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ORIGINAL ARTICLE

Risk stratification in chronic thromboembolic pulmonary hypertension predicts survival

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ABSTRACT

Objectives. To investigate if the pulmonary arterial hypertension (PAH) risk assessment tool presented in the 2015 ESC/ERS guidelines is valid for patients with chronic thromboembolic pulmonary hypertension (CTEPH) when taking pulmonary endarterectomy (PEA) into account. *Design.* Incident CTEPH patients registered in the Swedish PAH Registry (SPAHR) between 2008 and 2016 were included. Risk stratification performed at baseline and follow-up classified the patients as low-, intermediate-, or high-risk using the proposed ESC/ERS risk algorithm. *Results.* There were 250 CTEPH patients with median age (interquartile range) 70 (14) years, and 53% were male. Thirty-two percent underwent PEA within 5 (6) months. In a multivariable model adjusting for age, sex, and pharmacological treatment, patients with intermediate-risk or high-risk profiles at baseline displayed an increased mortality risk (Hazard Ratio [95% confidence interval]: 1.64 [0.69–3.90] and 5.39 [2.13–13.59], respectively) compared to those with a low-risk profile, whereas PEA was associated with better survival (0.38 [0.18–0.82]). Similar impact of risk profile and PEA was seen at follow-up. *Conclusion.* The ESC/ERS risk assessment tool identifies CTEPH patients with reduced survival. Furthermore, PEA improves survival markedly independently of risk group and age.

Take home message: The ESC/ERS risk stratification for PAH predicts survival also in CTEPH patients, even when taking PEA into account.

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CTEPH; risk stratification; survival; pulmonary endarterectomy; goal-oriented treatment

Introduction

Chronic thromboembolic pulmonary hypertension (CTEPH) is a rare progressive pulmonary vascular disease characterised by macroscopic thromboembolic lesions and microscopic pulmonary vascular changes [1,2]. It is generally believed that an acute episode of pulmonary embolism initiates the development of CTEPH, with an incidence of 0.6–4.4% [3]. The clinical consequence of these pathological changes increased pulmonary vascular resistance (PVR) leading to right heart failure and death. If left untreated, the prognosis for CTEPH patients is poor, with a 5-year survival rate of 30% for patients with mean pulmonary arterial pressure (mPAP) >40 mmHg and only 10% for patients with mPAP >50 mmHg [4]. Pulmonary endarterectomy (PEA) is the recommended treatment of choice and many patients experience substantial relief with normalisation of haemodynamic parameters and improved survival [5,6]. However, when PEA is not eligible, due to inaccessible thromboembolic lesions or substantial comorbidities, or if PEA is unsuccessful, balloon pulmonary angioplasty and/or pharmacological treatment should be considered [1,7]. Currently, the soluble guanylate cyclase stimulator, riociguat, is the only approved treatment for symptomatic patients

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Supplemental data for this article can be accessed here.

with inoperable CTEPH or persistent or recurrent CTEPH after PEA [8–10]. Due to similar microvascular histopathological changes in CTEPH and pulmonary arterial hypertension (PAH) [1], off-label treatment with drugs, such as endothelin receptor antagonists, phosphodiesterase type 5 inhibitors, and drug therapies targeting the prostacyclin pathway, has been considered among inoperable CTEPH patients, as well as in patients with persistent or recurrent pulmonary hypertension (PH) after surgery [11–15].

The 2015 European Society of Cardiology (ESC) and European Respiratory Society (ERS) guidelines for the diagnosis and treatment of pulmonary hypertension presented a risk assessment tool for assessing mortality in PAH [1]. The validity of this risk assessment tool has been tested in PAH patients [16–18]. Recently, the risk assessment tool was also validated in CTEPH within the European based PH-registry, COMPERA [19]. The aim of the present study was to investigate if the risk assessment tool is valid in incident patients with CTEPH reported in the Swedish PAH Registry (SPAHR), taking the effect of PEA into account.

Methods

Study population and data source

The present study included incident cases of CTEPH registered in SPAHR, from 1 January 2008 to 31 December 2016. Data from baseline (date of diagnosis) and first clinical follow-up assessment within two years from baseline were included. The diagnosis of CTEPH was set according to international guidelines at each PAH centre [1].

Altogether 250 patients were included, and 170 of them had a follow-up assessment within two years. The discrepancy was due to PEA before follow-up ($n = 44$), death before follow-up ($n = 20$), no follow-up within two years ($n = 13$), reclassified diagnosis ($n = 2$), and no registered follow-up visit according to SPAHR ($n = 1$). All patients were followed to death, lung transplantation or to the 5th of May 2017, whichever came first. The follow-up period was truncated at 5 years.

SPAHR was established in 2008 and includes incident cases of PH from all seven Swedish PAH centres in Gothenburg, Linköping, Lund, Stockholm, Umeå, Uppsala, and Örebro. Data from baseline as well as from subsequent follow-ups are reported to SPAHR, which include information on date of diagnostic right heart catheterisation (RHC), demographics, WHO functional class, 6-minutes walking distance (6MWD), biochemical markers, echocardiography, comorbidities, PEA, and pharmacological treatments. The registry is approved by the National Board of Health and Welfare and the Swedish Data Protection Authority. The present study is conducted in accordance to the Declaration of Helsinki and approved by the Regional Ethical Review Board at Umeå University, Umeå, Sweden (Dnr. 2015/349-31). All patients are informed about their participation in SPAHR and have the right to decline, according to Swedish rules for participation in national quality registries.

Risk stratification

In accordance to the 2015 ESC/ERS guideline risk assessment tool, patients were categorised as low, intermediate, or high risk based on cut-off values for eight out of 13 variables; WHO FC, 6MWD, NT-proBNP, right atrial area, pericardial effusion, mean right atrial pressure (mRAP), cardiac index (CI), and mixed venous oxygen saturation (SvO_2). Using these variables the patients were assigned a risk score based on the SWEDISH model, as previously described [16]. Each risk variable in every patient was graded from 1 to 3, where 1 was low risk and 3 was high risk, and the sum of the points was divided by the number of variables and the result defined the risk of the individual patient. Risk assessment was performed both at baseline and first follow-up.

Statistics

Values were summarised as frequencies (%) for categorical variables and as median (interquartile range (IQR)) for continuous variables. Differences between groups were tested with the Kruskal–Wallis test and the Mann–Whitney *U* test when appropriate. Survival was analysed both at baseline and follow-up using the Kaplan–Meier method with Log-Rank test. Predictors for survival were determined with univariable and multivariable Cox proportional regression analyses. Hazard ratios with 95% confidence intervals are presented. The multivariable model included age, sex, PEA (no/yes), risk group (low/intermediate/high), and pharmacological treatment (no/yes). All analyses were also performed separately in patients <70 and ≥ 70 years at diagnosis (the median age of the cohort). A p value less than .05 was considered statistically significant. SPSS Statistics (IBM, Armonk, NY, USA) v.24 was used for analyses.

Results

A total of 250 patients with incident CTEPH were identified. Follow-up was reported for 170 patients with a median time from baseline of 6 (4–9) months. The baseline and follow-up characteristics based on the risk group are shown in Table 1. Median number of variables for risk stratification at baseline were 6 (6–7) and at follow-up 5 (4–5). The proportion of the variables used for risk stratification at baseline and follow-up are presented in Supplementary Material Table 1.

PEA

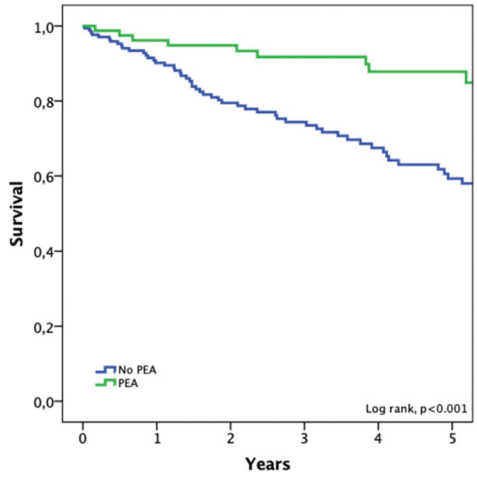
A total of 32% of all patients underwent PEA within a median of 5 (6) months after baseline (20% in the low-risk, 72% in the intermediate-risk, and 8% in the high-risk group). The 1, 3, and 5 years survival rates were 96%, 92%, and 88% for patients who underwent PEA, and 90%, 75%, and 59% for those without PEA ($p < .001$) (Figure 1). These differences remained after excluding patients ≥ 70 years at baseline (data not shown). PEA was associated with improved survival at baseline compared to non-operated patients even after adjustment for risk group,

Table 1. Baseline and follow-up characteristics stratified for risk profile in CTEPH patients.

	Baseline ($n = 250$)				Follow-up ($n = 170$)			
	All	Low risk	Intermediate risk	High risk	All	Low risk	Intermediate risk	High risk
N (%)		58 (23)	159 (64)	33 (13)		56 (33)	104 (61)	10 (6)
Age (year)	70 (62–76)	67 (57–72)	71 (64–76)*	70 (61–78)	72 (65–77)	70 (61–74)	73 (67–77)*	75 (67–82)*
Males (%)	53	66	49*	52	51	64	43*	60
WHO class (I/II/III/IV) (%)	0/20/74/6	0/51/49/0	0/13/84/3*	0/3/70/27*	1/37/61/1	2/77/21/0	1/20/78/1*	0/0/100/0*
6MWD (m)	355 (245–450)	462 (377–518)	344 (250–425)*	135 (95–271)*	378 (277–470)	488 (440–567)	320 (228–415*	255 (100–343)*
NT-proBNP (ng/L)	1262 (299–3320)	183 (73–279)	1490 (656–3247)*	4220 (3234–11,050)*	739 (195–2034)	175 (80–272)	1430 (435–2655)*	3130 (1795–9200)*
Co-morbidities								
Hypertension (%)	34	38	34	30				
Diabetes (%)	6	3	4	15*				
Atrial fibrillation (%)	8	5	5	24*				
Previous stroke (%)	5	3	6	3				
Ischaemic heart disease (%)	7	2	6	21*				
Thyroid disease (%)	8	2	11*	9				
Supportive therapy								
Anticoagulants (%)	96	95	97	94	98	96	98	100
Diuretics (%)	59	28	64*	94*	60	36	69*	100*
Oxygen (%)	18	3	20*	39*	20	4	26*	50*
PH-specific therapy								
sGC (%)	2	5	1	3	6	9	5	0
ERA (%)	29	14	33*	36*	37	27	42*	40
PDEi (%)	40	26	43*	49*	52	36	60*	70
Prostacyclin (%)	7	3	6	15*	6	4	5	30
Single therapy (%)	68	48	70*	91*	71	76	68	70
Dual therapy (%)	5	0	6	6	13	2	20*	20*
Triple therapy (%)	0	0	0	0	1	0	1	10

Data are presented as median (IQR) or proportions (%). WHO, World Health Organisation; 6MWD, 6-min walking distance; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; PEA, pulmonary endarterectomy; sGC, soluble guanylate cyclase agonist; ERA, endothelin receptor antagonist; PDE5i, phosphodiesterase type 5 inhibitor.

*p Value for comparison between low risk vs. intermediate risk and low risk vs. high risk was based on Kruskal–Wallis test and Mann–Whitney U test ($p < .05$).



Number exposed to risk						
Years	0	1	2	3	4	5
PEA	79	70	60	49	38	17
No PEA	171	128	97	76	58	29

Figure 1. Estimated five-year survival from date of diagnosis in operated patients versus not operated CTEPH patients.

pharmacological treatment, sex, and age (hazard ratio [95% confidence interval]: 0.38 [0.18–0.82]). Improved survival was seen in patients <70 years (0.11 [0.02–0.53]), but the impact of PEA was attenuated in those ≥70 years (0.80 [0.33–1.99]). Similarly, the point estimates indicated improved survival for those having PEA after the follow-up (0.57 [0.24–1.33]), although non-significant.

Risk stratification at baseline

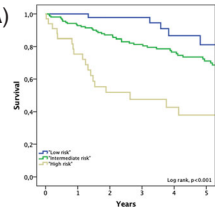
At diagnosis, 23% of the patients had a low-risk profile, 64% had an intermediate-risk profile, and 13% had a high-risk profile (Table 1). The 1, 3, and 5 years survival rates were 100%, 98%, and 82%, respectively, in the low-risk group; 93%, 81%, and 71%, respectively, in the intermediate-risk group; and 75%, 48%, and 38%, respectively in the high-risk group ($p < .001$) (Figure 2(A)). These differences remained after excluding patients ≥70 years at baseline (data not shown).

Patients in the intermediate-risk and high-risk groups displayed an increased mortality risk (1.64 [0.69–3.90] and 5.39 [2.13–13.60], respectively) compared to the low-risk group (Table 2). The differences remained after excluding patients ≥70 years at baseline (data not shown). The parameters of the risk score were tested individually, and high WHO FC, low 6MWD, high RAP, low CI, and low SvO_2 at baseline were associated with reduced survival (Table 3).

Risk stratification at follow-up

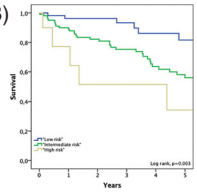
At follow-up, 33% of the patients had a low-risk profile, 61% had an intermediate-risk profile, and 6% had a high-risk profile (Table 1). Including all patients seen at follow-up, the survival 1, 3, and 5 years rates were, 96%, 93%, and 82%, respectively, in the low-risk group; 90%, 75%, and 56%, respectively, in the intermediate-risk group, and 78%, 52%, and 35%, respectively, in the high-risk group ($p = .003$) (Figure 2(B)). The difference remained after excluding patients ≥70 years at baseline (data not shown).

(A)



Number exposed to risk						
Years	0	1	2	3	4	5
Low risk	58	45	35	27	17	8
Intermediate risk	159	130	108	88	70	33
High risk	33	23	14	11	9	4

(B)



Number exposed to risk						
	0	1	2	3	4	5
Low risk	56	43	34	28	21	9
Intermediate risk	104	78	61	47	33	16
High risk	10	6	4	4	3	1

Figure 2. Estimated five-year survival in the entire study cohort based on individual (A) baseline risk ($n = 250$) and (B) follow-up risk ($n = 170$).

Patients in the intermediate-risk and high-risk groups displayed an increased mortality risk (2.78 [1.18–6.47] and 4.28 [1.30–14.08], respectively) compared to the low-risk group (Table 2). The differences remained after excluding patients ≥70 years at baseline (data not shown). At follow-up, the following parameters of the risk score were associated with reduced survival; high WHO FC, low 6MWD, and high NT-proBNP (Table 3).

Change in risk group between baseline and follow-up

Compared to the risk category status at baseline, 23% improved, 65% remained stable, and 12% worsened at follow-up. The 1, 3, and 5 years survival rates were 97%, 97%, and 90% in patients with stable low-risk group; 96%, 90%, and 75% in patients who improved to low-risk; 91%, 76%, and 60% in patients with stable intermediate-risk; 72%, 56%, and 34% in patients who improved to intermediate-risk; 94%, 86%, and 48% in patients who worsened to intermediate- or high-risk; and 80%, 40%, and 20% in patients with stable high-risk group ($p < .001$) (Figure 3). The difference

Table 2. Predictors for all-cause mortality based on risk profiles at baseline and follow-up.

	Univariable		Multivariable	
	HR (95% CI)	*p* Value	HR (95% CI)	*p* Value
Baseline (n = 250)				
Age	1.05 (1.03–1.08)	<.001	1.03 (1.01–1.06)	.011
Sex	1.58 (0.98–2.55)	.059	1.30 (0.78–2.15)	.304
PEA	0.25 (0.12–0.50)	<.001	0.38 (0.18–0.82)	.014
Risk stratification				
Low		.002		.000
Intermediate	1.95 (0.88–4.33)	.103	1.64 (0.69–3.90)	.265
High	6.33 (2.66–15.07)	<.001	5.39 (2.13–13.60)	<.001
PAH-specific therapy	2.00 (1.03–3–92)	.042	1.11 (0.54–2.30)	.779
Follow-up (n = 170)				
Age	1.04 (1.01–1.08)	.004	1.03 (1.00–1.06)	.087
Sex	1.23 (0.70–2.17)	.478	0.82 (0.45–1.50)	.526
PEA	0.57 (0.24–1.33)	.191	0.67 (0.28–1.64)	.382
Risk stratification				
Low		.006		.031
Intermediate	3.12 (1.39–7.031)	.006	2.78 (1.18–6.47)	.019
High	5.52 (1.75–17.42)	.004	4.28 (1.30–14.08)	.017
PAH-specific therapy	2.51 (0.78–8.06)	.123	1.72 (0.52–5.76)	.377

HR, hazard ratio; PEA, pulmonary endarterectomy. The discrepancy in numbers of patients between baseline and follow-up was due to PEA before follow-up ($n = 44$), death before follow-up ($n = 20$), no follow-up within two years ($n = 13$), reclassified diagnosis ($n = 2$) and no registered follow-up visit according to SPAHR ($n = 1$).

Table 3. Predictors of mortality in CTEPH patients based on individual risk variables.

	Baseline ($n = 250$)		Follow-up ($n = 170$)	
	HR (95% CI)	*p* Value	HR (95% CI)	*p* Value
WHO FC III–IV vs. I–II	2.52 (1.21–5.28)	.014	3.83 (1.79–8.22)	.001
6MWD ≤440 vs. >440 m	3.40 (1.34–8.59)	.010	3.53 (1.47–8.48)	.005
NT-proBNP ≥300 vs. <300 ng/L	1.91 (0.91–4.03)	.090	2.41 (1.16–4.99)	.018
SvO_2 ≤65% vs. >65%	2.40 (1.18–4.88)	.015	1.72 (0.37–8.03)	.491
CI ≤2.5 vs. >2.5 l/min/m^2	2.72 (1.34–5.51)	.005	1.60 (0.47–5.47)	.454
RAP ≥8 vs. <8 mmHg	2.97 (1.78–4.96)	<.001	2.62 (0.78–8.85)	.120
RA area ≥18 vs. <18 cm^2	2.28 (0.30–17.19)	.424	1.99 (0.75–5.28)	.167
Pericard fluid Yes vs. No	2.36 (0.73–7.63)	.151	1.52 (0.62–3.73)	.357

HR, hazard ratio; WHO, World Health Organisation; 6MWD, 6-min walking distance; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; SvO_2, mixed venous oxygen saturation; CI, cardiac index; RAP, right atrial pressure; RA, right atrium. The discrepancy in numbers of patients between baseline and follow-up was due to PEA before follow-up ($n = 44$), death before follow-up ($n = 20$), no follow-up within two years ($n = 13$), reclassified diagnosis ($n = 2$) and no registerde follow-up visit according to SPAHR ($n = 1$).

remained after excluding patients ≥70 years at baseline (data not shown).

Discussion

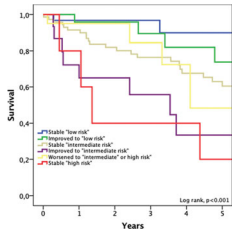
This study shows that the risk assessment strategy for PAH proposed in the 2015 ESC/ERS guidelines also predicts risk for mortality in CTEPH patients. Patients with a low-risk profile had a better long-term prognosis and survival than patients with intermediate or high-risk profiles. The estimated risk for mortality within one year in the 2015 ESC/ERS guidelines of <5%, 5–10%, and >10% in patients at low, intermediate, or high risk, respectively, were confirmed in CTEPH patients. This stratification tool was valid at both baseline and follow-up, even after taking the effect of PEA into account.

According to current guidelines, the main objective with risk stratification in PAH patients is to achieve and maintain a low-risk profile [1]. This has been confirmed in three studies from large European registries, showing also that the change in risk from baseline to follow-up was a strong predictor for survival and that achieving and maintaining a low-risk profile is associated with improved prognosis [16–18]. Similar findings have been presented for CTEPH patients according to the COMPERA registry [19].

In this study, and in accordance with recently findings in the CTEPH population [19,20], we show that achieving a low-risk profile in CTEPH is of high importance, since patients with low-risk profiles had better survival than patients with intermediate- or high-risk profiles at both baseline and follow-up. Notably, the 5-year mortality for patients with a stable low-risk profile at follow-up was similar (10%) to patients who underwent PEA (12%). In the COMPERA registry, the 5-year mortality for patients with a stable low-risk profile was 0% at follow-up [19]. Further, the 5-year mortality in SPAHR and COMPERA for patients with a low-risk or achieved low-risk profile at follow-up was 18% and 16%, respectively. Our findings strongly support that targeting and maintaining a low-risk profile is also a treatment goal in CTEPH. Furthermore, the fact that only 33% of the CTEPH patients were in the low-risk group at follow-up compared to 23% at baseline, may reflect that CTEPH patients are older, with more comorbidities, and more restrictive use of combination therapy, than PAH patients. Similar results were shown in the COMPERA registry [19].

We demonstrate a markedly improved survival outcome following PEA in the Swedish CTEPH population. This is in line with earlier published studies about PEA in CTEPH [5,21]. Although, fewer patients (32%) underwent PEA than in other European registries (60%), which may relate to differences in age, comorbidities and inclusion criteria to different registries. The median age of CTEPH patients in SPAHR is slightly older than in other countries [21,22]. Notably, the effect of PEA on survival in patients aged more than 70 years was attenuated, which possibly was due to comorbidities, frailty and a shorter expected survival. Patients with a high-risk profile had significantly more atrial fibrillation and ischaemic heart disease, than patients with low- or intermediate-risk profile, and a recently published study based on SPAHR data, showed that ischaemic heart disease and kidney dysfunction independently predicted outcome in PAH patients [23]. Notably, balloon pulmonary angioplasty was not performed in Sweden during the period studied.

Treatment with PH-specific drugs did not associate with improved survival in this study. However, the pharmacological treatment was highly biased towards patients with the highest risk profiles (Table 2), and no conclusions regarding efficacy should be drawn from these results.



Number exposed to risk						
Years	0	1	2	3	4	5
Stable “low risk”	32	23	18	16	10	4
Improved to “low risk”	24	20	16	13	11	5
Stable “intermediate risk”	73	56	44	37	29	14
Improved to “intermediate risk”	15	10	8	5	2	1
Worsened to “intermediate” or “high risk”	20	14	11	6	3	2
Stable “high risk”	5	4	2	2	2	1

Figure 3. Estimated five-year survival according to change in risk group from baseline to follow-up ($n = 170$).

Notably, in a newly published study pharmacological treatment improved prognosis in patients with CTEPH [20]. This display a need for effective pharmacological treatments for those not eligible for surgery or balloon dilatation.

The 2015 ESC/ERS guidelines recommend 13 variables in the risk assessment tool for PAH [1]. The present study demonstrated that the variables WHO FC, 6MWD, NT-proBNP, RAP, CI, and SvO_2 were closely linked to the mortality risk at baseline. At follow-up WHO FC, 6MWD, and NT-proBNP were linked to increased risk for mortality. To find the most optimal parameters for a specific CTEPH risk assessment tool was beyond the scope of this analysis, but should be done in the future. Finally, both Kylhammar et al. and Hoeper et al. have suggested that risk assessment could be considered as an end-point in future clinical trials [16,17], which we fully endorse also in studies involving CTEPH patients.

The major strength of the present study is that it includes all incident CTEPH patients in Sweden from 2008 and forward, although the sample size was relatively small. An important limitation is the lack of baseline variables due to the fact that SPAHR primarily is a quality registry with the purpose to improve patient care in Sweden, and not *per se* a research registry. Related to this, the diagnosis of CTEPH and number of referrals for PEA reflect the local traditions at the local PAH centres, which probably explains the lower than expected numbers of PEA. Despite these limitations, this study analyses the ESC risk assessment tool in CTEPH patients taking the effect of PEA into account. Still, further studies are needed to determine if the present risk stratification tool is the most appropriate in CTEPH or if alternative models – with selected clinical and hemodynamic parameters – might provide even better prognostication.

Conclusions

In conclusion, the present study shows that both the ESC/ERS risk assessment tool and PEA independent of each other predict survival in CTEPH patients. The treatment goal for CTEPH patients should be to achieve and maintain a low-risk profile which relates to better survival.

Acknowledgements

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Disclosure statement

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