diastole (Spearman's $\rho=0.042$, $p=0.690$).

Interobserver variability of RV strain and of RAR strain is shown in supplementary table S1.

Association of haemodynamic and echocardiographic variables with outcome

The median follow-up period after the first re-evaluation was 21 (5–24, 25, 26) months. During this period two patients died, one patient underwent lung transplantation, and 10 patients were hospitalised because of clinical worsening.

Baseline data

Haemodynamic, standard and advanced echocardiographic parameters recorded at diagnosis were not significantly associated with time to event-free survival (respectively: log rank χ^2 0.578, $p=0.74$ for haemodynamic parameters; log rank χ^2 0.85, $p=0.654$ for standard echocardiographic parameters and log rank χ^2 1.76, $p=0.415$ for advanced echocardiographic parameters).

Re-evaluation data

Model 1. Risk stratification according to SVi and RAP at re-evaluation is shown in figure 1. The model was significantly associated with time to event-free survival (log rank χ^2 11.033; $p=0.004$; Harrell's C Index 0.689).

Model 2. Risk stratification according to TAPSE, degree of TR and dilation of IVC at re-evaluation is shown in figure 2. The model was significantly associated with time to event-free survival (log rank χ^2 4.654; $p=0.031$, Harrell's C index 0.667). This model did not classify any patient as being at high risk.

Model 3. Risk stratification according to RV strain, RAR strain and degree of TR at re-evaluation is shown in the graphical abstract. The model was significantly associated with time to event-free survival (log rank χ^2 17.472; $p<0.001$; Harrell's C index 0.832). Patients classified as low-risk by advanced echocardiography (n=21) had no events during follow-up.

Validation cohort

Clinical characteristics (supplementary table S2)

Eighty-three consecutive prevalent PAH patients were included in the validation cohort; patients were included at reassessment after a median of 356 (IQR 341–371) days from diagnosis. Aetiology was

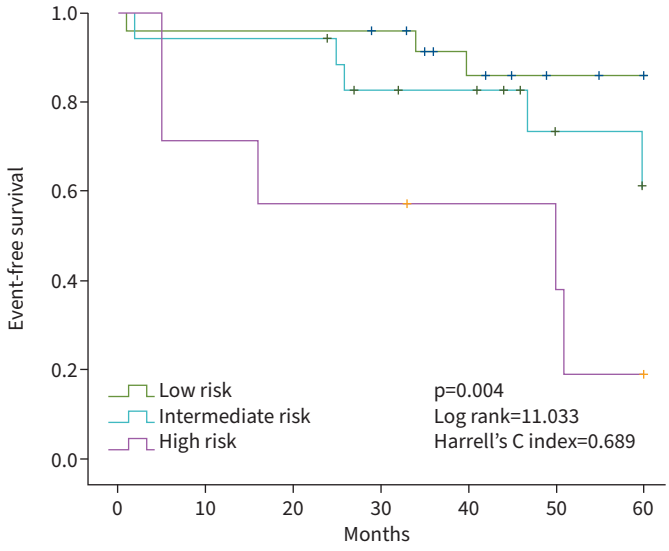

FIGURE 1 Risk stratification based on haemodynamic parameters at re-evaluation. Kaplan–Meier curves for low-, intermediate- and high-risk patients, defined on the basis of stroke volume index and right atrial pressure.

idiopathic PAH in 45 patients, associated PAH in 22 patients, and others in 16 patients. The majority of patients were women, median age 49 years, body mass index 22±2 $kg \cdot m^{-2}$, mainly in WHO class II or III at reassessment. Two-thirds of the patients were on double oral combination therapy at the time of second evaluation (68%), while 32% were on double oral combination plus parenteral prostanoids.

The low-risk group included 24 patients with RV strain ⩾19% and TR grade 0–1; the intermediate-risk group included 25 patients with RV strain ⩾19% and TR grade 2–3 or RV strain <19% and RAR strain ⩾25%; the high-risk group included 34 patients with RV strain <19% and RAR strain <25%.

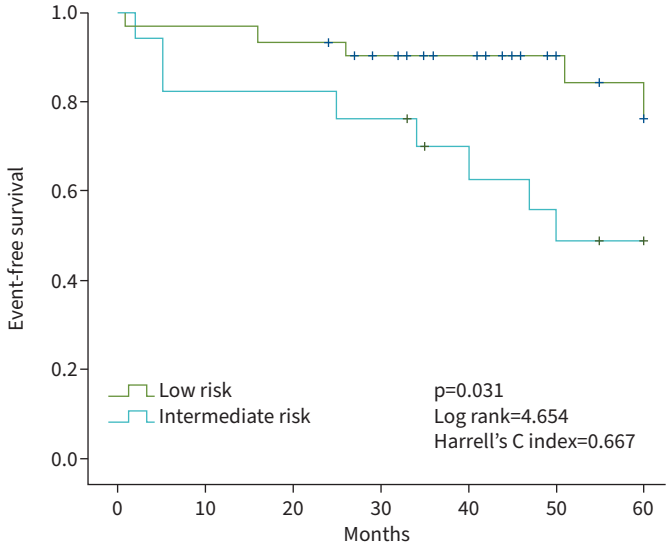

FIGURE 2 Risk stratification based on standard echocardiographic parameters at re-evaluation. Kaplan–Meier curves for low-, intermediate- and high-risk patients, defined on the basis of tricuspid annular plane systolic excursion, degree of tricuspid regurgitation and diameter of inferior vena cava.

A progressive impairment of clinical and haemodynamic conditions from Group 1 to Group 3 was observed. Additionally, RV and right atrium sizes and function were progressively, and respectively, dilated and reduced from Group 1 to Group 3 (supplementary table S2).

Association of echocardiographic variables with outcome

The median follow-up period was 22 (IQR 14–31) months. During this period 21 patients died and 24 were hospitalised because of clinical worsening. The advanced echocardiographic model (Model 3 in the derivation cohort) confirmed a significant association with event-free survival in this validation cohort (log rank χ^2 51.148, p<0.001; Harrell's C index 0.72, 95% CI 0.60–0.82, p=0.001). Event-free survival rates for the three groups of patients at 1, 2 and 3 years were, respectively, 100%, 100% and 80% in the low-risk group; 88%, 65% and 60% in the intermediate-risk group; 59%, 32% and 3% in the high-risk group (log-rank p<0.001 for all group comparisons) (figure 3).

Discussion

The main result of this pilot, proof-of-concept study is the demonstration that a comprehensive echocardiographic evaluation of right heart function, obtained through the combination of advanced echocardiographic indicators of RV pump function and of systemic venous congestion is feasible and provides an accurate prognostic stratification of prevalent patients with PAH. The accuracy of this method was superior to the risk stratification based on the haemodynamic parameters SVi and RAP.

There is a robust rationale for using echocardiography to obtain a comprehensive phenotype of right heart function rather than to detect the best single prognostic parameter. Indeed, this is exactly how right heart haemodynamics has long been used to stratify the prognosis of patients with PAH, *i.e.* combining information on RV pump function and on systemic venous congestion [8, 9]. There is also a robust rationale to combine advanced deformation parameters which have already been shown to be individually associated with prognosis in PAH patients but have never been combined in a comprehensive pathophysiology-based approach with the degree of TR [10–16]. The reason for including TR in the echocardiographic models is that assessment of right ventricular function using imaging methodologies is inherently limited by the load dependence of all parameters assessing cardiac motion, whatever the measure of RV function used. Indeed, the presence of significant TR regurgitation reduces ventricular afterload because the right ventricle ejects into both the pulmonary artery and the right atrium [19]. Therefore, ventricular motion can no longer be considered an accurate index of RV systolic function. In fact, a previous study demonstrated that patients with normal TAPSE but moderate to severe TR had a significantly worse prognosis than those with normal TAPSE without TR [7].

A first result of the study is that risk assessment at diagnosis, however assessed, is not significantly associated with prognosis. This finding seems in contrast to the results from seminal studies, but it is consistent with the results from a large, modern cohort of PAH patients; the discrepancy most likely

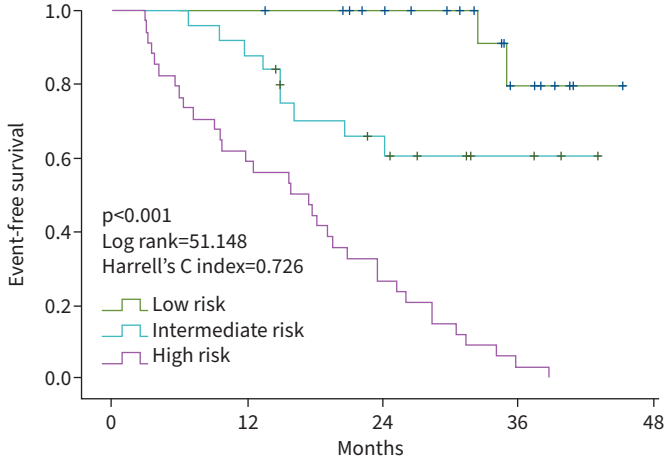

FIGURE 3 Risk stratification based on advanced echocardiographic parameters in the validation cohort. Kaplan–Meier curves for low-, intermediate- and high-risk patients, defined on the basis of strain imaging parameters and on the degree of tricuspid regurgitation.

reflects the more aggressive modern treatment of naive patients with severe PAH [8, 20, 21]. On the contrary, risk assessment at first re-evaluation was significantly associated with prognosis. In line with the hypothesis of the study, the use of deformation parameters allowed a substantially greater accuracy of risk stratification than the use of standard echocardiographic parameters, providing a remarkable c-statistic of 0.832. The reason beyond such findings relies on the tight association between imaging-derived RV functional parameters and invasive haemodynamics. Indeed, RV strain showed a better correlation with SVi than TAPSE and FAC, and RA reservoir strain showed a better correlation with RAP than left ventricular eccentricity index in end-diastole, IVC dilatation and RA pump strain. The good discriminatory ability of this advanced echocardiographic approach for risk stratification was confirmed in the validation cohort of PAH patients enrolled in a different centre, which also demonstrated a good c-index [22, 23]. It is important to notice that this echocardiographic approach also performed well in comparison with risk stratification based on haemodynamic parameters, yielding, in the derivation cohort, a numerically better predictive accuracy than the haemodynamic model. In particular, the low-risk group defined on the basis of deformation parameters was associated with few events in the follow-up period, both in the derivation and in the validation cohorts. Remarkably, the low-risk group included a substantial proportion of all patients studied (43% in the derivation cohort and 29% in the validation cohort). It is tempting to speculate that advanced echocardiography may identify functional changes which precede changes in right heart haemodynamics.

Limitations and strengths

The small sample size and the low number of events requires a cautious interpretation of the results. This was in fact designed as a pilot study. As such, the results necessitate to be validated in larger cohorts. However, the standardised recruitment of PAH patients in referral centres, the inclusion of naive patients in whom RHC and echocardiography were performed both at diagnosis and at a first re-evaluation within 1 year, the possibility to correlate echocardiographic and haemodynamic parameters, the reproducibility and the acceptable feasibility of strain analysis of RV and RA function and finally the robust pathophysiological basis for the proposed approach are all important strengths of the study. The external validation cohort confirms the strength of our analysis.

We acknowledge that the limited number of patients did not allow the possibility of verifying the usefulness of a precise and quantitative assessment of the degree of TR, today not only possible but also strongly recommended [24]. However, this limitation does not impact the accuracy of the method in the identification of low-risk patients who have trivial or no TR. The echocardiographic models did not include the size of the right ventricle or of the right atrium; this would be interesting since a failing right heart dilates to compensate for reduced systolic function and capturing dilatation can be specifically done with imaging techniques, not with a haemodynamic evaluation. However, assessing whether RV or RA dimensions are better prognosticators than RV function was beyond the scope of the present study and could be an interesting issue for future research. As a matter of fact, the current study does not establish whether the combination of strain parameters and TR includes all optimal prognostic indicators; this could be the objective of future studies. Finally, (as this was conceived as a proof-of-concept study) the integration of the proposed echocardiographic assessment into the multidimensional prognostic tools indicated by the international guidelines was not an achievable goal [1]. However, the interesting results presented here might pave the way to future larger, multicentre prospective studies, as recommended by the latest European guidelines to fill this important gap in the evidence.

Conclusions

Deep echocardiographic phenotyping by means of a combined assessment of RV strain, degree of TR and RAR strain provides powerful prognostic information in PAH patients.

As these results appear promising, this study can be considered a valid proof of concept for the implementation of a large multicentre study aimed at prospectively verifying the role of this pathophysiology-based approach of advanced echocardiographic phenotyping in risk stratification models of PAH.

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Ethics statement: The Institutional Review Boards in Pavia and Rome approved the study.

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