Clinical characteristics and prognosis in patients with chronic thromboembolic pulmonary hypertension and a concomitant psychiatric disorder

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Abstract

Chronic thromboembolic pulmonary hypertension (CTEPH) can cause right heart failure. A concomitant psychiatric disorder (PD) is thought to increase the risk of acute pulmonary thromboembolism; however, whether PDs are associated with deterioration in CTEPH pathophysiology is unclear. In this study, we evaluated the clinical characteristics and prognoses in patients with CTEPH and a co-existing PD. We retrospectively identified 229 consecutive patients (mean age $= 58.7 \pm 12.5$ years; 160 women) with CTEPH and categorized them according to whether they had a PD (PD group; n $= 22$, 9.7%) or not (non-PD group; n $= 207$, 90.3%). We compared the clinical characteristics, respiratory function, hemodynamics, and clinical courses in the two groups. Those in the PD group had significantly lower exercise tolerance compared to the non-PD group (6-min walk test, 309.5 ± 89.5 m vs. 369.4 ± 97.9 m, $P = 0.008$, percent vital capacity 85.5% $\pm$ 17.3% vs. 96.0% $\pm$ 15.5%, $P = 0.003$) and partial pressure of oxygen (PaO$_2$) (54.4 ± 8.6 mmHg vs. 59.3 ± 10.7 mmHg, $P = 0.039$). Three-year survival was significantly poorer in the PD group compared to the non-PD group (66.1% vs 89.7%, $P = 0.0026$, log-rank test), particularly in patients who underwent surgery (62.2% vs 89.5%, $P < 0.001$, log-rank test). A concomitant PD was associated with low exercise tolerance and impaired respiratory function in patients with CTEPH and predicted poor survival, especially in those who underwent a pulmonary endarterectomy.

Chronic thromboembolic pulmonary hypertension (CTEPH) is a type of pulmonary hypertension (PH) caused by chronic obstruction of the pulmonary arteries and secondary changes in the microcirculatory bed of the lungs.[1,2] The condition sometimes results in a progressive increase in pulmonary vascular resistance (PVR) and pulmonary artery pressure (PAP) with the development of right heart failure. The incidence and prevalence of CTEPH has been gradually increasing but may be underestimated because of its non-specific symptoms and variable disease course.[3]

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Pulmonary endarterectomy (PEA) is currently considered the definitive treatment for CTEPH. Medical therapies for pulmonary arterial hypertension (PAH), including guanylate cyclase agonists, phosphodiesterase-5 inhibitors, endothelin receptor antagonists, and prostacyclin analogs, have been developed for patients who are not candidates for surgery.[4,5] These drugs have improved the survival rate in patients with CTEPH.[4,6] Balloon pulmonary angioplasty is also used to improve pulmonary hemodynamics, right heart function, exercise tolerance, and other symptoms in these patients,[7,8] and has steadily improved prognoses in the short and long term.[9,10]

However, other complications can impact CTEPH prognoses. In routine clinical practice, it is not uncommon to encounter patients with CTEPH who also have a psychiatric disorder (PD). Moreover, it has been reported that patients on oral antipsychotic medication are more likely to develop a pulmonary thromboembolism.[11] Oral antidepressants and antipsychotics increase the risk of acute thromboembolism themselves and the use of these agents has been mentioned among the risk factors for thrombosis.[12,13] Furthermore, patients with chronic heart failure have been reported to have a significantly worse prognosis if they have concomitant depression.[14] However, the pathophysiology and prognoses in patients with a pulmonary thromboembolism, including CTEPH, and a chronic PD are not well defined.

The aim of the present study was to investigate the clinical characteristics and prognoses in patients with CTEPH and a concomitant PD.

Methods

Study population

This retrospective, single-centered, observational study included 229 consecutive patients with CTEPH confirmed by right heart catheterization (RHC) and chronic thromboembolism findings between January 2000 and March 2017. No exclusion criteria were applied. The study was approved by the ethics committee of Chiba University, Japan (approval no. 2584). Written informed consent was obtained from all patients who were enrolled since 2009, when this requirement became mandatory (approval no. 826).

Background patient characteristics

Many of the patients enrolled in the study had visited our hospital complaining of shortness of breath or palpitation during exercise. We performed echocardiography as an initial test to detect PH. If findings indicating PH were present, such as increased pressure across the tricuspid valve or increased right-sided filling pressure causing displacement of the left ventricle, RHC was performed to confirm the presence of PH. Ventilation/perfusion scans, pulmonary angiography, and contrast-enhanced computed tomography (CT) were performed to confirm the presence of pulmonary thromboemboli and exclude other types of PH. A diagnosis of CTEPH was confirmed when chronic occlusion of the pulmonary arteries by organized thrombi leading to PH was present despite anticoagulation therapy for >3 months. Surgical treatment included PEA only. The observation period was calculated from the date of the first RHC at our institution until death or the end of the study period.

Patients with a history of psychiatric attendances and ongoing use of psychiatric medication were defined as having a PD. Sex, age, smoking history, and use of oral antipsychotics were recorded at the time of diagnosis. Subjective symptoms were categorized according to the World Health Organization (WHO) functional classification for PH. The central disease score was calculated by adding the number of abnormal central portions, defined as proximal to the segmental branches and divided into four portions.[15] The Jamieson classification (types I–IV) according to the location and morphology of thromboembolic and vascular wall diseases at the time of surgery was also used.[16] Although the Jamieson classification could not be estimated preoperatively, it is important for the proper judgment of surgery adaptation and prognosis estimation.[17]

Blood tests

We collected data on cardiac loads and coagulation by measuring brain natriuretic peptide, D-dimer, coagulation factor VIII, fibrinogen, protein C, and lupus anticoagulant levels for all patients.

Right heart catheterization

A 7.5-Fr Swan-Ganz thermodilution catheter (Edwards Lifesciences, Irvine, CA, USA) was inserted using a jugular approach. Pressure was measured at the superior vena cava, right atrium, right ventricle, and main pulmonary artery. Pulmonary artery wedge pressure (PAWP) was measured at the end-expiration point. The zero point was defined as mid-thoracic. Cardiac output (CO) was determined using the thermodilution method by averaging a minimum of three measurements. Left-to-right shunting was ruled out using oximetry. PVR was calculated in Wood units using the following equation:

$$PVR = (mean\ PAP\ [mPAP] - PAWP)/CO.$$

Pulmonary angiography

Digital subtraction angiography using a 7-Fr Berman angiographic balloon catheter (Teleflex, Wayne, PA, USA) was performed to confirm typical findings of chronic embolisms including pouch defects, webs and bands, intimal irregularities, abrupt narrowing, and complete obstruction.

Six-minute walk test

The 6-min walk test (6MWT) was conducted in accordance with the American Thoracic Society guidelines,[18] whereby patients are requested to walk as far as possible in 6 min. The heart rate, Borg scale score, and oxygen saturation were recorded before and after the test and the distance walked was noted. The test was performed with oxygen inhalation use in patients requiring home oxygen therapy.

Spirometry

Spirometry was performed using a Chestac-8900 (Nihon Kohden, Tokyo, Japan) or Fudac-60 (Fukuda Denshi, Tokyo, Japan) device following the Japanese Respiratory Society guidelines, which are based on the American Thoracic Society guidelines.[19] Vital capacity (VC), forced VC, and forced expiratory volume in 1 s were measured using standard techniques. Diffusing capacity for carbon monoxide (DL_{CO}) and DL_{CO}/alveolar ventilation (V_A) values were measured by the helium dilution and single-breath methods. These data were calculated as percentages of predicted values.

Statistical analysis

The results are expressed as the mean ± standard deviation. The means of continuous variables were compared between groups using the Mann–Whitney U test and the proportions of categorical variables were compared using the chi-square test. Univariate regression analysis was used to compare two parameters where appropriate. Univariate and multivariate Cox proportional hazards models were also used to identify factors contributing to poor long-term outcomes. Survival was estimated using the Kaplan–Meier method and survival estimates were compared using the log-rank test. All statistical analyses were performed using JMP Pro 13 software (SAS Institute Inc., Cary, NC, USA). The threshold for statistical significance was set at $P < 0.05$.

Results

Patient characteristics

Table 1 shows the patient characteristics at baseline. The study population comprised 229 consecutive patients (mean age = 58.7 ± 12.5 years; 160 women) with CTEPH confirmed by RHC and pulmonary angiography. A total of 130 (56.8%) of the 229 patients underwent PEA. The Jamieson classification after PEA was I in 81 patients, II in 32, III in 14, IV in one, and unknown in two cases. The remaining 99 patients in the study (43.2%) received medication and/or underwent balloon pulmonary angioplasty (BPA; n = 29, 12.7%). Twenty-two (9.7%) of the 229 patients had a concomitant PD (schizophrenia, n = 9, 41%; depression, n = 10, 45%; bipolar disorder, n = 3, 14%) and were defined as the PD group. Four (18.2%) of

these patients were being treated with a single psychiatric agent while the rest were receiving a variety of psychiatric medications. The patients with depression were receiving tricyclic or tetracyclic antidepressants or selective serotonin reuptake inhibitors; those with schizophrenia were being treated with typical antipsychotic agents, serotonin-dopamine antagonists, multi-acting receptor-targeted antipsychotics agents, or dopamine stabilizers. Nine patients (40.9%) in the PD group underwent PEA and the others underwent BPA or received medication alone. The patients without a PD were enrolled as members of the non-PD group.

Body weight and body mass index (BMI) values were significantly higher in the PD group than in the non-PD group (62.8 ± 12.7 kg vs. 56.6 ± 10.9 kg, $P = 0.014$, and 25.3 ± 3.62 vs. 22.2 ± 3.12, $P < 0.001$, respectively). There was no significant difference in age, sex, interval between onset of symptoms and diagnosis of CTEPH, smoking history, or WHO functional classification of PH between the two groups. The statistical significance of differences between the PD and non-PD groups did not change when the data were analyzed according to whether or not PEA had been performed (Supplementary Tables 1 and 2).

Pulmonary hemodynamics

Table 2 shows the results of the clinical examination in the PD group and the non-PD group. There were some missing data points as follows: four instances of lupus anticoagulants; 10 instances of protein C; and 20 instances of coagulation factor VIII. All the missing data were values for patients in the non-PD group. There was no significant difference in the level of brain natriuretic peptide or that of any other biomarker between the study groups. RHC did not reveal any significant between-group differences in PAP, CO, or cardiac index.

Exercise tolerance and respiratory function

The 6MWT results indicated that exercise tolerance was significantly lower in the PD group than in the non-PD group (309.5 ± 89.5 m vs. 369.4 ± 97.9 m, $P = 0.006$). Furthermore, spirometry revealed significantly lower %VC and %DL_{CO} in the PD group (%VC, 85.5% ± 17.3% vs. 96.0% ± 15.5%, $P = 0.003$, and %DL_{CO}, 65.4% ± 19.5% vs. 79.3% ± 17.3%, $P < 0.001$, respectively). Blood gas analysis while breathing room air revealed that the partial pressure of oxygen (PaO_2) was significantly lower and partial pressure of carbon dioxide ($PaCO_2$) was significantly higher in the PD group than in the non-PD group (PaO_2, 54.4 ± 8.6 mmHg vs. 59.3 ± 10.7 mmHg, $P = 0.039$, and $PaCO_2$, 40.6 ± 4.8 mmHg vs. 37.4 ± 4.1 mmHg, $P < 0.001$, respectively). In this study, four patients in the non-PD group were unable to perform a respiratory function test. Also, two in the PD group and 14 in the non-PD group could not perform the 6MWT.

Table 1. Characteristics of patients with CTEPH.

Variable	PD group (n = 22)	Non-PD group (n = 207)	P value
Age (years)	58.6 ± 13.0	58.7 ± 11.9	0.911
Sex, n (female/male)	19/3 (86.4%)	141/66 (68.1%)	0.090
Interval until diagnosis (months)	28.0 ± 29.3	34.8 ± 39.7	0.440
Smoking (yes/no)	10/12 (45.5%)	61/146 (29.5%)	0.149
Surgical treatment (yes/no)	9/13 (40.9%)	121/86 (58.5%)	0.173
Height (m)	1.57 ± 0.097	1.60 ± 0.098	0.185
Weight (kg)	62.8 ± 12.7	56.6 ± 10.9	**0.027**
Body mass index	25.3 ± 3.62	22.2 ± 3.12	**<0.001**
WHO classification	2.77 ± 0.53	2.66 ± 0.63	0.407
Diabetes mellitus	0/22 (0.0%)	12/207 (5.8%)	0.114
COPD	5/17 (22.7%)	48/157 (23.4%)	0.942

The data are presented as the mean $\pm$ standard deviation.
The bold letters indicate significant correlations.
COPD, chronic obstructive pulmonary disease; PD, psychiatric disorder; WHO, World Health Organization

Table 2. Characteristics of patients with CTEPH.

Parameter	PD group (n = 22)	Non-PD group (n = 207)	P value
Blood test			
BNP (pg/mL)	171.8 ± 285.4	212.2 ± 293.0	0.709
D-dimer (μg/mL)	0.50 ± 0.65	1.14 ± 1.73	0.089
Coagulation factor VIII (%)	158.4 ± 85.6	161.9 ± 101.3	0.876
Fibrinogen (mg/dL)	292.2 ± 76.5	299.3 ± 74.9	0.677
Protein C (%)	56.5 ± 24.1	62.9 ± 25.5	0.260
Lupus anticoagulant ($\pm$)	7/15 (31.8%)	41/161 (20.3%)	0.271
RHC			
mPAP (mmHg)	45.5 ± 10.6	43.8 ± 11.6	0.423
CO (L/min)	4.27 ± 1.36	4.15 ± 1.13	0.911
Cardiac index	2.77 ± 0.63	2.65 ± 0.67	0.113
PVR (Wood units)	8.69 ± 4.07	9.37 ± 4.43	0.587
PVR one month after PEA (Wood units)	5.53 ± 3.54	3.82 ± 2.24	0.083
PaO_2 (mmHg)	54.4 ± 8.6	59.3 ± 10.7	**0.0498**
$PaCO_2$ (mmHg)	40.6 ± 4.8	37.4 ± 4.1	**0.005**
PvO_2 (mmHg)	32.93 ± 3.80	33.26 ± 4.05	0.865
$AaDO_2$ (mmHg)	47.2 ± 9.8	45.6 ± 11.1	0.507
Respiratory function tests			
6-min walk distance (m)	309.5 ± 89.5	369.4 ± 97.9	**0.005**
Modified Borg scale	4.36 ± 3.17	3.59 ± 2.24	0.165
Percent vital capacity (%)	85.5 ± 17.3	96.0 ± 15.5	**0.020**
FEV_1 (%)	75.7 ± 8.33	75.3 ± 8.20	0.810
DL_{CO} (%)	65.4 ± 19.5	79.3 ± 17.3	**0.022**
DL_{CO} / V_A	3.85 ± 0.99	4.03 ± 0.84	0.362

The data are presented as the mean $\pm$ standard deviation.
The bold letters indicate significant correlations.
BNP, brain natriuretic peptide; CO, cardiac output; FEV_1, forced expiratory volume in 1 s; mPAP, mean pulmonary arterial pressure; RHC, right heart catheterization; PD, psychiatric disorder; PVR, pulmonary vascular resistance; DL_{CO}, diffusing capacity for carbon dioxide; V_A, alveolar ventilation, PaO_2, partial pressure of oxygen; $PaCO_2$, partial pressure of carbon dioxide; PvO_2, venous oxygen tension; $AaDO_2$, alveolar-arterial oxygen gradient.

Prognosis

The median observation period was 66.0 months (95% confidence interval [CI] = 55.8–76.3) in the PD group and 72.4 months (95% CI = 61.4–83.3) in the non-PD group. Thirty-nine patients (17.0%) died during the study period. The cause of death was exacerbation of PH in 26 patients and perioperative complications in the other 13. There were no deaths attributable to deterioration of a PD or suicide. There were more deaths attributable to CTEPH in the PD group than in the non-PD group (7/22 [31.8%] vs. 32/207 [15.5%], $P = 0.052$). There were also more perioperative deaths in the PD group than in the non-PD group (3/9 [33.3%] vs. 10/121 [8.3%], $P = 0.016$). There were three deaths in the PD group that were the result of perioperative complications after PEA (suspected recurrence of pulmonary thromboembolism [n = 2], lung bleeding [n = 1]). In the non-PD group, 10 of the surgically treated patients died of perioperative complications (residual PH [n = 2], lung bleeding [n = 4], other [n = 4]).

Figure 1 shows the patient survival data in the two study groups. Three-year survival was significantly worse in the PD group than in the non-PD group (66.1% vs. 89.7%, $P = 0.0026$). Kaplan–Meier survival estimates for patients with medically and surgically treated CTEPH in the study groups are shown in Figs. 2 and 3. The patients in the PD group who underwent PEA had significantly poorer survival than in the non-PD group ($P < 0.001$). However, there was no between-group difference in survival when the patients were treated without surgery ($P = 0.280$). Even when patients treated with BPA were excluded from the medically treated group, there was no significant difference in survival between the two study groups ($P = 0.843$; Suppl. Fig. 1). Tables 3 and 4 show the results of the univariate and multivariate analyses in the surgically and medically treated patients. In the PEA group, univariate analysis identified having a concomitant PD, poor performance on the 6MWT, high PVR, and a Jamieson classification of III or IV to be poor prognostic factors. In the multivariate analysis, coexistence of a PD was associated with low survival rates (hazard ratio = 9.11; 95% CI = 1.85–35.2; $P = 0.017$). In contrast, there was no significant association between having a PD and the prognosis in the medically treated group.

Discussion

To the best of our knowledge, this is the first study to investigate the characteristics and prognoses of patients with CTEPH and a concomitant PD. These patients had a poorer prognosis than their counterparts without a PD, especially if they underwent PEA, and tended to have lower exercise tolerance and poorer pulmonary function.

A PD emerged as a risk factor for mortality in patients with CTEPH; their long-term prognosis was significantly poor, especially if they had undergone PEA. Some reports from Japan have suggested an important relationship
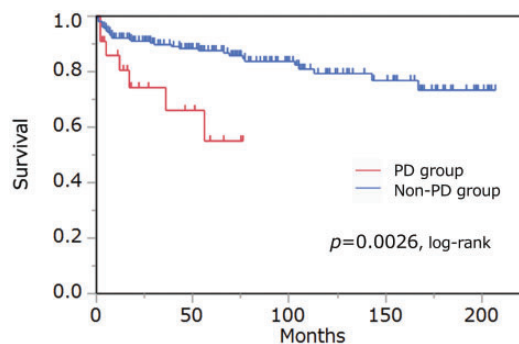

Fig. 1. Kaplan–Meier survival curves for patients with CTEPH classified according to the presence or absence of a concomitant psychiatric disorder. Survival was poorer in patients with a psychiatric disorder than in those without ($P = 0.0026$, log-rank test). CTEPH, chronic thromboembolic pulmonary hypertension.
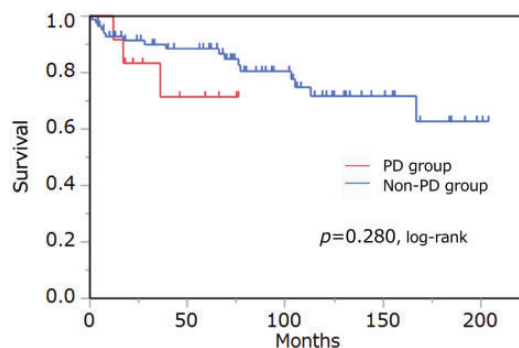

Fig. 2. Kaplan–Meier survival curves for patients with medically treated CTEPH with and without a concomitant psychiatric disorder. Survival tended to poorer in the patients with a psychiatric disorder but not to the point of statistical significance ($P = 0.280$, log-rank test).
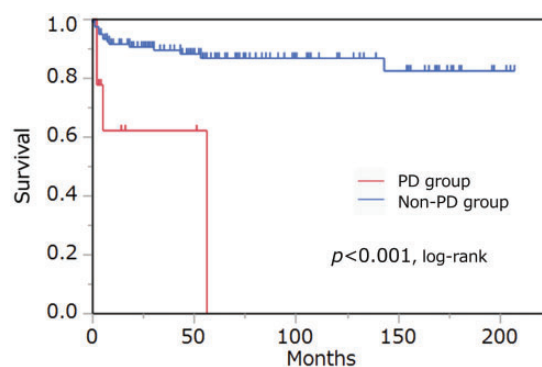

Fig. 3. Kaplan–Meier survival curves for patients with surgically treated CTEPH with and without a concomitant psychiatric disorder. Survival was significantly poorer in the patients with a psychiatric disorder ($P < 0.001$, log-rank test).

between CTEPH and a psychiatric diagnosis. For example, Suzuki et al. reported that 7% of their patients with CTEPH had a diagnosis of schizophrenia,[20] as did 3.9% of our patients; both these figures are higher than the prevalence

Table 3. Univariate and multivariate analyses of prognostic factors in patients with CTEPH who had a psychiatric disorder and underwent pulmonary endarterectomy (n = 130).

Parameter	Univariate		Multivariate	
	Odds ratio (95% CI)	P value	Odds ratio (95% CI)	P value
Psychiatric disorder (±)	6.17 (1.72–17.6)	**0.002**	8.39 (1.93–31.8)	**0.0064**
Sex (female/male)	1.01 (0.41–2.73)	NS		
Age (years)*	0.995 (0.96–1.04)	NS	0.996 (0.95–1.04)	NS
Body mass index (kg/m^2)*	1.06 (0.92–1.19)	NS		
Smoking (±)	1.44 (0.56–3.56)	NS		
Diabetes mellitus (±)	1.13 (0.062–5.49)	NS		
COPD (±)	1.73 (0.58–7.44)	NS		
%VC (%)*	0.087 (0.0079–0.95)	**0.046**	0.971 (0.934–1.008)	NS
%DL$_{CO}$ (%)*	0.99 (0.96–1.01)	NS		
mPAP (mmHg)*	1.04 (0.99–1.08)	0.085		
Cardiac index (mL/min/m^2)*	0.60 (0.27–1.19)	NS		
PVR (Wood units)*	1.11 (1.00–1.23)	**0.037**	1.12 (0.95–1.31)	NS
6-min walk test (m)*	0.99 (0.987–0.997)	**0.002**	0.999 (0.993–1.006)	NS
PaO$_2$ (mmHg)*	1.03 (0.98–1.08)	NS		
Jamieson classification III–IV (vs. I–II)	3.67 (1.17–9.88)	**0.028**	4.45 (1.29–13.7)	**0.021**
WHO functional class 3–4 (vs. 1–2)	2.54 (0.84–10.9)	NS	1.89 (0.52–9.03)	NS
Selective pulmonary vasodilators (±)	0.34 (0.053–1.20)	0.099	0.34 (0.06–1.31)	NS

The data are presented as the mean ± standard deviation.
The bold letters indicate significant correlations. $P < 0.05$. Significant differences between patients with CTEPH who had and did not have a psychiatric disorder were determined using univariate and multivariate regression analyses.
*Per-unit increase.
CI, confidence interval; COPD, chronic obstructive pulmonary; DL$_{CO}$, diffusing capacity for carbon monoxide; mPAP, mean pulmonary arterial pressure; NS, not statistically significant ($P \geq 0.05$); PaO$_2$, partial pressure of oxygen; PVR, pulmonary vascular resistance; V$_A$, alveolar ventilation; VC, vital capacity; WHO, World Health Organization.

of schizophrenia in the general population.[21] Furthermore, Funabashi et al. reported a higher frequency of depression in patients with CTEPH.[22] Our group has recently identified that a Jamieson classification of III or IV and a high PVR were associated with poor survival, although similar survival rates were recently observed in patients with CTEPH treated by BPA, PEA, and medication between 2009 and 2016.[23] The findings of the present study are similar in that a Jamieson classification of III or IV was a poor prognostic factor, providing evidence that having a PD may be an additional important risk factor for perioperative death in patients with CTEPH.

Several studies have suggested a relationship between antipsychotic or antidepressant treatments and thromboembolism,[24,25] although studies of long-term prognoses in patients with CTEPH have not been performed. In our study, four of seven patients with a PD who died had depression and three had schizophrenia. All seven patients had been prescribed multiple medications. However, because of the small number of cases, it was not possible to establish whether there was a definite relationship between the medication and mortality.

Furthermore, the poor prognosis of the patients in the PD group despite their similar pulmonary hemodynamics at baseline may be associated with a higher risk of post-surgical complications. Previous studies in patients undergoing general surgery or cardiovascular surgery have suggested that those with a concomitant PD have an increased risk of operative complications.[26] This increase in risk might be attributable to severe comorbidity, a delay in diagnosis and treatment, the adverse effects of medication or anesthesia, poor nutrition, and difficulty describing symptoms.[26] Moreover, there are several potential mechanisms via which thromboembolism can occur in such patients, including a sedation-related decrease in physical activity, induction of antiphospholipid antibodies, and enhancement of platelet aggregation via serotonin.[27,28] In our study, there were two sudden perioperative deaths in the PD group; recurrence of pulmonary embolism was confirmed at autopsy in one patient (who had required physical restraint) and was suspected in the other patient. The postoperative PVR of patients with PD was higher, although the difference was not statistically significant. These results indicate that CTEPH patients with PDs may have some potential risks with PEA. Therefore, even if PEA is a curative treatment, the indication for surgery in a patient with CTEPH and a concomitant PD needs to be judged carefully. However, whether the risk is due to psychotic drugs or PDs themselves

Table 4. Univariate and multivariate analyses of prognostic factors in patients with CTEPH who had a psychiatric disorder and did not undergo pulmonary endarterectomy (n = 99).

Parameter	Univariate		Multivariate	
	Odds ratio (95% CI)	P value	Odds ratio (95% CI)	P value
Psychiatric disorder (±)	2.00 (0.45–6.42)	0.32	2.61 (0.36–12.3)	NS
Sex (female/male)	0.87 (0.34–2.69)	NS		
Age (years)*	1.004 (0.97–1.04)	NS	0.99 (0.95–1.03)	NS
Body mass index (kg/m^2)*	0.92 (0.77–1.08)	NS		
Smoking (±)	1.20 (0.43–3.03)	NS		
Diabetes mellitus (±)	6.42 (1.82–17.8)	**0.0065**		
COPD (±)	1.17 (0.42–4.16)	NS		
% VC (%)*	0.94 (0.061–29.7)	NS		
% DL$_{CO}$ (%)*	0.997 (0.98–1.02)	NS		
mPAP (mmHg)*	1.04 (0.99–1.08)	0.063		
Cardiac index (mL/min/m^2)*	0.26 (0.092–0.63)	**0.0060**		
PVR (Wood units)*	1.18 (1.08–1.29)	**< 0.001**		
6-min walk test (m)*	0.992 (0.987–0.997)	**0.0032**	0.99 (0.987–0.998)	**0.012**
PaO$_2$ (mmHg)*	0.94 (0.89–0.98)	**0.0090**	0.94 (0.88–1.001)	NS
Central disease score 2–4 (vs. 0–1)	1.47 (0.47–3.80)	NS	1.13 (0.29–3.63)	NS
WHO functional class 3–4 (vs. 1–2)	3.11 (0.93–10.0)	NS		
Selective pulmonary vasodilators (±)	0.47 (0.18–1.18)	0.12	0.29 (0.083–0.88)	**0.029**

The data are presented as the mean ± standard deviation.

The bold letters indicate significant correlations. P < 0.05. Significant differences between patients with chronic thromboembolic pulmonary hypertension who did and did not have a psychiatric disorder were determined using univariate and multivariate regression analyses.

*Per-unit increase.

CI, confidence interval; DL$_{CO}$, diffusing capacity for carbon monoxide; mPAP, mean pulmonary arterial pressure; NS, not statistically significant; PVR, pulmonary vascular resistance; V$_A$, alveolar ventilation; VC, vital capacity; WHO, World Health Organization.

could not be clarified in this study. We plan to search for detailed risk factors in further examinations in the future.

In our study, patients with CTEPH and a co-existing PD tended to have decreased exercise tolerance and impaired pulmonary function and gas exchange; decreased respiratory function and impaired gas exchange diminish quality of life. Also, patients in the PD group were more often smokers than those in the non-PD group (45.5% vs. 29.8%, P = 0.230). A previous study also identified an association between expiratory spirometry parameters and limitations in activities of daily living in patients with schizophrenia.[29] In addition, a relationship between obesity and deterioration of lung function has been identified in patients with schizophrenia.[30] Moreover, in our study, patients with CTEPH and a concomitant PD had a significantly higher BMI, which may have caused a decrease in exercise tolerance.

Further, compliance with medication in patients with PDs is suggested to be lower which may make them facilitate a poor prognosis.[31] Meanwhile, early detection and appropriate treatment is important in patients with CTEPH.[32] Therefore, when a patient with a PD complains of dyspnea, CTEPH should be included in the differential diagnosis, and appropriate therapeutic intervention and careful follow-up is necessary.

This study had some limitations. First, it had a retrospective single-center cohort design and low statistical power; this is inevitable, given that CTEPH is a relatively rare disease. Second, the medical and surgical treatment of CTEPH has been evolving yearly, so the clinical status of some of the patients in the early years of this study may not be comparable with that of those in the later years because of improvements in treatment over time. Third, it was difficult to guarantee accurate diagnoses of PDs. Even if the diagnosis was provided by a psychiatric specialist, some patients were diagnosed at other hospitals and we did not perform screening tests of PDs on patients with CTEPH.

In summary, a concomitant PD may predict poor survival in patients with CTEPH, especially in those who undergo PEA, so the recommendation for PEA should be considered carefully. Furthermore, a PD may be associated with reduced exercise tolerance and poor respiratory function in these patients.

Conflict of interest

Supplemental Material

Supplementary material for this paper can be found at http://journals.sagepub.com/doi/suppl/10.1177/2045894019836420

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References

1. Chazova IE and Martynyuk TV. [Clinical guidelines for the diagnosis and treatment of chronic thromboembolic pulmonary hypertension (Part 1)]. *Ter Arkh* 2016; 88: 90–101. (In Russian).
2. Jujo T, Sakao S, Ishibashi-Ueda H, et al. Evaluation of the microcirculation in chronic thromboembolic pulmonary hypertension patients: the impact of pulmonary arterial remodeling on postoperative and follow-up pulmonary arterial pressure and vascular resistance. *PLoS One* 2015; 10: e0138040.
3. Tapson VF and Humbert M. Incidence and prevalence of chronic thromboembolic pulmonary hypertension: from acute to chronic pulmonary embolism. *Proc Am Thorac Soc* 2006; 3: 564–567.
4. Ghofrani HA, D'Armini AM, Grimminger F, et al. Riociguat for the treatment of chronic thromboembolic pulmonary hypertension. *N Engl J Med* 2013; 369: 319–329.
5. Ozsu S and Cinarka H. Chronic thromboembolic pulmonary hypertension: medical treatment. *Pulm Circ* 2013; 3: 341–344.
6. Nishimura R, Tanabe N, Sugiura T, et al. Improved survival in medically treated chronic thromboembolic pulmonary hypertension. *Circ J* 2013; 77: 2110–2117.
7. Yandrapalli S, Tariq S, Kumar J, et al. Chronic thromboembolic pulmonary hypertension: epidemiology, diagnosis, and management. *Cardiol Rev* 2018; 26: 62–72.
8. Mizoguchi H, Ogawa A, Munemasa M, et al. Refined balloon pulmonary angioplasty for inoperable patients with chronic thromboembolic pulmonary hypertension. *Circ Cardiovasc Interv* 2012; 5: 748–755.
9. Sugimura K, Fukumoto Y, Satoh K, et al. Percutaneous transluminal pulmonary angioplasty markedly improves pulmonary hemodynamics and long-term prognosis in patients with chronic thromboembolic pulmonary hypertension. *Circ J* 2012; 76: 485–488.
10. Olsson KM, Meyer B, Hinrichs J, et al. Chronic thromboembolic pulmonary hypertension. *Dtsch Arztebl Int* 2014; 111: 856–862.
11. Thomassen R, Vandenbroucke JP and Rosendaal FR. Antipsychotic medication and venous thrombosis. *Br J Psychiatry* 2001; 179: 63–66.
12. Wolstein J, Grohmann R, Ruther E, et al. Antipsychotic drugs and venous thromboembolism [letter]. *Lancet* 2000; 356: 252.
13. Wu CS, Chang CM, Chen CY, et al. Association between antidepressants and venous thromboembolism in Taiwan. *J Clin Psychopharmacol* 2013; 33: 31–37.
14. Jiang W, Kuchibhatla M, Cuffe MS, et al. Prognostic value of anxiety and depression in patients with chronic heart failure. *Circulation* 2004; 110: 3452–3456.
15. Bergin CJ, Sirlin C, Deutsch R, et al. Predictors of patient response to pulmonary thromboendarterectomy. *AJR Am J Roentgenol* 2000; 174: 509–515.
16. Thistlethwaite PA, Mo M, Madani MM, et al. Operative classification of thromboembolic disease determines outcome after pulmonary endarterectomy. *J Thorac Cardiovasc Surg* 2002; 124: 1203–1211.
17. Jamieson SW, Kapelanski DP, Sakakibara N, et al. Pulmonary endarterectomy: experience and lessons learned in 1,500 cases. *Ann Thorac Surg* 2003; 76: 1457–1462.
18. ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories. ATS statement: guidelines for the six-minute walk test. *Am J Respir Crit Care Med* 2002; 166: 111–117.
19. Miller MR, Hankinson J, Brusasco V, et al. Standardisation of spirometry. *Eur Respir J* 2005; 26: 319–338.
20. Suzuki H, Sugimura K, Tatebe S, et al. Chronic thromboembolic pulmonary hypertension and schizophrenia. *Int J Cardiol* 2016; 207: 363–364.
21. McGrath J, Saha S, Chant D, et al. Schizophrenia: a concise overview of incidence, prevalence, and mortality. *Epidemiol Rev* 2008; 30: 67–76.
22. Funabashi S, Kataoka M, Inami T, et al. Depressive status in patients with chronic thromboembolic pulmonary hypertension. *Circ J* 2017; 81: 1051–1053.
23. Miwa H, Tanabe N, Jujo T, et al. Long-term outcome of chronic thromboembolic pulmonary hypertension at a single Japanese pulmonary endarterectomy center. *Circ J* 2018; 82: 1428–1436.
24. Conti V, Venegoni M, Cocci A, et al. Antipsychotic drug exposure and risk of pulmonary embolism: a population-based, nested case-control study. *BMC Psychiatry* 2015; 15: 92.
25. Hsu WY, Lane HY, Lin CL, et al. A population-based cohort study on deep vein thrombosis and pulmonary embolism among schizophrenia patients. *Schizophr Res* 2015; 162: 248–252.
26. Maeda T, Babazono A, Nishi T, et al. Influence of psychiatric disorders on surgical outcomes and care resource use in Japan. *Gen Hosp Psychiatry* 2014; 36: 523–527.
27. Barbui C, Conti V and Cipriani A. Antipsychotic drug exposure and risk of venous thromboembolism: a systematic review

and meta-analysis of observational studies. *Drug Saf* 2014; 37: 79–90.

28. Zhang R, Dong L, Shao F, et al. Antipsychotics and venous thromboembolism risk: a meta-analysis. *Pharmacopsychiatry* 2011; 44: 183–188.

29. Vancampfort D, Probst M, Stubbs B, et al. Associations between expiratory spirometry parameters and limitations in daily life activities in patients with schizophrenia. *Gen Hosp Psychiatry* 2014; 36: 172–176.

30. Vancampfort D, Probst M, Stubbs B, et al. Metabolic syndrome and lung function in schizophrenia: a pilot study. *Psychiatry Res* 2014; 220: 58–62.

31. Cramer JA and Rosenheck R. Compliance with medication regimens for mental and physical disorders. *Psychiatr Serv* 1998; 49: 196–201.

32. Fedullo P, Kerr KM, Kim NH, et al. Chronic thromboembolic pulmonary hypertension. *Am J Respir Crit Care Med* 2011; 183: 1605–1613.