Risk assessment and survival of patients with pulmonary hypertension: Multicenter experience in Turkey

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Abstract

Objective: Risk stratification continues to evolve in pulmonary arterial hypertension (PAH). Our aim was to further confirm the risk assessment strategy in our cohort and to determine the most reliable model.

Methods: We enrolled incident patients with idiopathic PAH (IPAH), heritable, drug-induced, congenital heart disease (CHD), connective tissue diseases (CTD) subsets, and chronic thromboembolic pulmonary hypertension (CTEPH) from January 2008 to February 2018. Data from the baseline and subsequent follow-ups within 1 year of diagnosis were included. An abbreviated risk assessment strategy was applied using the following variables: functional class (FC), 6-minute walk distance (6 MWD), N-terminal pro–brain natriuretic peptide (NT-proBNP) or BNP, right atrial (RA) area, pericardial effusion, the mean RA pressure, cardiac index, and mixed venous oxygen saturation. Three different methods were applied to categorize patients.

Results: A total of 189 subjects (46±17 years, 23% male) were included. Sixty-one patients had died. The survival differed significantly between the risk groups both at diagnosis and during the follow-up. Patients with a low-risk profile had a better survival rate. An abbreviated risk assessment tool predicted mortality at early follow-up in the entire group and CHD, CTD subsets, and CTEPH, separately. An overall mortality among risk categories was significantly different according to each categorization method. The most reliable model comprised FC, 6 MWD, NT pro-BNP/BNP, and the RA area at the follow-up.

Conclusion: The abbreviated risk assessment tool may be valid for the PAH subsets and CTEPH. Echocardiographic variables do matter. A model comprising FC, 6 MWD, NT pro-BNP/BNP, and the RA area at the follow-up could be useful for better prognostication. *(Anatol J Cardiol 2019; 21: 322-30)*

Keywords: chronic thromboembolic pulmonary hypertension, pulmonary arterial hypertension, pulmonary arterial hypertension subsets, risk assessment, survival

Introduction

Risk stratification and treatment strategies still continue to evolve in pulmonary arterial hypertension (PAH). Guidelines have recommended a goal-oriented treatment approach since 2009, and a comprehensive risk assessment using a risk assessment instrument is also recommended (1, 2), which has been recently evaluated in multiple registries. The estimated mortality risk predictors reported in the guidelines have been studied mostly in idiopathic PAH. Kylhammar et al. (3) reported that the use of comprehensive risk assessments and in particular the recommendation of achieving a low-risk profile are valid in PAH. Hoeper et al. (4) reported that an abbreviated version of the risk assessment strategy proposed by the guidelines provides accurate mortality estimates in patients with PAH. Boucly et al. (5) reported that a simplified risk assessment tool that quantifies the number of low-risk criteria present accurately predicted transplant-free survival in PAH. Despite these important insights from the mentioned studies, several questions regarding the risk assessment remain: it is still unclear whether the risk assessment tool is useful equally for the PAH subsets, such as associated PAH [connective tissue diseases, congenital heart disease or portopulmonary hypertension (PoPH)], which were not well represented in those studies, and it is still unknown whether this tool is applicable to chronic thromboembolic pulmonary hypertension (CTEPH); in addition, there is limited evidence regarding the use of risk assessment in sclero-

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derma-associated PAH and CTEPH: Mercurio et al. (6) suggested that an abbreviated version of the risk assessment may be valid to estimate the mortality risk in scleroderma-related PAH, and Sandqvist et al. (7) suggested that the risk assessment strategy could follow the same principles in CTEPH as for PAH. Follow-up assessments were not standardized, that is, not all variables included in the risk stratification strategy proposed by the guidelines were available at the follow-up, which limited the ability to fully analyze the predictive value of invasive and noninvasive variables; it was assumed that invasive and noninvasive criteria bore equal weight on risk assessment. Therefore, further independent confirmation of the risk assessment strategy in real-world cohorts that are enriched in those subsets is needed. It is still unknown how many low-risk criteria must be present to identify a particular patient as truly low risk or intermediate risk. Serial follow-up assessments using noninvasive variables would be preferable to those that incorporate invasive hemodynamic variables; particularly the addition of echocardiography to the assessment criteria could further improve the prognostic utility, and alternative models might provide even better prognostication.

The objectives of the present study were to apply the PAH risk assessment tool presented in the recent guidelines to an incident cohort of patients enriched with those subsets and CTEPH, and to test the benefit of reaching a low-risk profile at early follow-up. We aimed to determine survival according to the mean grade, the number of low-risk criteria, and the number of high-risk criteria at diagnosis and during the first year of treatment, to determine the most reliable subset of variables, and to explore the ability of the European Society of Cardiology/ European Respiratory Society (ESC/ERS) guidelines' risk assessment tool to accurately predict mortality in our cohort.

Preliminary results of this study have been recently reported in the form of an abstract (8).

Methods

The study design was retrospective. This study collected data from patients with PAH including idiopathic (IPAH), heritable, drug induced, and associated with other diseases [congenital heart disease (CHD), connective tissue disease (CTD), PoPH] and inoperable or residual CTEPH after pulmonary endarterectomy with the follow-up period of at least 1 year. From January 2008 to February 2018, all incident cases with available follow-up data were enrolled from five PAH centers. The study protocol was approved by the Medical Ethics Committee of the university of the lead investigator. The designation of PAH subset according to the current guidelines was based on the diagnosis provided by the treating physician. PAH was defined by right-heart catheterization (RHC) exhibiting a mean pulmonary artery pressure (mPAP) of 25 mm Hg or greater at rest and a pulmonary artery wedge pressure (PAWP) or left ventricular end-diastolic pressure of 15 mm Hg or less at normal or reduced cardiac output, according to the 2009 guidelines, or a mPAP ≥25 mm Hg, a PAWP ≤ 15 mm Hg, and a pulmonary vascular resistance (PVR) >3 WU, according to the 2015 guidelines. PAH therapy had been given at the discretion of the treating physician. Survival status was determined by the treating physician by either contacting the patient or checking an electronic database. Data from the baseline and subsequent follow-ups within 1 year of diagnosis and 5 years after diagnosis were included. Either brain natriuretic peptide (BNP) or N-terminal pro-brain natriuretic peptide (NT pro-BNP) was included. A recently validated and abbreviated version of the risk assessment strategy proposed by the recent European PH guidelines was applied, using the following variables: the World Health Organization (WHO) functional class (FC), 6-min walking distance (6 MWD), NT-proBNP/BNP, right atrial area (RAA), pericardial effusion (PE), mean right atrial pressure (RAP), cardiac index (CI), and mixed venous oxygen saturation (mVO2), which were graded 1–3 according to cut-off values, where 1=low risk, 2=intermediate risk, and 3=high risk. Dividing the sum of all grades by the number of variables for each patient rendered a mean grade, which defined the patients' risk group (3). Three different methods were applied to categorize patients using the abbreviated variables of the risk table of European PH Guidelines: 1) according to the presence of none, 1, 2, 3, 4, 5, 6, 7, or 8 of the following low-risk criteria (5): WHO FC I-II, 6 MWD>440 m, NT pro-BNP<300 ng/L or BNP<50 ng/L, RAA <18 cm^2, absence of PE by echocardiography, RAP<8 mm Hg, CI ≥2.5 L/min/m^2, and mVO2 > 65%; 2) according to the presence of none, 1, 2, 3, 4, 5, 6, 7, or 8 of the following high-risk criteria: WHO FC IV, 6 MWD<165 m, NT pro-BNP>1400 ng/L or BNP>300 ng/L, RAA>26 cm^2, presence of PE by echocardiography, RAP>14 mm Hg, CI<2 L/min/m^2, and mVO2<60%; 3) according to a mean grade of 1 (low risk), 2 (intermediate risk), or 3 (high risk) (3).

Statistical analysis

Data were collected, checked, and entered by the treating physician. The Kaplan-Meier curves were constructed, and the Gehan–Breslow tests were performed to compare survival distributions. Survival analysis was performed using the Kaplan–Meier analysis. Survival analyses were performed for the entire group and separately for the IPAH, CTD, CHD subsets, and CTEPH. The univariate Cox proportional hazard regression model was used to test baseline variables associated with survival, followed by the multiple Cox proportional hazard regression model to examine the independent effect of selected variables on survival, controlling for possible confounders. To determine the most reliable subset of variables as to identify the risk status of an individual patient, Quadratic Discriminant Analysis models have been created. We used this method because the variables in our dataset were not normally distributed. The level of statistical significance was set at $p \leq 0.05$. Statistical analysis was performed using the SPSS v.24.0 for Windows (SPSS Inc., Armonk, NY, USA), R (version 3.4.3, Vienna, Austria) in RStudio (Version 1.1.463–© 2009–2018 RStudio, Inc.).

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Packages used for the analysis were survAUC, survminer, ggplot2, and DiscriMiner (9-14).

Results

Baseline characteristics of 189 subjects are shown in Table 1. The mean age was 46±17 years, and 23% were male. Sixty-one (32%) patients had died. One-third of the patients had CHD. Only 9 patients with IPAH were ≥65 years. The majority of the patients were in WHO FC III. Sixteen percent of patients were ≥65 years, who had significantly more hypertension (HT), diabetes mellitus (DM), obesity, and CAD than patients <65 years. The presence of HT (p=0.010) and CAD (p=0.026) increased the risk of death. At diagnosis, all variables of the tool but WHO FC and RAA were significantly associated with increased risk of death on univariate analysis, whereas age, 6MHW, and mean grade had the most effect on mortality. On multiple analysis after the adjustment for age and specific comorbidities, only 6 MWD remained associated with mortality. During the follow-up, all criteria of the guidelines were significantly associated with survival, whereas 6MHW and mean grade had the most effect on mortality. On multiple analysis after adjustment for age and specific comorbidities, age and the presence of PE remained associated with mortality (Table 2). The number of low risk criteria and the number of high risk criteria were associated with mortality at early follow up: as the ratio of low risk criteria increased, the survival increased (Fig. 1).

Table 1. Baseline characteristics

	Frequency (n)	Percentage (%)
Age 65 (</≥)	159/30	84.1%/15.9%
Age at diagnosis**	46.34±16.95	48 (16-82)
Gender (Female/Male)	145/44	76.7%/23.3%
HT (+/-)	43/146	22.8%/77.2%
DM (+/-)	24/165	12.7%/87.3%
CAD (+/-)	11/178	5.8%/94.2%
Obesity	23/166	12.2%/87.8%
CHD	63	33.3%
CTD	42	22.2%
CTEPH	29	15.3%
IPAH	42	22.2%
Po PH	4	2.1%
Heritable	6	3.2%
Drug induced	3	1.6%
WHO FC II	39	20.6%
WHO FC III	129	68.3%
WHO FC IV	21	11.1%

**Mean±standard deviation and Median (min.–max.) values are given
CAD - coronary artery disease; CHD - pulmonary arterial hypertension associated with congenital heart disease; CTD - pulmonary arterial hypertension associated with connective tissue disease; CTEPH - chronic thromboembolic pulmonary hypertension; DM - diabetes mellitus; IPAH - idiopathic pulmonary arterial hypertension; PoPH - portopulmonary hypertension

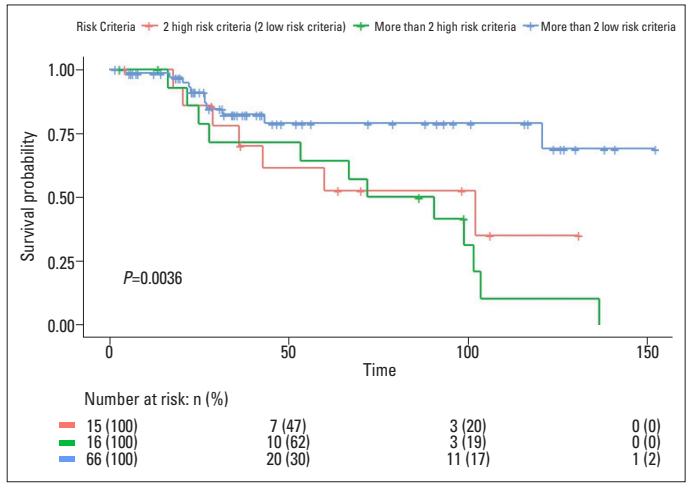

Figure 1. Survival plot according to the number of low-/high-risk criteria at early follow-up

Survival differed significantly between the risk groups both at diagnosis and during the follow-up (p<0.001). Patients with a low-risk profile had better survival than those with worse risk profiles (Fig. 2). Abbreviated risk assessment tool predicted mortality better at early follow-up (1 year mortality: 0% in low risk, 5% in intermediate risk, and 12% in high risk groups) than at diagnosis (1 year mortality: 0% in low risk, 5% in intermediate risk, and 5% in high risk groups). At diagnosis, 20% of patients were low risk, 69% were intermediate risk, and 11% were high risk. During follow-up, 36% of patients were low risk, 46% were intermediate risk, and 18% were high risk. Sixteen percent of low-risk patients at diagnosis remained low risk during the follow-up, 37% of intermediate risk patients remained intermediate risk during the follow-up, and 5% of high risk patients remained high risk during the follow-up (Fig. 3). Survival rates for PAH subsets and CTEPH are shown in Table 3. Due to small number of patients in PoPH, heritable and drug-related PAH, we could not analyze mortality separately in these subsets. Mortality did not differ by gender.

Abbreviated risk assessment tool predicted mortality at diagnosis in CHD, CTD subsets, and during the follow-up in CHD, CTD, subsets and CTEPH (Fig. 4, 5).

According to our quadratic discriminant analysis model; The most reliable subset of variables were the functional class, 6 MWD, NT pro-BNP/BNP, and the RA area by echocardiography at follow-up, which predicted the mean grade with an 11% error rate.

Discussion

The main finding of this study was that the risk assessment criteria proposed in the 2015 ESC/ERS guidelines accurately predicted the mortality in incident patients with PH during the

Table 2. Univariate and multiple cox proportional hazard regression analysis of parameters both at diagnosis and follow-up associated with survival

Diagnosis	Univariate analysis			Multiple analysis		
	Hazard ratio (95% CI)	Wald	*P*-value	Hazard ratio (95% CI)	Wald	*P*-value
Gender (Ref: Female)	0.935 (0.513-1.702)	0.049	0.825	-		-
Age (+)	1.057 (1.038-1.077)	34.28	<0.001*	1.028 (0.995-1.061)	2.788	0.095
Hypertension (Ref: Absent) (+)	2.143 (1.204-3.814)	6.71	0.010*	1.393 (0.524-3.701)	0.441	0.507
Diabetes (Ref: Absent)	1.648 (0.83-3.27)	2.039	0.153	-		-
Coronary artery disease (Ref: Absent) (+)	2.918 (1.14-7.468)	4.987	0.026*	0.378 (0.044-3.259)	0.783	0.376
Obesity (Ref: Absent)	1.401 (0.629-3.118)	0.682	0.409	-		-
WHO FC at diagnosis	1.46 (0.998-2.137)	3.798	0.051	-		-
6 MWD at diagnosis (+ ; +)	3.424 (2.153-5.446)	27.05	<0.001*	2.246 (1.062-4.749)	4.481	0.034*
NT pro-BNP at diagnosis (+)	1.633 (1.076-2.479)	5.312	0.021*	1.158 (0.677-1.983)	0.287	0.592
RA area at diagnosis	1.171 (0.788-1.741)	0.609	0.435	-		-
Pericardial effusion at diagnosis (+)	1.804 (1.345-2.42)	15.49	<0.001*	1.324 (0.859-2.040)	1.619	0.203
Mean RAP at diagnosis (+)	1.47 (1.036-2.087)	4.657	0.031*	0.938 (0.513-1.713)	0.044	0.834
CI at diagnosis (+)	1.384 (1.006-1.904)	3.985	0.046*	1.331 (0.811-2.187)	1.278	0.258
mVO2 at diagnosis (+)	2.028 (1.429-2.879)	15.64	<0.001*	1.405 (0.911-2.167)	2.367	0.124
Mean grade at diagnosis (+)	3.032 (1.868-4.922)	20.16	<0.001*	-		-
Ratio of low risk criteria >0.5 at diagnosis (–)	0.045 (0.011-0.179)	19.55	<0.001*	-		-
Follow up	**Hazard ratio (95% CI)**	**Wald**	***P*-value**	**Hazard ratio (95% CI)**	**Wald**	***P*-value**
Gender (Ref: Female)	0.935 (0.513-1.702)	0.049	0.825	-		-
Age (+; +)	1.057 (1.038-1.077)	34.28	<0.001*	1.056 (1.003-1.113)	4.234	0.040*
Hypertension (Ref: Absent) (+)	2.143 (1.204-3.814)	6.71	0.010*	1.856 (0.446-7.719)	0.724	0.395
Diabetes (Ref: Absent)	1.648 (0.83-3.27)	2.039	0.153	-		-
Coronary artery disease (Ref: Absent) (+)	2.918 (1.14-7.468)	4.987	0.026*	**		**
Obesity (Ref: Absent)	1.401 (0.629-3.118)	0.682	0.409	-		-
WHO FC at follow-up (+)	1.839 (1.429-2.366)	22.46	<0.001*	0.554 (0.248-1.236)	2.082	0.149
6 MWD at follow-up (+)	4.172 (2.569-6.776)	33.33	<0.001*	1.606 (0.581-4.444)	0.833	0.361
NT pro-BNP at follow-up (+)	2.86 (1.773-4.613)	15.54	<0.001*	1.002 (0.412-2.435)	0	0.997
RA area at follow-up (+)	1.833 (1.247-2.693)	9.506	0.002*	0.763 (0.278-2.092)	0.276	0.599
Pericardial effusion at follow-up (+; +)	2.137 (1.624-2.811)	29.4	<0.001*	2.224 (1.058-4.675)	4.445	0.035*
Mean RAP at follow-up (+)	2.131 (1.2-3.784)	6.67	0.010*	1.21 (0.428-3.423)	0.129	0.72
CI at follow-up (+)	1.938 (1.238-3.034)	8.361	0.004*	1.611 (0.628-4.133)	0.984	0.321
mVO2 at follow-up (+)	2.26 (1.403-3.64)	11.23	0.001*	1.419 (0.688-2.926)	0.898	0.343
Mean grade at follow-up (+)	3.529 (2.387-5.219)	39.92	<0.001*	-		-
Ratio of low-risk criteria >0.5 at follow-up (–)	0.009 (0.002-0.036)	44.76	<0.001*	-		-

**P*<0.05 statistically significant; **Could not compute due to a small number of patients.
Ref - reference group; CI - cardiac index; mVO2 - mixed venous oxygen saturation; 6 MWD - 6-minute walk distance; NT pro-BNP - N-terminal pro–brain natriuretic peptide; RA - right atrial; RAP - right atrial pressure; WHO FC - World Health Organization functional class; Harrell C value for multiple model at diagnosis, 0.663; Harrell C value for multiple model at follow-up, 0.717; variables with (+) decrease survival time and increase mortality rate at diagnosis; variables with (–) increased survival time and a decreased mortality rate at diagnosis; variables with (+; +) decreased survival time and an increased mortality rate at both diagnosis and follow-up; variables of European PH guidelines' risk table were graded 1–3 according to cut-off values, where 1=low risk, 2=intermediate risk, and 3=high risk (HR values show a 1-point-increase status)

first year of treatment. The number of low-risk criteria achieved during the first year of follow-up discriminated patients at low risk better than did the number of criteria present at baseline. The number of high-risk criteria remaining during the first year of follow-up discriminated patients at high risk better than did the number of criteria present at baseline. Risk prediction proved accurate for subsets of patients with associated PAH and CTEPH. Echocardiographic parameters do matter. A model comprising

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Table 3. Survival in patients with pulmonary arterial hypertension subsets and chronic thromboembolic pulmonary hypertension

	CHD	CTD	CTEPH	IPAH	Total
Patients. n	**63**	**42**	**29**	**42**	**176**
Survival (%)					
At 1 year	96.80%	95.20%	93.10%	100.00%	96.60%
	143.57±11.75	50.8±6.8	84.94±11.15	106.28±10.39	121.3±8.53
	(120.55-166.6)	(37.47-64.13)	(63.07-106.8)	(85.91-126.65)	(104.58-138.02)
At 3 year	88.90%	66.70%	75.90%	88.10%	81.30%
	155.87±11.66	68.43±8.55	109.66±8.63	119.87±10.21	145.13±9.35
	(133.01-178.74)	(51.68-85.18)	(92.75-126.58)	(99.87-139.88)	(126.81-163.45)
At 5 year	84.10%	57.10%	72.40%	81.00%	75.00%
	163.97±11.67	83.38±13.33	117.01±5.54	131.91±9.24	160.52±9.71
	(141.49-179.55)	(57.25-109.51)	(106.15-127.88)	(113.8-150.02)	(141.11-186.84)
At Total	69.80%	52.40%	69.00%	73.80%	66.50%
	139.07±1.77	48.54±6.66	78.41±11.12	106.28±10.39	117.18±8.39
	(115.99-162.14)	(35.49-61.58)	(56.62-100.2)	(85.91-126.65)	(100.74-133.61)

Survival time estimations are presented as the mean±standard error (95% confidence interval: lower bound–upper bound)
CHD - pulmonary arterial hypertension associated with congenital heart disease; CTD - pulmonary arterial hypertension associated with connective tissue disease; CTEPH - chronic thromboembolic pulmonary hypertension; IPAH - idiopathic pulmonary arterial hypertension

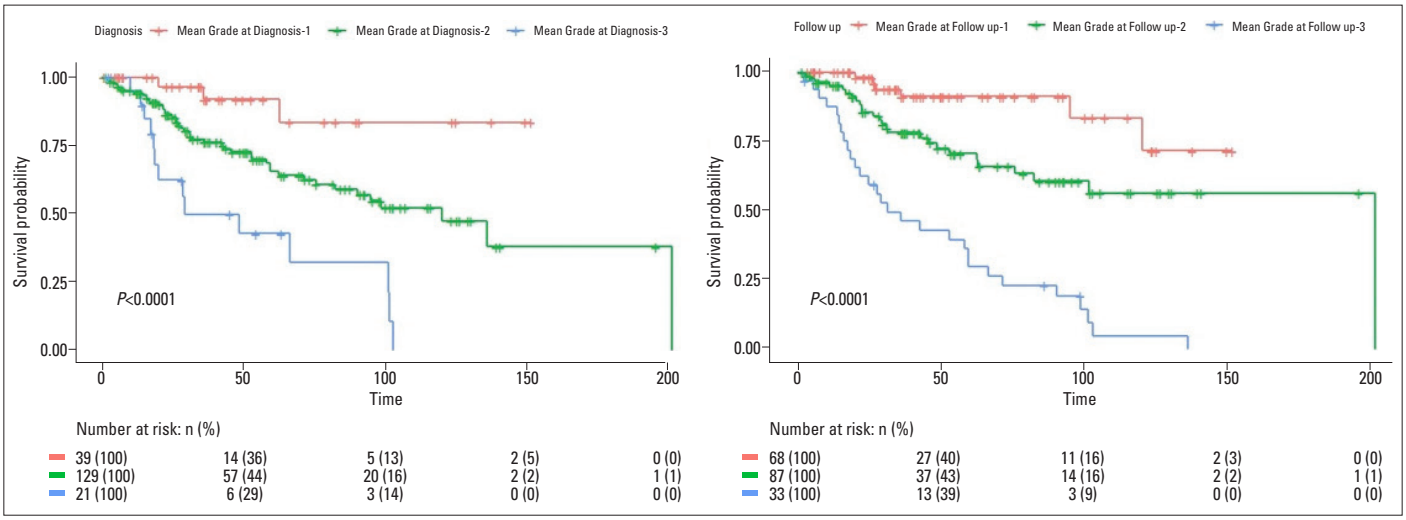

Figure 2. Survival plot of the entire group according to the mean grade (1=low, 2=intermediate, and 3=high risk) at diagnosis (left) and early follow-up (right)

WHO FC, 6 MWD, NT pro-BNP/BNP, and RAA at early follow-up could be useful for better prognostication.

The present study like recently reported registries supports the use of comprehensive risk assessments and the recommendation of achieving a low-risk profile as well (2). However, at diagnosis, the categorization into a high-risk group according to the score derived from guidelines' cut-off values was not consistent with ESC/ERS guidelines' estimated 1-year mortality. One-year mortality rates based on the follow-up risk groups corresponded well to those suggested by the guidelines. This is in line with previous findings by Kylhammar and Hoeper who used basically the same subset of variables (3, 4). In the present analysis, we found the following 1-year mortality: 0% in low-risk, 5% in intermediate-risk, and 12% in high-risk groups at the follow-up, which corresponded well to their findings.

Patients with CHD have the best survival (89% and 84% at 3 and 5 years, respectively); this is in line with previous reports, showing good long-term survival in patients with CHD (15-17). The survival of patients with IPAH is better than outcomes from the PHSANZ, US-REVEAL, European COMPERA, and UK and Ire-

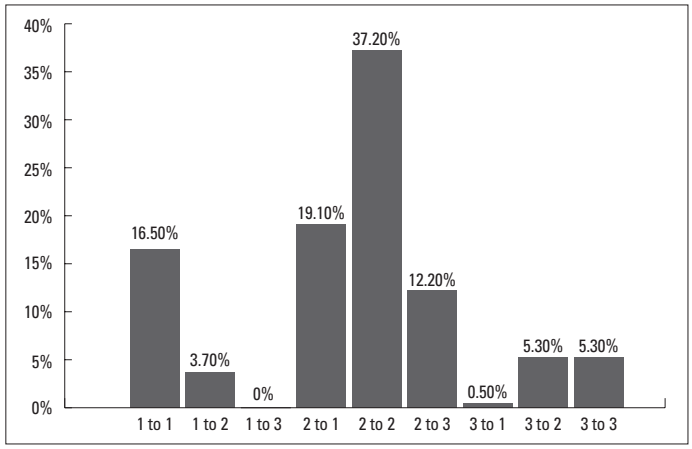

Figure 3. Change of the risk groups during follow-up (1=low, 2=intermediate, and 3=high risk)

land registries (18-21). It is conceivable that our higher survival rates could be due to the fact that the vast majority of IPAH group had a mean grade of 1 at diagnosis, and 36% had received combination therapy at diagnosis. The survival of patients with CTD (66% and 57% at 3 and 5 years, respectively) compares favorably with outcomes from the Giessen PH registry (9). The survival of our CTEPH group (76% and 72% at 3 and 5 years, respectively) is similar to results from some CTEPH registries (22-24) and slightly better than those from others (15, 25).

In our analysis, patients attaining more low-risk criteria at the follow-up had a better long-term prognosis than those who attained fewer low-risk criteria. Furthermore, patients achieving or maintaining fewer high-risk criteria had a better long-term prognosis than those with more high-risk criteria during the follow-up. Similarly to previous registry studies of IPAH patients, we observed that clinical variables in response to initial management predicted long-term prognosis better than did baseline values (3, 5). In our study, 20% of patients presented in the low-risk group at the time of diagnosis. This proportion increased to 36% during early follow-up, which is slightly better than results from other registries (3, 4). By comparison, intermediate- and high-risk patients remained at 64% at early follow-up, which reflects the limitations of current treatment options and strategies such as underutilization of parenteral prostanoids due to several reasons, or the graveness of the disease. The enrollment period for the present analysis started in 2008, when there was less evidence for the combination therapy. In addition, the combination therapy was sometimes not available in this country. It is also possible

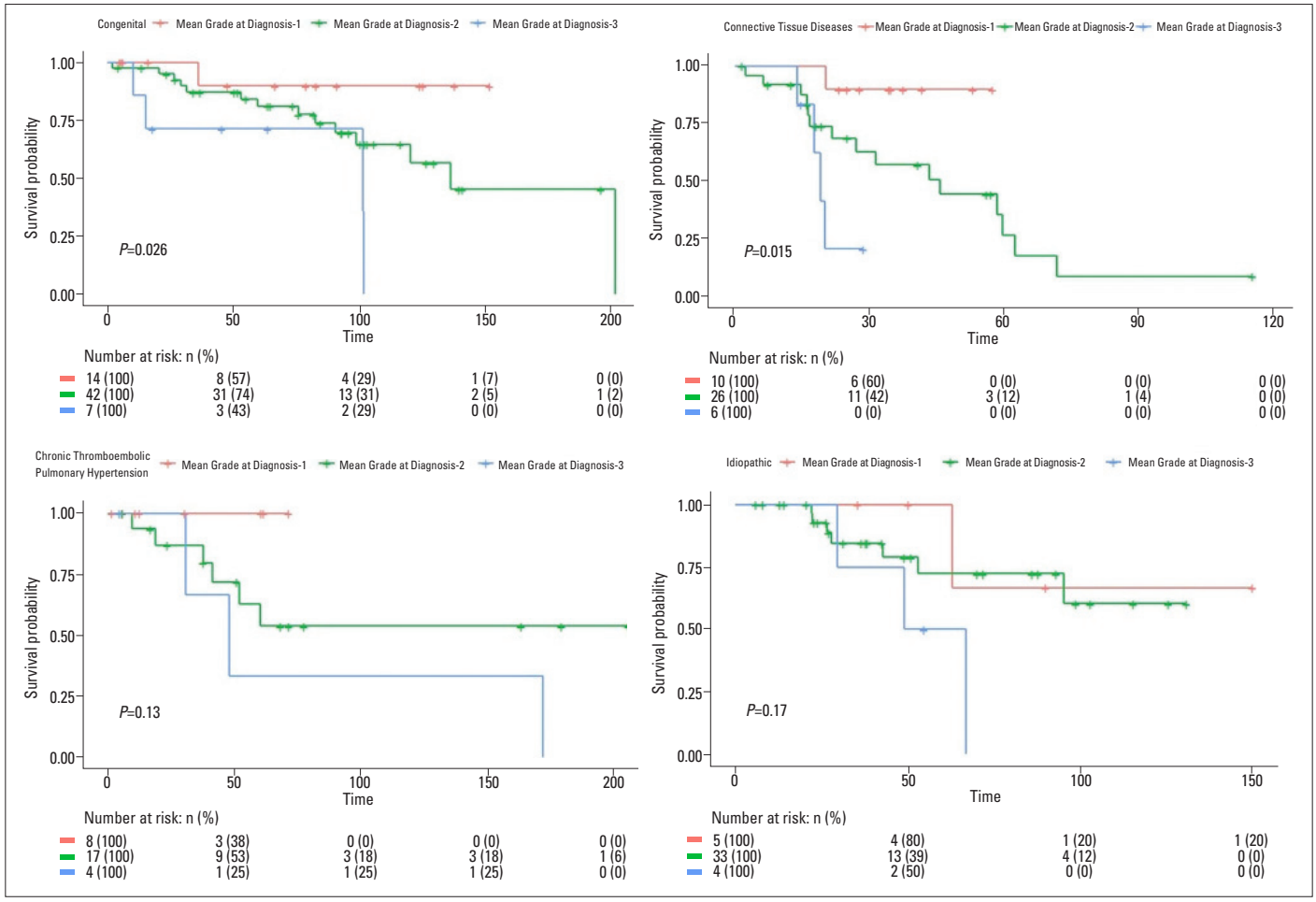

Figure 4. Survival plots of subsets of pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension according to the mean grade at diagnosis (1=low, 2=intermediate, and 3=high risk)

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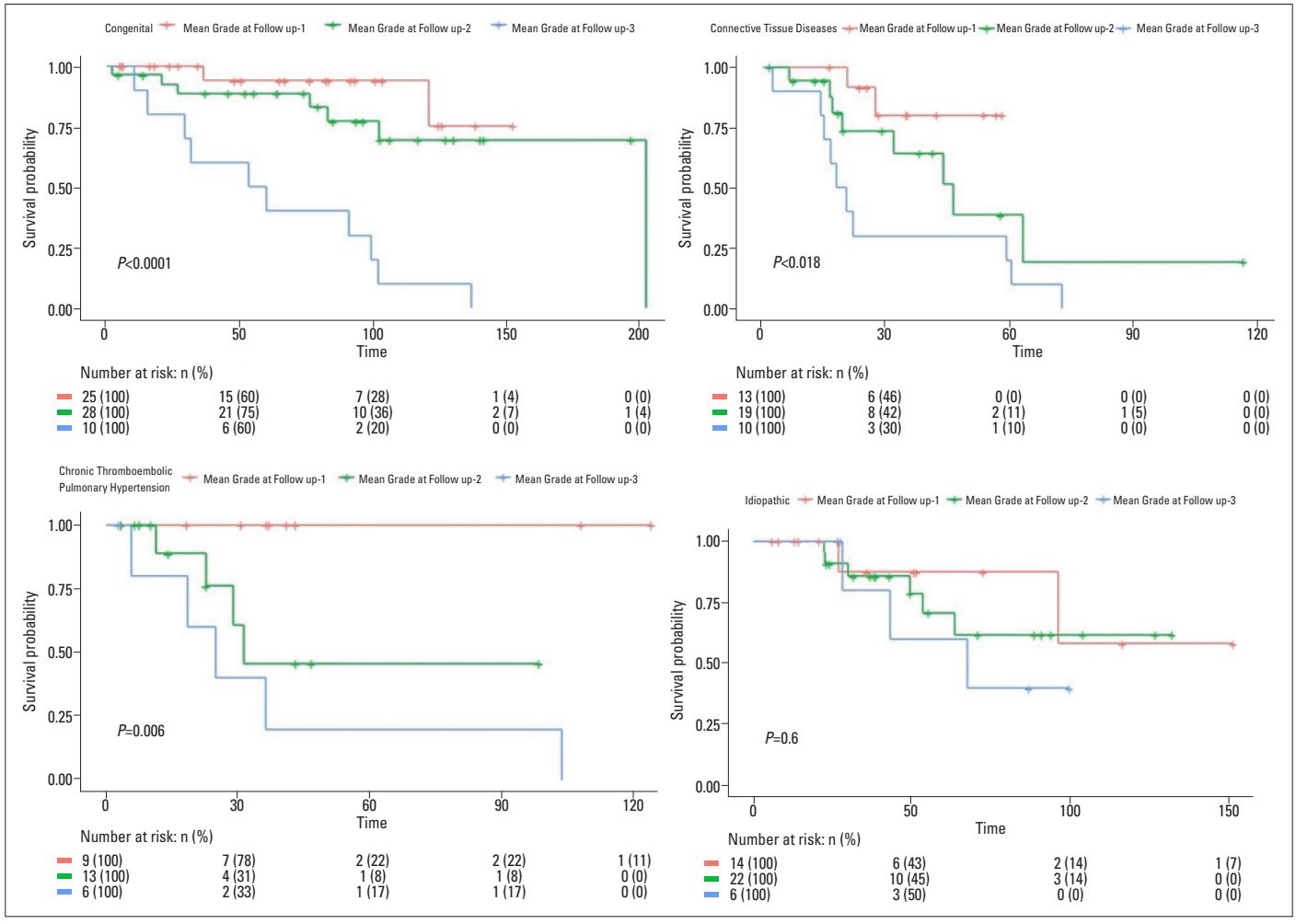

Figure 5. Survival plots of subsets of pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension according to the mean grade at early follow-up (1=low, 2=intermediate, and 3=high risk)

that the presence of comorbidities could have led physicians to prefer monotherapies.

We have demonstrated the importance of the mean grade, the absolute number of low- and high-risk criteria present both at baseline and during early follow-up, which is in line with a previous study by Boucly et al. (5). We extended these findings to other subsets of PAH, namely CHD and CTD, and CTEPH. Our study evaluated eight modifiable clinical and hemodynamic variables, which were useful both at diagnosis and follow-up. In a study of 109 patients, Nickel et al. (26) assessed prognosis according to changes in each variable individually and demonstrated that response to therapy was at least as important as baseline values in terms of known prognostic factors. Age and 6 MWD were associated with survival across all subsets in multivariate Cox regression analysis, which is consistent with the findings of the PHSANZ registry (15). Pulmonary hypertension registries have recently showed that the prevalence among the elderly is increasing (15, 19, 21, 22), with a mean age of 50 to 65 years reported at diagnosis. In this study, patients aged ≥65 years had more HT, DM, and CAD, and the presence of HT and CAD was associated with an increased risk of death. These findings suggest that specific comorbidities may be important as prognostic markers of outcome and could be taken into account in risk assessment. Kaymaz et al. (27) have recently evaluated several risk assessment strategies and proposed a novel risk scheme called "dart to the target". This "smart-looking" risk scheme could be useful if each parameter was taken into account based on its weight on risk assessment. However, as the authors noted, each parameter could bear different weight on survival as reported in previous registries (15, 18). We believe that there is still an unmet need to define prognostic value of each and subsets of prognostic variables in prospective studies.

Study limitations

This is a retrospective and observational study with a small sample size compared to other registries. We studied a cohort of patients from five different regions, and therefore survival data may be representative of the PH population. We have included all patients from five PAH centers with all noninvasive variables recommended in the guidelines, which were available both at diagnosis and follow-up. We had invasive variables in only 40% of patients at follow-up, which somewhat limited the comparison

of invasive vs. noninvasive criteria; however, this is unlikely to have introduced selection bias. Our findings reflect treatment of patients with PH in the modern era. Long-term response to therapy beyond 1 year was not assessed. Our survival analyses for the entire group were more reliable than survival analyses performed separately for the IPAH, CTD, CHD subsets, and CTEPH due to small sample sizes, which could only suggest a trend.

Conclusion

Our findings suggest that a comprehensive risk assessment at early follow-up using an abbreviated version of the risk assessment instrument could be valid to estimate the mortality risk in incident patients with PAH and inoperable or residual CTEPH. A goal-oriented management strategy (achieving a low-risk profile at early follow-up) could be useful. Specific comorbidities should be taken into account in risk assessment as the mean age is increasing at diagnosis. We propose a model comprising WHO FC, 6 MWD, NT pro-BNP/BNP, and RAA at early follow-up, which could be useful for better prognostication.

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