Risk assessment in scleroderma patients with newly diagnosed pulmonary arterial hypertension: application of the ESC/ERS risk prediction model

To the Editor:

Pulmonary arterial hypertension (PAH) is characterised by sustained pulmonary vasoconstriction and remodelling of the pulmonary circulation leading to progressive right ventricular (RV) dysfunction. Although recent registry data suggest improving outcomes, PAH still carries a high morbidity and mortality burden [1].

Baseline indices of clinical status, exercise performance and RV function are known predictors of mortality [2]. To provide prognostic information and guide therapeutic decisions, the 2015 European Society of Cardiology/European Respiratory Society guidelines on pulmonary hypertension highlight the importance of a multidimensional and comprehensive approach to risk assessment in PAH [3]. Based on variables and cut-off values established by expert consensus, three distinct risk categories were defined with estimated 1-year mortality rates ranging from <5% (low risk) to >10% (high risk). Recent studies have validated this risk assessment tool in distinct PAH cohorts [4–6].

PAH due to systemic sclerosis (SSc) is phenotypically unique and carries one of the worst prognoses amongst different aetiologies, including idiopathic PAH (IPAH) and connective tissue disease (CTD)-PAH [7]. Though rare in the general population, PAH is relatively common in SSc (estimated prevalence 7–12%) and a leading cause of SSc morbidity and mortality [8]. Given our unique patient population, we explored the ability of a modified guidelines' risk assessment tool to predict mortality in newly diagnosed SSc-PAH patients. Some of these results have been reported in abstract form [9].

Consecutive SSc-PAH patients prospectively enrolled in the Johns Hopkins Pulmonary Hypertension Programme between January 2000 and June 2016 were included. The study protocol was approved by the local Institutional Review Board, and informed consent was obtained for all patients. SSc diagnosis was confirmed by expert rheumatologists [10], and PAH was defined by right heart catheterisation [3]. Patients with significant chronic obstructive pulmonary disease or interstitial lung disease, portal hypertension, left heart disease or chronic thromboembolic disease were excluded.

Baseline demographics, medical history, World Health Organization functional class (WHO-FC), 6-min walk distance (6MWD) and haemodynamics were collected. Patients underwent regular follow-up visits according to clinical needs. The primary outcome was all-cause mortality.

We applied two different methods of risk categorization. 1) Having none, 1, 2, 3 or 4 of the following "green" low-risk criteria: WHO-FC I–II, 6MWD >440 m, right atrial pressure (RAP) <8 mmHg and/or cardiac index $\geqslant$2.5 L·min^{-1}·m^{-2}. 2) Having a score of 1 (low risk), 2 (intermediate risk) or 3 (high risk) resulting from the average of the sum obtained after grading each of the variables from 1 to 3 according to guideline cut-offs: WHO-FC (1 if I–II, 2 if III and 3 if IV), 6MWD (1 if >440 m, 2 if 440–165 m and 3 if <165 m), RAP (1 if <8 mmHg, 2 if 8–14 mmHg and 3 if >14 mmHg), cardiac index (1 if $\geqslant$2.5 L·min^{-1}·m^{-2}, 2 if 2.4–2.0 L·min^{-1}·m^{-2} and 3 if <2 L·min^{-1}·m^{-2}) and, when available, N-terminal pro-brain natriuretic peptide (1 if <300 ng·L^{-1}, 2 if 300–1400 ng·L^{-1} and 3 if >1400 ng·L^{-1}).

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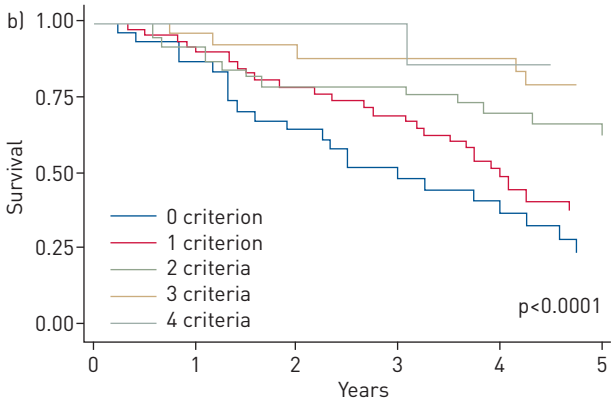
Sex- and age-adjusted Cox proportional hazards multivariate analysis was used to calculate hazard ratios for 1-year mortality of each parameter. Survival from diagnostic right heart catheterisation was assessed with Cox regression and Kaplan–Meier survival curves truncated at 5 years. A p-value <0.05 was considered significant. Statistical analysis was performed using Stata version 14 (StataCorp, College Station, TX, USA).

151 SSc-PAH patients, mostly female (84.8%), with a mean age of 61 years were analysed. The majority had limited SSc and WHO-FC II or III symptoms, with a reduced 6MWD, high RAP, normal wedge pressure, borderline low cardiac index, and elevated pulmonary vascular resistance.

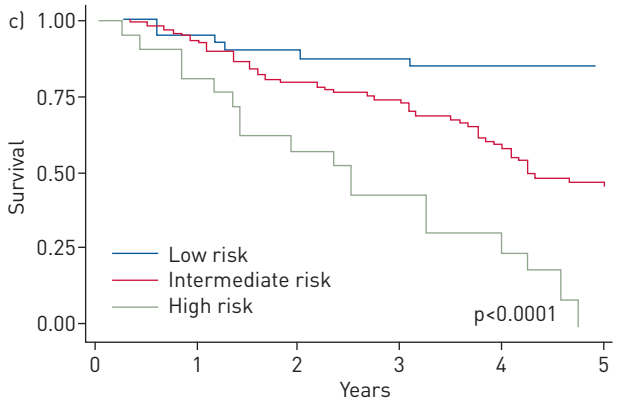
Hazard ratios for mortality in SSc-PAH patients on baseline parameters are reported in figure 1. First follow-up assessment was performed after at least 3 months from baseline (median 11.0 months). 92 patients had at least two parameters available at first follow-up (mainly 6MWD and WHO-FC); 19 (20.7%) had three, 31 (33.7%) had four and 17 (18.5%) had five parameters at follow-up. At first

a)

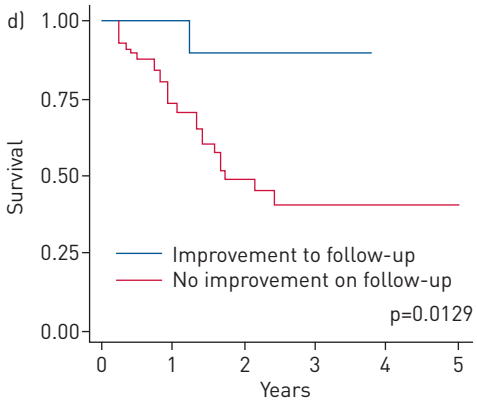
Parameter	Hazard ratio (CI)	p-value
WHO functional class		
I-II	Reference	N/A
III	2.65 (1.49–4.74)	0.001
IV	7.62 (3.52–16.52)	<0.0001
6MWD		
>440 m	Reference	N/A
165–440 m	2.70 (0.96–7.60)	0.059
<165 m	9.27 (3.03–28.35)	<0.0001
Right atrial pressure		
<8 mmHg	Reference	N/A
8–14 mmHg	0.96 (0.54–1.69)	0.882
>14 mmHg	2.51 (1.33–4.73)	0.004
Cardiac index		
≥2.5 L·min^{-1}·m^{-2}	Reference	N/A
2.0–2.4 L·min^{-1}·m^{-2}	2.14 (1.11–4.14)	0.024
<2.0 L·min^{-1}·m^{-2}	3.76 (2.08–6.81)	<0.0001
NTproBNP[#]		
<300 ng·L^{-1}	Reference	N/A
300–1400 ng·L^{-1}	1.45 (0.63–3.33)	0.386
>1400 ng·L^{-1}	2.74 (1.34–5.63)	0.006



At risk n						
0 criterion	31	27	20	14	10	5
1 criterion	48	43	36	31	22	16
2 criteria	38	35	30	27	20	18
3 criteria	26	25	23	22	20	17
4 criteria	8	8	7	7	6	5



At risk n						
Low risk	41	39	35	33	28	25
Intermediate risk	89	82	69	61	46	36
High risk	21	17	12	7	5	0



At risk n						
Low risk at follow-up	20	10	4	3	0	0
Intermediate or high risk at follow-up	72	31	13	6	3	3

FIGURE 1 a) Hazard ratios for mortality in systemic sclerosis (SSc)-pulmonary arterial hypertension (PAH) patients on baseline parameters using Cox proportional hazards multivariate analysis adjusted for age and sex. b) Kaplan–Meier curves for all-cause mortality from PAH diagnosis among SSc-PAH patients according to the presence at baseline of "green" low-risk criteria. c) Kaplan–Meier curves for all-cause mortality from PAH diagnosis among SSc-PAH patients according to the averaged risk score at baseline. d) Kaplan–Meier curves for all-cause mortality from the first follow-up among SSc-PAH patients according to change in risk category from baseline to first follow-up. WHO: World Health Organization; 6MWD: 6-min walk distance; NT-proBNP: N-terminal pro-brain natriuretic peptide; N/A: not applicable. [#]: available for 126 patients.

follow-up, 20 (21.7%) patients had a low-risk score, 65 (70.7%) had an intermediate-risk score and seven (7.6%) had a high-risk score. In particular, 10 (10.9%) patients out of 92 remained in the low-risk category, 10 (10.9%) improved from intermediate or high risk to low risk, 49 (53.2%) remained stable intermediate or high risk or improved from high to intermediate risk, and 23 (25%) deteriorated.

After a 38-month median follow-up, 87 deaths occurred. Overall 1-, 3- and 5-year survival was 91.4%, 66.9% and 40.4%, respectively.

When categorised according to the number of "green" criteria at baseline, 1-, 3- and 5-year survival rates were 100%, 87.5% and 62.5% for patients with four criteria; 96.2%, 84.6% and 65.4% for patients with three criteria; 92.1%, 71.1% and 47.4% for patients with two criteria; 89.6%, 64.6% and 33.3% for patients with one criterion, and 87.1%, 64.5% and 16.1% for patients with no "green" criterion.

When categorized according to the averaged risk score at baseline, 1-, 3- and 5-year survival rates were 95.1%, 80.5% and 61.0%, respectively, for patients with low-risk score; 92.1%, 68.5% and 40.4%, respectively, for patients with intermediate-risk score; and 81%, 33.3% and 0%, respectively, for patients with high-risk score.

Survival differed significantly among risk categories regardless of the method of categorization (log-rank $p<0.0001$) (figure 1).

At first follow-up, patients who remained or improved to low risk had a better prognosis in comparison to those who remained in the intermediate- or high-risk category or worsened (log-rank $p=0.01$) (figure 1). Survival also differed significantly when restricting this analysis to patients who had at least three variables available at follow-up (67 patients, log-rank $p=0.0065$; data not shown). Survival analysis according to the number of "green" criteria at first follow-up among the patients with at least three variables available at follow-up was borderline significant (log-rank $p=0.0626$; data not shown).

Our results demonstrate that an abbreviated version of the guideline risk assessment is accurate in predicting survival in newly diagnosed SSc-PAH. 1-year mortality rates, particularly according to the number of "green" criteria, corresponded well to the guidelines' estimated 1-year mortality [3]. This approach, previously proposed by Boucly *et al.* [6] and validated in their cohort of IPAH, hereditable and drug-induced PAH, is not only accurate in our SSc-PAH population but also easy to apply. Our data confirm and expand on previous findings by Kylhammar *et al.* [5] and Hoeper *et al.* [4]. Our study broadens the application of this risk assessment tool to SSc-PAH, which typically carries a dismal prognosis compared to other groups [11].

The risk stratification according to the average score also proved to be valid during follow-up assessment. Notably, only 22% of patients had a low-risk profile at follow-up, while 26.4% deteriorated, stressing the relative worse course of SSc-PAH and their blunted response to pulmonary vasodilator treatment.

Guideline validation in real-world cohorts is of essential importance. The multidimensional approach in risk assessment proposed in guidelines revealed to be powerful in terms of short-, mean- and long-term prognostication in our SSc-PAH cohort.

Among the study limitations, follow-up data were available only for 61% of patients. Additionally, we did not incorporate all of the parameters suggested in the guidelines (particularly syncope occurrence, echocardiographic and cardiopulmonary exercise testing-derived measurements). Nevertheless, the unavailability of this information is a common clinical scenario, thus reflecting the real-life setting. Furthermore, many patients were enrolled prior to the publication of high-impact studies supporting initial combination therapy in CTD-PAH [12, 13]. However, the majority of patients with SSc-PAH alive at 1 and 5 years were on dual or triple therapy. Lastly, this was a single-centre experience based on a relatively small and perhaps unique population, reflecting referral bias to our programme.

In conclusion, our study supports the use of a multidimensional approach to risk assessment in SSc-PAH and highlights the need for implementing treatment regimens and achieving a low-risk status.

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