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Prognostic and aetiological factors in chronic thromboembolic pulmonary hypertension

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ABSTRACT: Several prognostic variables have previously been identified in patients with chronic thromboembolic pulmonary hypertension (CTEPH). Specific medical conditions have also been associated with the development and prognosis of CTEPH. Using a national registry, the current authors have assessed the prognostic value of a larger number of variables and have also attempted to validate the clinical importance of previously identified aetiological factors.

Baseline information for all 469 CTEPH patients diagnosed in the UK pulmonary hypertension service between January 2001 and June 2006 was collected from hospital records.

Although univariate analysis confirmed the prognostic importance of pulmonary resistance, in multivariate analysis gas transfer and exercise capacity predicted pulmonary endarterectomy perioperative mortality. Cardiac index and exercise capacity independently predicted outcome in patients with nonoperable disease. Previous splenectomy was noted in 6.7% of patients, being significantly more common in patients with nonoperable than operable disease (13.7 *versus* 3.6%). Medical risk factors were not found to predict mortality.

In a large national cohort, predictors of outcome in patients with both operable and nonoperable chronic thromboembolic pulmonary hypertension have been identified. These may be useful in planning treatment. The aetiological importance of previously identified medical risk factors has been confirmed, although the current authors were unable to validate their prognostic strength.

KEYWORDS: Endarterectomy, prognosis, pulmonary hypertension, thromboembolism

Chronic thromboembolic pulmonary hypertension (CTEPH) is thought to result primarily from incomplete lysis of acute pulmonary embolism with subsequent organisation of the obstructing material into vessel walls and obstruction of pulmonary vascular blood flow [1]. The definitive treatment for CTEPH is pulmonary endarterectomy (PEA) which has proven symptomatic and survival benefit [2]. In a proportion of patients, the pulmonary vascular resistance (PVR) is disproportionate to the degree of lobar and segmental arterial obstruction revealed by imaging. The risk of post-operative mortality related to distal vasculopathy may therefore outweigh the potential benefits and these cases are therefore classified as being nonoperable. Treatment in this group of patients has increasingly involved the disease-modifying therapies used in other forms of pulmonary hypertension (PH). Survival before effective treatments became available was poor, with 2-yr survival of 10% in patients with a mean pulmonary arterial pressure ($\bar{P}_{pa}$) >50 mmHg [3]. Survival in patients with both surgical and nonsurgical disease has, however, recently been shown to have improved [2].

In view of the increasing use of surgical and medical therapy in patients with CTEPH, reliable prognostic markers are important to help guide appropriate management. In surgical patients, PVR has previously been identified as an important predictor of perioperative mortality [4–7]. Various medical risk factors for the development of CTEPH have been identified, which have subsequently been highlighted as potential predictors of poor outcome in both surgical and nonsurgical disease [8–11].

Since 2001, the diagnosis and management of all cases of CTEPH in the UK has been centralised to six PH centres, one of which is also the national surgical referral centre for PEA. This has provided the opportunity to study prognostic factors in patients with both surgically treated and

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nonsurgical CTEPH within a large cohort comprising all of the diagnosed patients within a single country. It has also been possible to validate the various risk factors for developing CTEPH that have been identified in smaller series.

METHODS

Details of patients in the national registry have been described elsewhere [2]. Briefly, demographic details of all patients diagnosed with CTEPH at a UK PH centre between January 1, 2001 and June 31, 2006 were entered prospectively into local databases. Supplementary data regarding diagnosis, baseline characteristics and risk factors were then obtained retrospectively from local hospital medical records by a single investigator (R. Condliffe). In the vast majority (87%) of cases, disease distribution was assigned following review of clinical details and radiological investigations by the multidisciplinary meeting (consisting of PEA surgeons, pulmonary vascular physicians and pulmonary vascular radiologists) at the national surgical referral centre (Pulmonary Vascular Disease Unit, Papworth Hospital, Cambridge, UK). The diagnosis assigned at this meeting was used in the registry. In a minority of cases, where referral was either not deemed appropriate or was refused by the patient, it was assigned by experienced pulmonary vascular physicians and radiologists at one of the five other national pulmonary hypertension centres. Disease was classified as operable on the basis of whether abnormalities in pulmonary haemodynamics, especially pulmonary resistance, were deemed to be proportional to the degree of surgically accessible thromboembolic obstruction demonstrated using multiple radiological modalities. Mortality status was ascertained at the censoring date of January 27, 2007. A small proportion of patients was lost to follow-up (n=4) or underwent lung transplantation (n=3); in these patients, the date of last contact or transplantation was taken as the censoring date. Percentage of predicted gas transfer of the lung for carbon monoxide ($T_{L,CO}$) was assessed by the single breath technique according to British Thoracic Society/Association of Respiratory Technologists and Physiologists guidelines [12].

The national registry was designed to define current care and so formal ethics approval was not required. The national Patient Information Advisory Group was, however, fully informed regarding the use of patient data.

Statistical analysis

Quantitative data were described using the mean$\pm$SD or confidence interval. Comparison of continuous data was performed using the t-test (unpaired) and of categorical data using the Chi-squared test. Predictors of survival in patients with nonsurgical disease were investigated using multiple-variable Cox regression analysis and factors associated with perioperative mortality using multiple-variable logistic regression analysis. Haemodynamic variables were coded into two-level variables by splitting the variables at their median value. Variables with >10% of values missing had a missing category added. Two different exercise tests are presently used to assess patients with PH in the UK. Walk distances were therefore standardised into a single variable by conversion into a z-score, which corresponded to the number of standard deviations from the mean. Exercise tolerance could thus be incorporated into multiple-variable analysis, which was performed using manual forward stepwise regression. Variables with p-values $\leqslant$0.2 in univariate regression analysis were considered for multiple regression analyses. The likelihood ratio test p-value was used at each iteration to decide which variable would enter the model. The variable with the smallest likelihood ratio test p-value was entered into the model and this was repeated until all variables with p-values <0.05 had been entered. Limiting this analysis to subjects with non-missing data in the regression analysis of perioperative mortality meant modelling was done using approximately half of the patients, so the base model from the stepwise regression was then tested with each remaining variable in turn in the subset of patients for whom there was data for the variables in question. Survival was estimated using the Kaplan–Meier method, with comparisons performed using the log-rank test. A p-value <0.05 was regarded as statistically significant throughout.

RESULTS

Study population

During the study period, 469 patients were diagnosed with CTEPH, out of whom 236 underwent PEA and 148 patients had distal, nonoperable disease. All patients had been investigated with computed tomography pulmonary angiography, with a large proportion also having undergone isotope perfusion scanning and pulmonary or magnetic resonance angiography. Right heart catheter details were located for 97% of cases, while all cases had clear evidence of significant PH with no evidence of significant left ventricular systolic or diastolic function on echocardiography. PH was defined as $\bar{P}_{Pa}$ $\geqslant$25 mmHg and a PVR $\geqslant$240 dyn·s·cm^{-5}. In 19% of cases, the pulmonary capillary wedge pressure was found to be >15 mmHg. As this measurement can be more difficult to obtain in this group of patients, due to an organised clot within the arterial lumen, patients with a high wedge pressure were included in the registry and total pulmonary resistance (TPR) rather than PVR was used in the analysis. Two forms of exercise test are in use within the UK PH service. The distance walked in the 6-min walking test (6MWT) was located for 69% of patients and in the incremental shuttle walking test (ISWT) for 20% of patients.

Predictors of survival in surgically treated disease

The median time to surgery from diagnostic catheter was 210 days (interquartile range 190 days). The results of both the univariate and multiple-variable analyses of predictors of perioperative mortality are shown in table 1. In univariate analysis, non-white patients had a greater risk of not surviving to hospital discharge (perioperative death) than those of white ethnicity. Higher TPR was associated with increased perioperative death and higher cardiac index (CI), walk distance and $T_{L,CO}$ with better perioperative survival. In multiple-variable analysis, $T_{L,CO}$ and walk distance were independent predictors of perioperative mortality. The outcome in surgically treated patients improved from the third year onwards (data not shown) which is likely to be due, in part, to the learning effect that has been seen in other PEA programmes [6]. Perioperative mortality in patients diagnosed from 2003 onwards, according to both the independent predictors of exercise tolerance (6MWT distance) and $T_{L,CO}$, as well as TPR, are shown in figure 1. Mean 6MWT distance was 262$\pm$128 m and mean ISWT distance was 188$\pm$167 m.

TABLE 1 Predictors of perioperative mortality

Variable (reference)	Univariate OR	p-value	Multiple OR	p-value
Age (⩽median (58.9 yrs))	1.00 (0.50–2.00)	>0.99		
Sex (female)	1.080 (0.53–2.18)	0.84		
Ethnicity (white)	4.69 (1.75–12.55)	0.002		
Symptom duration				
< 24 months	1.85 (0.84–4.04)	0.12		
>24months	Reference			
WHO class (I/II)	1.15 (0.38–3.54)	0.81		
$\bar{P}_{ra}$ (⩽median (8.5 mmHg))	1.71 (0.83–3.54)	0.15		
$\bar{P}_{pa}$ (⩽median (48.0 mmHg))	1.12 (0.55–2.25)	0.76		
CI (⩽median (1.90 L·min^{-1}·m^{-2}))	0.37 (0.17–0.83)	0.015		
TPR (⩽median (1000 dyn·s·cm^{-5}))	2.42 (1.15–5.11)	0.020		
S_{V,O_2} (⩽median (62.0%))	0.40 (0.18–0.91)	0.029		
Walk z-score (⩽median (-0.02))	0.26 (0.11–0.61)	0.002	0.31 (0.13–0.74)	0.009
$T_{L,CO}$ % pred (⩽median (71.0%))	0.25 (0.09–0.69)	0.004	0.30 (0.11–0.87)	0.03
Missing	1.62 (0.72–3.61)		1.51 (0.56–4.04)	
FEV1/FVC (⩽median (71.7%))	0.74 (0.34–1.61)	0.45		
Associated medical condition	1.034 (0.28–3.76)	0.96		

Odds ratios (OR) are presented with 95% confidence intervals. WHO: World Health Organization; $\bar{P}_{ra}$: mean right atrial pressure; $\bar{P}_{pa}$: mean pulmonary artery pressure; CI: cardiac index; TPR: total pulmonary resistance; S_{V,O_2}: mixed venous oxygen saturation; $T_{L,CO}$: transfer coefficient of the lung for carbon monoxide; % pred: % predicted; FEV1: forced expiratory volume in one second; FVC: forced vital capacity.

Predictors of survival in nonoperable disease

In univariate analysis, patients in World Health Organization (WHO) functional class III or IV had more than three times the mortality of patients in WHO class I or II. Mean right atrial pressure, $\bar{P}_{pa}$ and TPR above the median were associated with an increased risk of death, although this did not reach significance for $\bar{P}_{pa}$. Conversely, CI, mixed venous oxygen saturation, walk distance, $T_{L,CO}$ and forced expiratory volume in one second/forced vital capacity (FEV1/FVC) ratio above the median were associated with better survival. In multivariate analysis, CI and walk distance were independent predictors of survival. The results of the Cox analysis are shown in table 2 and survival based on the median value of the independent predictor of CI is shown in figure 2a. Mean pre-operative 6MWT distance was 239 ± 133 m and mean ISWT distance was 140 ± 119 m. Survival based on the 6MWT distance (228 m) corresponding to the median z-score (-0.08) is shown in figure 2b.

Medical risk factors for developing CTEPH

Data regarding medical risk factors was present for 96% of cases and are shown in table 3. A previously documented venous thromboembolic event (VTE) was significantly more common in patients with operable disease, whereas a previous splenectomy was significantly more common in those with nonoperable disease. The underlying reason for splenectomy was haemolytic anaemia in 42%, myeloproliferative disease in

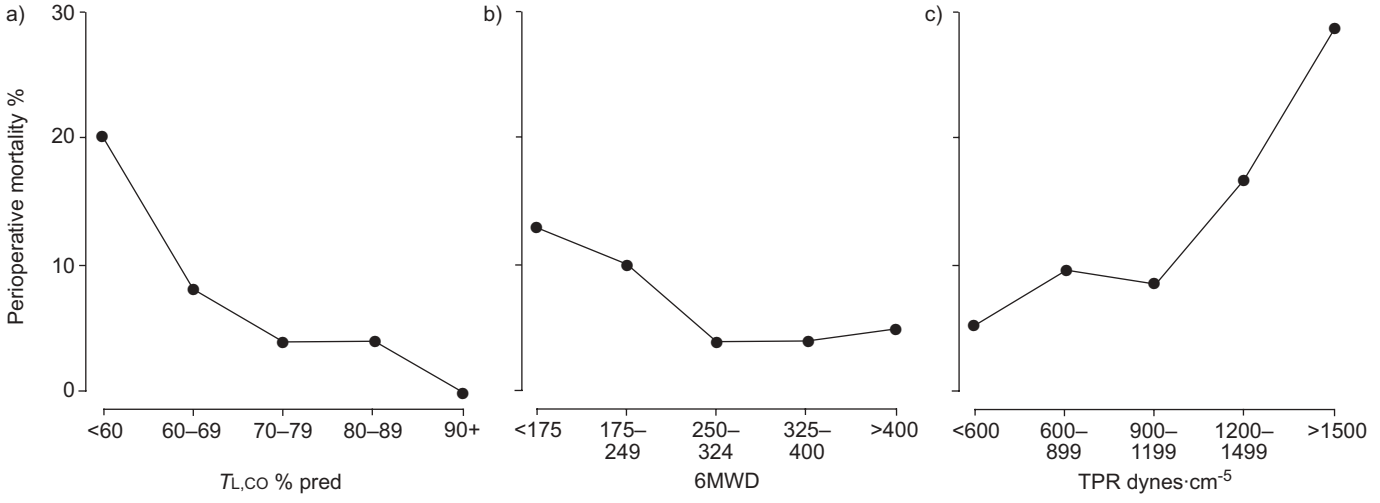

FIGURE 1. Perioperative mortality according to a) 6-min walk distance (6MWD), b) transfer coefficient of the lung for carbon monoxide ($T_{L,CO}$) and c) total pulmonary resistance (TPR). % pred: % predicted.

TABLE 2 Predictors of mortality in patients with nonoperable chronic thromboembolic pulmonary hypertension

Variable (reference)	Univariate HR	p-value	Multiple HR	p-value
Age yrs				
20–49	1.04 (0.49–2.23)	0.40		
50–59	0.63 (0.30–1.32)			
⩾60	Reference			
Sex (female)	1.19 (0.64–2.20)	0.59		
WHO class				
I/II	Reference	0.04		
III/IV	3.52 (1.08–11.50)			
$\bar{P}_{ra}$ (⩽median (10.0 mmHg))	2.19 (1.11–4.34)	0.024		
$\bar{P}_{pa}$ (⩽median (49.0 mmHg))	1.80 (0.92–3.52)	0.087		
CI (⩽median (2.00 L·min^{-1}·m^{-2}))	0.26 (0.12–0.56)	0.001	0.23 (0.09–0.58)	0.002
TPR (⩽median (1010.5 dyn·s·cm^{-5})	4.60 (2.13–9.94)	<0.001		
S_{V,O_2} (⩽median (60%))	0.34 (0.16–0.73)	0.005		
Walk z-score (⩽median (-0.08))	0.30 (0.14–0.66)	0.003	0.34 (0.15–0.79)	0.012
$T_{L,CO}$ % pred (⩽median (67.5%))	0.52 (0.23–1.15)	0.024		
Missing	1.61 (0.79–3.25)			
FEV_1/FVC (⩽median (71.9%))	0.43 (0.21–0.90)	0.024		
Treatment regime				
Single	Reference			
Combination	1.10 (0.53–2.30)	0.87		
No prescription	1.75 (0.79–3.87)	0.17		
Associated medical conditions	1.17 (0.54–2.54)	0.68		

Hazard ratios (HR) are presented with 95% confidence intervals. WHO: World Health Organization; $\bar{P}_{ra}$: mean right atrial pressure; $\bar{P}_{pa}$: mean pulmonary artery pressure; CI: cardiac index; TPR: total pulmonary resistance; S_{V,O_2}: mixed venous oxygen saturation; $T_{L,CO}$: transfer factor of the lung for carbon monoxide; % pred: % predicted; FEV_1: forced expiratory volume in one second; FVC: forced vital capacity.

29% and road traffic accident in 29% of cases. The presence or absence of the associated medical conditions of previous splenectomy, ventriculo-atrial shunt, pacemaker lead and inflammatory bowel disease did not affect survival in either operable or nonoperable disease (p=0.7), although the total number of patients with these conditions was relatively small. There was, however, a nonsignificant trend towards these associated medical conditions being more common in surgically treated patients who had persistent PH 3 months after surgery (12.9 *versus* 5.4%; p=0.096).

DISCUSSION

Using the first national registry of all CTEPH patients diagnosed and treated within a single country, the present authors have been able to study in detail prognostic markers for both surgically treated and nonoperable disease. It was demonstrated that exercise capacity and $T_{L,CO}$ independently predicted perioperative mortality in surgical patients, while exercise capacity and CI independently predicted outcome in patients with nonoperable disease.

In a series of 34 patients undergoing PEA, HARTZ *et al.* [4] reported in 1996 that the perioperative mortality of patients with a PVR >1,100 dyn·s·cm^{-5} was six times greater than that of patients with a PVR below this figure. TSCHOLL *et al.* [5] reviewed 69 patients treated with PEA and found that in univariate analysis age, right atrial pressure, functional class, cardiac output and creatinine predicted outcome [5]. In the present study, PVR did not significantly predict survival. However, in a subsequent, larger series of 275 PEA cases, DARTEVELLE *et al.* [7] did observe a prognostic significance of PVR, with mortality increasing when the baseline PVR exceeded 900 dyn·s·cm^{-5} and a further increase in mortality at resistances >1,200 dyn·s·cm^{-5} [7]. In the present study, it was found that in surgically treated patients, pulmonary resistance was a significant prognostic factor in univariate, but not in multivariable analysis. As there was likely collinearity between variables such as TPR and exercise capacity, prognostic importance can still be assigned to pulmonary resistance. Patients with a TPR >1,000 dyn·s·cm^{-5} had 2.4 times the risk of dying in the perioperative period as patients with a TPR below this figure. Pulmonary resistance should, therefore, continue to be central to the decision-making process regarding suitability for surgery.

The current authors have also, however, identified $T_{L,CO}$ and exercise capacity as being independent prognostic markers in patients undergoing PEA. A reduction in $T_{L,CO}$ in patients with CTEPH has previously been described, due primarily to a reduction in pulmonary membrane diffusing capacity (D_M) with a lesser reduction in pulmonary capillary blood volume (V_c) [13]. SUNTHARALINGAM *et al.* [14] observed that $T_{L,CO}$ was lower in patients with idiopathic pulmonary arterial hypertension or distal CTEPH than in patients with proximal CTEPH [14]. They postulated that this may have been due to D_M being more affected in patients with distal disease. It is therefore possible that the increased perioperative mortality observed by the present authors in patients with lower $T_{L,CO}$ was due to a higher degree of distal vasculopathy. STEENHUIS *et al.* [15] were, however, unable to demonstrate a difference in D_M or V_c in patients with idiopathic pulmonary arterial hypertension and

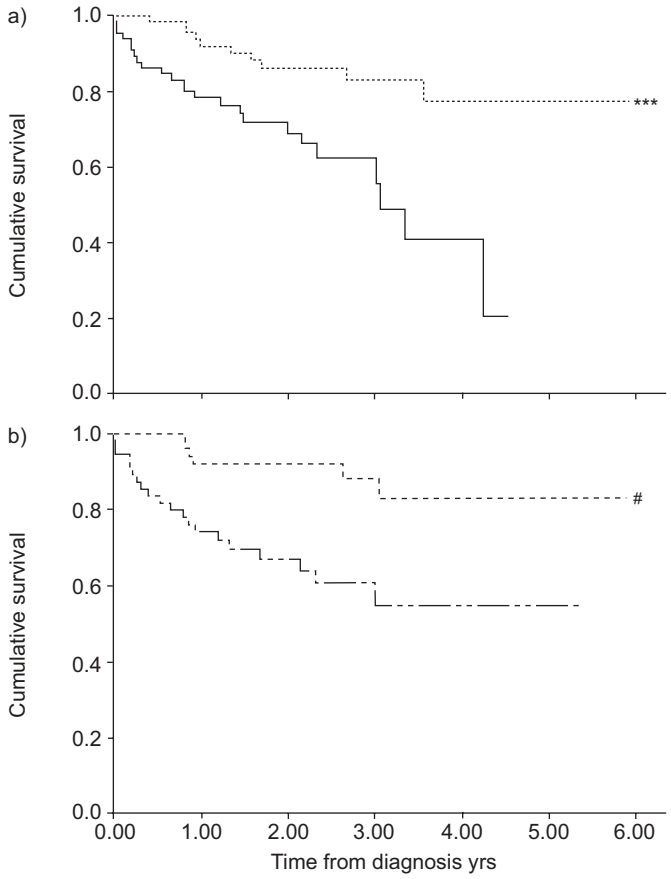

FIGURE 2. Survival from diagnosis of nonoperable patients, grouped by a) baseline cardiac index (CI) and b) 6-min walk distance (6MWD) above or below the median. ·····: CI >2 L·min^{-1}·m^{-2}; ——: CI <2 L·min^{-1}·m^{-2}; – – – –: 6MWD >228 m; ––··––··––: 6MWD <228 m; ***: p<0.001; #: p=0.01.

CTEPH [15]. Furthermore, there was no significant difference in the $T_{L,CO}$ of patients in the present study with either operable or nonoperable disease (69.1 *versus* 68.4%; p=0.72) [2]. Although a low FEV1/FVC ratio suggestive of airflow obstruction did not increase perioperative mortality, it is possible that the prognostic significance of a low $T_{L,CO}$ may, in part, also be due to coexisting respiratory disease.

The prognostic significance of exercise tolerance in surgically treated patients has not been extensively studied. SUNTHARALINGAM *et al.* [14] found that a 6MWT distance ⩽345 m predicted perioperative mortality with a sensitivity of 100%, although specificity was only 36% [16]. The results of the present study demonstrated that a 6MWT distance ⩾250 m was associated with a perioperative mortality of ~5%, while a 6MWT distance <250 m was associated with a perioperative mortality of ⩾10%.

The current study has also provided important insight into prognostic factors in patients with nonoperable disease. LEWCZUK *et al.* [17] studied 49 patients with conservatively treated CTEPH and found that an exercise capacity of <2 metabolic equivalents, a $\bar{P}_{pa}$ >30 mmHg or the presence of significant chronic obstructive pulmonary disease were predictive of poorer survival [17]. In the present study, multiple-variable analysis demonstrated that exercise capacity as well as CI were independent predictors of survival. BONDERMAN *et al.* [11] studied 181 CTEPH patients and found that CI did not independently predict survival; however, this analysis also included 105 patients who had undergone PEA, which may have introduced a therapeutic bias to the results [11]. Patients with nonoperable disease who did not receive disease-modifying therapy were not significantly more likely to die during follow-up. However, only 15% of patients received no such therapy, and the majority of those had mild symptoms and/or pulmonary haemodynamics. It is therefore unlikely that this analysis would demonstrate a survival benefit from disease-modifying therapy even if such a benefit does exist.

As well as investigating prognostic factors the current authors have also been able to assess the previously described clinical risk factors for the development of CTEPH. It is interesting to note that in the present study a significant proportion (42%) of patients did not have a history of a previously documented VTE. In their study of 109 patients BONDERMAN *et al.* [8] found no history of VTE in 52% of cases while LANG [18] reported that 63% of 142 consecutive patients had no previously documented VTE. It is possible that a proportion of patients, especially those with a history of sudden-onset symptoms, had a previous VTE which at the time was undiagnosed. It is interesting to note that the lack of a previously documented VTE in the current cohort was significantly more common in those with distal disease. This fact could lend credence to a hypothesis that in a proportion of patients a process of *in situ* thrombosis may occur [19].

A history of previous splenectomy was present in almost 7% of all cases, and in 13.7% of patients with nonoperable disease. The

TABLE 3 Clinical risk factors for developing chronic thromboembolic pulmonary hypertension

	All patients	Surgically accessible	Nonsurgical disease	p-value
Patients n	469	321	148	
Previous VTE	58	62	49	0.01
Splenectomy	6.7	3.6	13.7	<0.001
Ventriculo-atrial shunt or pacemaker lead	2.7	2.9	2.1	0.64
IBD	1.6	1.3	1.4	0.91
AMC	10.5	7.4	17.1	0.002

Data are presented as %, unless otherwise stated. VTE: venous thromboembolic event; IBD: inflammatory bowel disease; AMC: associated medical conditions (splenectomy, ventriculo-atrial shunt or pacemaker lead and IBD).

association of splenectomy and CTEPH, especially in nonoperable disease, has previously been described [8, 9, 20]. Several potential mechanisms for this phenomenon have been postulated, including loss of splenic function leading to the circulation of platelet-derived mediators, which, when acting in conjunction with abnormal erythrocytes, promote thrombus formation in the pulmonary circulation [9]. Although in the present study ventriculo-atrial shunts and pacemaker leads were found in under half of the proportion that was noted by BONDERMAN *et al.* [8], the present figures were still higher than those observed in the control patients in that study. In a subsequent study, the same group found that the associated medical conditions of splenectomy, central *i.v.* lines and chronic inflammatory conditions were strong predictors of mortality in both surgically and nonsurgically treated patients [11]. The present authors have been unable to reproduce this observation, although a trend was seen towards persistent PH following PEA being more common in patients with these conditions.

The main limitation of the present study is the retrospective nature of much of the data collection. Retrieval bias may therefore have been introduced because information was gathered from notes which had different levels of completeness. The effects of having missing haemodynamic and functional data were accounted for somewhat by including missing categories variables in the regression models. Furthermore, the number of patients with missing data concerning previous thromboembolic events and associated medical conditions was low. It is unlikely that important features such as previous splenectomy, ventriculo-atrial shunt, pacemaker lead or inflammatory bowel disease would have been missed when reviewing patient notes and letters. Data regarding thrombophilias has not been presented, as such data was incomplete and involved multiple centres with different assays, and in many cases patients were already receiving treatment with warfarin, which made interpretation difficult. The associated medical conditions highlighted in the previous studies discussed above also included osteomyelitis [11]. Although the present study did not collect data regarding this condition, it is unlikely that doing so would have significantly affected the findings regarding their prognostic strength.

The present study, the first to involve a national registry of chronic thromboembolic pulmonary hypertension patients, has found the independent predictors of survival in patients undergoing pulmonary endarterectomy to be transfer factor of the lung for carbon monoxide and exercise capacity, and in patients with nonoperable disease to be cardiac index and exercise capacity. The current findings have also confirmed the importance of pulmonary resistance in predicting perioperative mortality in surgically treated patients These variables could be incorporated into risk stratification at the time of decision-making processes regarding proposed treatments. Although the current authors have confirmed the aetiological importance of previously described medical risk factors, it has not been possible to validate their prognostic value.

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