Long-Term Outcome of Patients With Chronic Thromboembolic Pulmonary Hypertension

Results From an International Prospective Registry

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Background—Chronic thromboembolic pulmonary hypertension, a rare complication of acute pulmonary embolism, is characterized by fibrothrombotic obstructions of large pulmonary arteries combined with small-vessel arteriopathy. It can be cured by pulmonary endarterectomy, and can be clinically improved by medical therapy in inoperable patients. A European registry was set up in 27 centers to evaluate long-term outcome and outcome correlates in 2 distinct populations of operated and not-operated patients who have chronic thromboembolic pulmonary hypertension.

Methods and Results—A total of 679 patients newly diagnosed with chronic thromboembolic pulmonary hypertension were prospectively included over a 24-month period. Estimated survival at 1, 2, and 3 years was 93% (95% confidence interval [CI], 90–95), 91% (95% CI, 87–93), and 89% (95% CI, 86–92) in operated patients (n=404), and only 88% (95% CI, 83–91), 79% (95% CI, 74–83), and 70% (95% CI, 64–76) in not-operated patients (n=275). In both operated and not-operated patients, pulmonary arterial hypertension–targeted therapy did not affect survival estimates significantly. Mortality was associated with New York Heart Association functional class IV (hazard ratio [HR], 4.16; 95% CI, 1.49–11.62; *P*=0.0065 and HR, 4.76; 95% CI, 1.76–12.88; *P*=0.0021), increased right atrial pressure (HR, 1.34; 95% CI, 0.95–1.90; *P*=0.0992 and HR, 1.50; 95% CI, 1.20–1.88; *P*=0.0004), and a history of cancer (HR, 3.02; 95% CI, 1.36–6.69; *P*=0.0065 and HR, 2.15; 95% CI, 1.18–3.94; *P*=0.0129) in operated and not-operated patients, respectively. Additional correlates of mortality were bridging therapy with pulmonary arterial hypertension–targeted drugs, postoperative pulmonary hypertension, surgical complications, and additional cardiac procedures in operated patients, and comorbidities such as coronary disease, left heart failure, and chronic obstructive pulmonary disease in not-operated patients.

Conclusions—The long-term prognosis of operated patients currently is excellent and better than the outcome of not-operated patients. **(*Circulation*. 2016;133:859-871. DOI: 10.1161/CIRCULATIONAHA.115.016522.)**

Key Words: endarterectomy ■ hypertension, pulmonary ■ pulmonary embolism ■ survival ■ thromboembolism

Chronic thromboembolic pulmonary hypertension (CTEPH) is a rare complication of acute pulmonary embolism with uncertain prevalence, ranging from 0.4% to 9.1%.[1] Diagnosis is strongly associated with a history of acute venous thromboembolism (VTE).[2,3] It is caused by nonresolving fibrothrombotic obstructions of large pulmonary arteries, combined

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with small-vessel arteriopathy in some patients. Both proximal and small-vessel obstruction increase pulmonary vascular resistance (PVR), leading to progressive pulmonary hypertension, right heart failure, and ultimately death. CTEPH can be cured by pulmonary endarterectomy (PEA)[4] and clinically improved by medical therapy.[5,6] Therefore, current guidelines recommend PEA as first-choice therapy, whereas the use of pulmonary arterial hypertension (PAH)–targeted drugs is restricted to inoperable patients or patients with persistent/recurrent pulmonary hypertension after PEA.[7] Balloon pulmonary angioplasty, a new and promising treatment method for patients with inoperable CTEPH, is currently under evaluation.[7]

In patients undergoing surgery, single-center series reported a 3-year survival between 76% and 91%.[8–15] Bridging therapy with PAH-targeted drugs before PEA may improve hemodynamics before PEA[16–18] but does not seem to affect post-PEA outcome and hemodynamics.[19] In inoperable patients, only small-size, single-center series of patients, treated with either intravenous prostacyclin analogs or oral PAH-targeted drugs, have been published, reporting 3-year survival varying from 41% to 80%.[9,14,20–24] In older series, patients receiving only oral anticoagulants had a 3-year survival as low as 30% if mean pulmonary artery pressure (mPAP) was >30 mm Hg.[25,26]

Here, we present long-term data from the first prospective, large-scale, international registry of newly diagnosed patients with CTEPH, including operated and not-operated cases, treated in a broad sample of small to large pulmonary hypertension centers. We have previously described baseline characteristics of the cohort and short-term evolution of surgical patients,[2,27] and now report on long-term survival and long-term prognostic factors in operated (with or without bridging therapy) and not-operated patients (with or without medical treatment).

Methods

Study Design

This prospective registry included newly diagnosed (≤6 months) consecutive patients with CTEPH, who did not receive PAH-targeted treatment before diagnosis, from 27 centers in Europe and Canada, between February 2007 and January 2009, and followed these patients for at least 3 years, with a maximum of ≈5 years (data cutoff, February 26, 2012).

The registry protocol did not interfere with the management of patients by their physician. Data were obtained from assessments that are routinely performed for CTEPH patients in clinical practice including medical history, clinical signs and symptoms, and diagnosis and treatment procedures. Formal ethics approvals were obtained when required by country regulatory agency or site regulations.

Inclusion Criteria

At all participating institutions, the diagnosis of CTEPH was established according to clinical guidelines valid at study initiation[28] and within 6 months of inclusion in the registry. To qualify for inclusion, patients had to be ≥18 years with pulmonary hypertension confirmed by right heart catheterization demonstrating a mPAP ≥ 25 mm Hg at rest or ≥30 mm Hg with exercise and a pulmonary capillary wedge pressure ≤15 mm Hg (or >15 mm Hg if justified).

CTEPH had to be confirmed as the cause of pulmonary hypertension by abnormalities in a ventilation/perfusion scan (at least 1 mismatched segmental perfusion defect) and in a computed tomography scan or a pulmonary angiography. Proximal lesions (webs, bands, and narrowed vessels) were identified by computed tomography scan/pulmonary angiography. Before diagnosis, patients were required to have at least 3 months of anticoagulation therapy (to exclude patients with subacute pulmonary embolism) and no PAH-targeted treatment.

Surgery

The PEA procedure has been described previously.[4,27] Predefined criteria for inoperability were assessed by participating centers and included distal pulmonary artery obstructions, imbalance between increased PVR and the amount of accessible occlusions suggesting microvascular disease, PVR >1500 dyn.s.cm^{-5}, age (an age limit was not specified but left to be decided by the study site), and comorbidity. Postoperative pulmonary hypertension was defined as mPAP ≥25 mm Hg by right heart catheterization or systolic pulmonary arterial pressure ≥40 mm Hg by echocardiography at day 2 to 3 after surgery.

Statistical Analysis

Data analysis was performed by using the SAS software package version 9.3 (SAS Institute Inc, Cary, NC). The effect of explanatory variables on survival time was first analyzed separately in operated and not-operated patients. Selection of 47 covariates in operated patients and 33 in not-operated patients was based on expert opinion and included demographics, clinical status, hemodynamics, pulmonary function tests, imaging, conditions associated to VTE (history of cancer) and CTEPH (inflammatory conditions including rheumatoid arthritis, osteoarthritis, inflammatory bowel disease, dialysis-dependent renal failure, spherocytosis, splenectomy, pacemaker, and ventriculoatrial shunt[29]), comorbidities (obesity, coronary disease, left heart failure, left-sided valvular heart disease, and chronic obstructive pulmonary disease), PAH-targeted treatment, other therapies, and surgical aspects. They are listed in Tables 1, 2, and 3.

Descriptive statistics (median, minimum-maximum or percentage of patients with assessment) were provided for the selected covariates. Wilcoxon 2-sample test was used for comparing continuous variables, and the Fisher exact 2×2 test was used to test the specified category against the other categories combined. All inferential statistical analyses were performed in an exploratory sense. Hazard ratio (95% confidence interval, *P* value) were calculated by using univariable Cox regression. Stepwise selection method of SAS procedure PHREG was used for variable selection in the multivariable Cox analysis. The significance level for entry and removal of explanatory variables was 0.10. Covariates were selected as input into the stepwise selection of the Cox regression analysis as they fulfilled the inclusion criterion of a percentage of nonmissing values ≥90% and an univariable *P* value ≤0.25. Missing values were handled as missing in all statistical analyses. No substitution of missing values was performed.

Time to death (all cause) were estimated by the Kaplan–Meier method and analyzed by the log-rank test to compare operated and not-operated patients.

A bivariate Cox regression analysis was run in all CTEPH patients including PEA as a predictor of death, providing adjusted hazard ratios for each single covariate (eg, age) and for covariate PEA. Stepwise variable selection in the multivariable Cox regression using all CTEPH patients was performed analogously as in operated and not-operated patients. The covariate PEA was then forced in the multivariable model.

Results

Study Population

Six hundred seventy-nine patients were enrolled in the registry: at the time of registry closure, 404 (60%) had been operated on and 275 (40%) had not, of whom 38 patients refused an operation. The other reasons for not being operated on were surgical inaccessibility of vascular occlusions (n=112), imbalance between increased PVR and the amount of accessible occlusions (n=24), PVR >1500 dyn.s.cm^{-5} (n=4), age (n=5), comorbidities (n=32), other (n=42) or unknown (n=18) reasons.

Table 1. Baseline Characteristics of Subsequently Operated and Not-Operated Patients

	Operated n=404 (60%)	n	Not-Operated n=275 (40%)	n	*P* Value
Age, y	60 (18–84)	–	67 (22–86)	–	<0.0001
Sex, % male	55	–	43	–	0.0038
BMI, kg/m^2	26 (15–49)		26 (15–55)		0.78
Time from symptoms to diagnosis, mo	15 (0.2–441)	390	14 (0.1–214)	247	0.64
NYHA class I–II/III/IV, %	19/69/12	–	18/69/13	–	0.76/ 0.93/ 0.81
6MWD, m	340 (20–700)	353	315 (11–677)	237	0.0045
RAP, mm Hg	9 (0–38)	390	8 (0–40)	266	0.25
PAP, mm Hg	48 (17–80)	402	45 (14–81)	273	0.0164
CI, L·min^{-1}·m^{-2}	2.2 (0.9–7.0)	383	2.3 (1.1–5.1)	253	0.0201
PCWP, mm Hg	10 (1–35)	362	10 (1–40)	251	0.49
PVR, dyn.s.cm^{-5}	728 (97–2880)	361	676 (165–2800)	247	0.12
FEV1, L in 1 s	2.5 (0.9–5.0)	360	2.2 (0.7–4.7)	235	<0.0001
DLCO/VA, % of predicted	74.0 (19.0–107.4)	233	73.0 (15.0–109.0)	155	0.88
Angiographic obstruction*		302		171	
Main PA, %	26		11		<0.0001
Lobar, %	62		48		0.0050
Segmental, %	12		41		<0.0001
Perfusion defects*		295		182	
Total lung defect, %	9		4		0.0414
Segmental, %	88		76		0.0016
Subsegmental, %	4		20		<0.0001
History of acute VTE, %	81	387	72	260	0.0040
IVC filter for acute PE, %	14	312	9	180	0.0880
Thrombophilic disorder, %	41	369	33	216	0.0777
Blood group O/non-O, %	20/80	296	33/68	126	0.0056
History of cancer, %	12	398	16	265	0.20
Smoking, %	34	396	34	266	0.93
Obesity, %	17	–	20	–	0.31
Inflammatory conditions	8	391	12	260	0.11
Coronary disease/ myocardial infarction, %	10	395	15	263	0.0699
CHF or LV dysfunction, %	5	–	9	–	0.0606
Left-sided valvular disease, %	0.5	–	3.7	–	0.0088
Dialysis-dependent renal failure, %	0.5	–	0.4	–	1.00
COPD, %	8	384	13	257	0.0594
PAH-targeted treatment started at diagnosis, %	29	–	51	273	<0.0001
PAH-targeted treatment at any time, %	36	–	61	–	<0.0001
Calcium channel blockers	8	–	17		0.0005
β-Blockers, %	8	–	15	–	0.0040
Diuretics, %	37	–	57	–	<0.0001

Values are expressed as medians (min–max) or percentages; n: patients with available data (for incomplete data set). BMI indicates body mass index; CHF, congestive heart failure; CI, cardiac index; COPD, chronic obstructive pulmonary disease; DLCO, diffusion capacity; FEV1, forced expiratory volume in 1 second; IVC, inferior vena cava; LV, left ventricle; 6MWD, 6 minutes walking distance; NYHA, New York Heart Association; PA, pulmonary artery; PAH, pulmonary arterial hypertension; PAP, pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; PE, pulmonary embolism; PVR, pulmonary vascular resistance; RAP, right atrial pressure; VA, alveolar volume; and VTE, venous thromboembolism.

*Most proximal vascular lesions. Inflammatory conditions included rheumatoid arthritis, osteoarthritis, inflammatory bowel disease, dialysis-dependent renal failure, spherocytosis, splenectomy, pacemaker, and ventriculoatrial shunt.

Table 2. Baseline and Postoperative Characteristics of Operated Patients Stratified by Whether They Received Bridging Therapy With PAH-Targeted Drugs

	No Bridging Therapy n=286 (71%)	n	Bridging Therapy n=118 (29%)	n	*P* Value
Age, y	61 (18–84)	–	58 (18–80)	–	0.11
Sex, % male	55	–	53	–	0.74
BMI, kg/m^2	26 (15–49)	–	27 (16–49)	–	0.30
Time from symptoms to diagnosis, mo	15 (0.6–441)	276	14 (0.2–400)	114	0.57
NYHA class I–II/III/IV, %	22/66/12	–	12/75/13	–	0.0180/ 0.0601/ 0.87
6MWD, m	342 (20–700)	248	323 (58–630)	105	0.61
RAP, mm Hg	8 (0–27)	281	10 (0–38)	109	0.0033
PAP, mm Hg	47 (17–80)	284	50 (29–79)	–	0.0005
CI, L·min^{-1}·m^{-2}	2.3 (0.9–7.0)	276	1.9 (1.1–4.6)	107	<0.0001
PCWP, mm Hg	9 (1–26)	268	10 (3–35)	94	0.0252
PVR, dyn.s.cm^{-5}	697 (97–2682)	263	864 (272–2880)	98	0.0007
FEV1, L in 1 s	2.5 (1.0–5.0)	254	2.5 (0.9–4.8)	106	0.88
DLCO/VA, % of predicted	74.0 (38.0–107.4)	177	72.0 (19.0–100.0)	56	0.40
Angiographic obstruction*		228		74	
Main PA, %	25		28		0.65
Lobar, %	61		62		1.00/
Segmental, %	13		10		0.54
Perfusion defects*		238		57	
Total lung defect, %	10		5		0.44
Segmental, %	87		90		0.82/
Subsegmental, %	3		5		0.45
History of acute VTE, %	81	276	82	111	0.89
IVC filter for acute PE, %	17	226	7	86	0.0196
Thrombophilic disorder, %	49	268	20	101	<0.0001
Blood group O/non-O, %	19/81	204	22/78	92	0.53
History of cancer, %	13	283	10	115	0.49
Smoking, %	33	281	36	115	0.64
Obesity, %	16	–	20	–	0.38
Inflammatory conditions	9	278	6	113	0.42
Coronary disease/myocardial infarction, %	14	282	3	113	0.0008
CHF or LV dysfunction, %	6	–	3	117	0.15
Left-sided valvular disease, %	0.8	266	0	110	1.00
Dialysis-dependent renal failure, %	0.7	282	0	113	1.00
COPD, %	9	272	6	112	0.54
PAH-targeted therapy started at diagnosis, %	0	–	98	–	<0.0001
PAH-targeted therapy at any time, %	10	–	100	–	<0.0001
Calcium channel blockers	10	–	2	–	0.0019
β-Blockers, %	10	–	3	–	0.0269
Diuretics, %	37	–	38	–	0.82
PAH-targeted therapy started before PEA, %	0	–	100	–	<0.0001
Site experience in PEA		–		–	
0%	0		0		–
1%–10%	14		16		0.64
11%–50%	54		37		0.0022
>50%	32		47		0.0062
Number of PEA per center	62 (1–99)	–	30 (1–99)	117	0.0001

(*Continued*)

Table 2. Continued

	No Bridging Therapy n=286 (71%)	n	Bridging Therapy n=118 (29%)	n	*P* Value
Time from symptoms to PEA, mo	19 (2–447)	276	21 (3–413)	114	0.14
Time from most recent PE to PEA, mo	14 (0.3–411)	194	19 (3–351)	83	0.0306
Time from CTEPH diagnosis to PEA, mo	2.1 (0.0–44)	–	4.6 (0.1–38)	–	<0.0001
IVC filter, all, %	32	285	62	117	<0.0001
Duration of circulatory arrest, min	35 (0–158)	284	38 (0–177)	–	0.17
Last PVR in ICU, dyn.s.cm^{-5}	245 (53–1440)	197	248 (32–1440)	95	0.66
Change in PVR, dyn.s.cm^{-5}	–452 (–2256 to 554)	182	–598 (–2261 to 271)	80	0.0329
Postoperative PH, %	18	–	15	–	0.66
Reperfusion edema, %	8	–	12	–	0.27
All other complications, %	46	–	44	–	0.74
Additional cardiac procedure, %	17	281	11	117	0.13

Values are expressed as medians (min–max) or percentages; n: patients with available data (for incomplete dataset). BMI indicates body mass index; CHF, congestive heart failure; CI, cardiac index; COPD, chronic obstructive pulmonary disease; CTEPH, chronic thromboembolic pulmonary hypertension; DLCO, diffusion capacity; FEV1, forced expiratory volume in 1 second; ICU, intensive care unit; IVC, inferior vena cava; LV, left ventricle; 6MWD, 6 minutes walking distance; NYHA, New York Heart Association; PA, pulmonary artery; PAH, pulmonary arterial hypertension; PAP, pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; PE, pulmonary embolism; PEA, pulmonary endarterectomy; PVR, pulmonary vascular resistance; RAP, right atrial pressure; VA, alveolar volume; and VTE, venous thromboembolism.

*Most proximal vascular lesions in right or left lung. Inflammatory conditions included rheumatoid arthritis, osteoarthritis, inflammatory bowel disease, dialysis-dependent renal failure, spherocytosis, splenectomy, pacemaker, and ventriculoatrial shunt.

Patient Characteristics

Operated Versus Not-Operated Patients

Operated patients were younger, predominantly male, had higher 6 minutes walking distance, higher mPAP, lower cardiac index, higher forced expiratory volume in 1 second, more main pulmonary artery and lobar obstruction at angiography, and more total lung and segmental perfusion defects than not-operated patients (Table 1). However, New York Heart Association (NYHA) functional class, right atrial pressure (RAP), and PVR were similar. A history of acute VTE and blood group non-O was more common in operated patients. They had less left-sided valvular heart disease, PAH-targeted therapy was started less frequently, and treatments with calcium channel blockers, β-blockers, and diuretics were less frequently ongoing or started at diagnosis.

Operated Patients, Stratified by Whether They Received Bridging Therapy to PEA

Twenty-nine percent of operated patients received bridging therapy with PAH-targeted drugs: 15% received a phosphodiesterase-5 inhibitor (sildenafil), 13% received an endothelin receptor antagonist (bosentan), and 1% received a prostacyclin analog (epoprostenol or iloprost; Table 2). In comparison with patients who did not receive bridging therapy, these patients were less frequently in NYHA class I to II, had a more compromised hemodynamic profile with higher RAP, mPAP, PVR (864 versus 697 dyn.s.cm^{-5}), and lower cardiac index. They were less likely to have an inferior vena cava filter, and fewer had a history of thrombophilic disorders and coronary disease. Fewer had treatments with calcium channel blockers and β-blockers ongoing or started at diagnosis. Although PVR at diagnosis was higher in patients receiving bridging therapy, the last postoperative PVR measured in the intensive care unit was similar, as a consequence of a greater decrease in PVR induced by the combination of medical and surgical treatment. PEA complications were not differently distributed in patients receiving bridging therapy or not: infection was observed in 20% versus 20%, postoperative pulmonary hypertension in 15% versus 18%, neurological complications in 9% versus 13%, bleeding in 11% versus 9%, reperfusion edema in 12% versus 8%, and pericardial effusion in 5% versus 9%, respectively. Operated patients with neurological complications had longer circulatory arrest times (42 versus 35 minutes, P=0.0026).

Not-Operated Patients, Medically Treated Versus Not Medically Treated

Sixty-one percent of not-operated patients were treated with PAH-targeted drugs at diagnosis (82%) or later (18%), 17% with phosphodiesterase-5 inhibitor (sildenafil), and 24% with endothelin receptor antagonist (bosentan, and a few with sitaxentan), 18% with both drug classes, and 2% with prostacyclin analog (epoprostenol, treprostinil, and iloprost; Table 3). In comparison with not medically treated patients, they had a shorter time from symptoms to diagnosis, were less frequently NYHA class I to II, had lower 6 minutes walking distance, more severe hemodynamic profile with higher mPAP, PVR, and lower cardiac index and pulmonary capillary wedge pressure. They had fewer thrombophilic disorders, blood group non-O, coronary disease and left-sided valvular heart disease, treatments with calcium channel blockers and β-blockers ongoing or started at diagnosis, and more treatments with diuretics.

Outcome

During the observation period of 1287 days (median, 3–1902 range), from the date of diagnosis to the date of death or last observation, 143 (21%) patients died, 51 in the operated group and 92 in the not-operated group. Causes of death were right heart failure (15/49), perioperative complications (22/0), infection (5/6), malignancy (3/6), sudden death (0/6), bleeding (0/5), respiratory failure (0/4), renal failure (1/3), others (4/4:

Table 3. Baseline Characteristics of Not-Operated Patients Stratified by Whether They Received PAH-Targeted Drugs

	Not Medically Treated n=107 (39%)	n	Medically Treated n=168 (61%)	n	*P* Value
Age, y	66 (30–85)	–	68 (22–86)	–	0.80
Sex, % male	43	–	44	–	1.00
BMI, kg/m^2	26 (15–46)	–	25 (16–55)	–	0.30
Time from symptoms to diagnosis, mo	20 (0.7–214)	92	11 (0.1–182)	155	0.0001
NYHA class I–II/III/IV, %	27/63/10	–	12/73/15	–	0.0020/ 0.0816/ 0.36
6MWD, m	340 (18–605)	89	300 (11–677)	148	0.0406
RAP, mm Hg	8 (0–40)	103	8 (0–37)	163	0.68
PAP, mm Hg	41 (14–73)	105	47 (25–81)	–	<0.0001
CI, L·min^{-1}·m^{-2}	2.5 (1.2–4.0)	99	2.2 (1.1–5.1)	154	0.0171
PCWP, mm Hg	11 (1–26)	102	9 (2–40)	149	0.0018
PVR, dyn.s.cm^{-5}	480 (165–2304)	98	778 (181–2800)	149	<0.0001
FEV1, L in 1 s	2.3 (0.7–4.7)	86	2.2 (0.7–4.6)	149	0.15
DLCO/VA, % of predicted	74.0 (15.0–107.1)	52	71.0 (27.0–109.0)	103	0.40
Angiographic obstruction*		67		104	
Main PA, %	15		9		0.22
Lobar, %	42		52		0.21
Segmental, %	43		39		0.64
Perfusion defects*		74		108	
Total lung defect, %	5		3		0.44
Segmental, %	73		78		0.48
Subsegmental, %	22		19		0.71
History of acute VTE, %	71	101	72	159	1.00
IVC filter for acute PE, %	11	72	7	108	0.43
Thrombophilic disorder, %	53	73	23	143	<0.0001
Blood group O/non-O, %	18/82	49	42/58	77	0.0069
History of cancer, %	13	104	17	161	0.30
Smoking	36	102	32	164	0.50
Obesity	24	–	17	–	0.17
Inflammatory conditions	10	102	14	158	0.44
Coronary disease/myocardial infarction, %	23	102	11	161	0.0129
CHF or LV dysfunction, %	11	105	8	167	0.67
Left-sided valvular disease, %	10	93	0	152	0.0001
Dialysis-dependent renal failure, %	0	103	0.6	159	1.00
COPD, %	16	97	11	160	0.34
PAH-targeted therapy started at diagnosis, %	0	105	82	–	<0.0001
PAH-targeted therapy at any time, %	0	–	100	–	<0.0001
Calcium channel blockers, %	27	105	10		0.0008
β-Blockers, %	25	105	10	–	0.0010
Diuretics, %	48	105	63	–	0.0167

Values are expressed as medians (min–max) or percentages; n: patients with available data (for incomplete dataset). BMI indicates body mass index; CHF, congestive heart failure; CI, cardiac index; COPD, chronic obstructive pulmonary disease; DLCO, diffusion capacity; FEV1, forced expiratory volume in 1 second; IVC, inferior vena cava; LV, left ventricle; 6MWD, 6 minutes walking distance; NYHA, New York Heart Association; PA, pulmonary artery; PAH, pulmonary arterial hypertension; PAP, pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; PE, pulmonary embolism; PVR, pulmonary vascular resistance; RAP, right atrial pressure; VA, alveolar volume; and VTE, venous thromboembolism.

*Most proximal vascular lesions in right or left lung. Inflammatory conditions included rheumatoid arthritis, osteoarthritis, inflammatory bowel disease, dialysis-dependent renal failure, spherocytosis, splenectomy, pacemaker, and ventriculoatrial shunt.

cerebrovascular accident, trauma, acute myocardial infarction, Wegener granulomatosis, pulmonary embolism, and cachexia), and unknown (1/9), in operated and not-operated patients, respectively. Among the 22 patients who died of perioperative complications, 10 experienced persistent pulmonary hypertension, 9 had bleeding complications, 7 had pulmonary reperfusion edema, 7 experienced infection, 2 had pericardial effusion, 1 had neurological complications, and 8 needed extracorporeal membrane oxygenation (numbers not mutually exclusive). These 22 patients died within 15±19 days (mean±standard deviation) of surgery, with a median of 7 days (95% CI, 5–13).

Estimated survival at 1, 2, and 3 years was higher in the operated group, respectively, 93% (95% CI, 90–95), 91% (95% CI, 87–93), and 89% (95% CI, 86–92), than in the not-operated group 88% (95% CI, 83–91), 79% (95% CI, 74–83), and 70% (95% CI, 64–76; χ^2=48.49, P<0.0001; Figure 1). In operated patients, those medically treated before PEA had similar survival (χ^2=2.96, P=0.0855; Figure 2) but a more compromised hemodynamic profile than not medically treated (Table 2). Also in not-operated patients, survival curves of medically treated and not medically treated patients were not different (χ^2=0.45, P=0.50; Figure 3), again with a much worse hemodynamic profile in the treated patients (Table 3).

Survivors Versus Nonsurvivors

In operated patients, survivors were 8 years younger, less frequently NYHA class IV, had higher 6 minutes walking distance (350 versus 290 m), lower RAP (8 versus 12 mm Hg) and PVR (710 versus 844 dyn.s.cm^{-5}), and higher cardiac index (2.2 versus 2.0 L·min^{-1}·m^{-2}; Table I in the online only Data Supplement). They also had fewer inflammatory conditions. Last PVR in intensive care unit was lower (241 versus 289 dyn.s.cm^{-5}) and fewer patients had postoperative pulmonary hypertension (14% versus 37%). Reperfusion edema (8% versus 20%), other surgery complications (41% versus 78%) and additional cardiac surgery (14% versus 28%) were less frequent. PAH-targeted treatment at any time was started less frequently (34% versus 51%).

In not-operated patients, survivors were more frequently NYHA class II and less frequently class IV. They had a much higher 6 minutes walking distance (349 versus 252 m), lower RAP (7 versus 11 mm Hg), mPAP (43 versus 47 mm Hg), and PVR (640 versus 779 dyn.s.cm^{-5}), and higher diffusion capacity (76% versus 66% of predicted value). They had less history of cancer (12% versus 22%), coronary disease (11% versus 23%), left heart failure (6% versus 17%), and chronic obstructive pulmonary disease (9% versus 21%).

Outcome Correlates

Separate Analyses of Operated and Not-Operated Patients

Results of the univariable analyses are reported in Table II and Figures I and II in the online only Data Supplement.

Independent mortality correlates, discovered in the multivariable analysis, differed in operated and not-operated patients (Table 4, Figures 4 and 5). In operated patients, the preoperative characteristics increasing mortality were dialysis-dependent renal failure (HR, 11.52; 95% CI, 1.42–93.48; P=0.0221), bridging therapy with PAH drugs (HR, 2.62; 95% CI, 1.30–5.28; P=0.0072), and the need for additional cardiac procedures (HR, 3.10; 95% CI, 1.54–6.24; P=0.0015). Operative complications (HR, 3.82; 95% CI, 1.72–8.51; P=0.0010) and postoperative pulmonary hypertension (HR, 3.66; 95% CI, 1.72–7.82; P=0.0008) further increased mortality. In contrast, a higher preoperative mPAP and a history of acute VTE were associated with lower mortality. In not-operated patients, mortality was mainly increased by the presence of comorbidities such as coronary disease (HR, 1.81; 95% CI, 1.00–3.28; P=0.0492), left heart failure (HR, 1.98; 95% CI, 1.02–3.83; P=0.0440), and chronic obstructive pulmonary disease (HR, 2.14; 95% CI, 1.22–3.73; P=0.0075). Importantly, NYHA class IV was the most

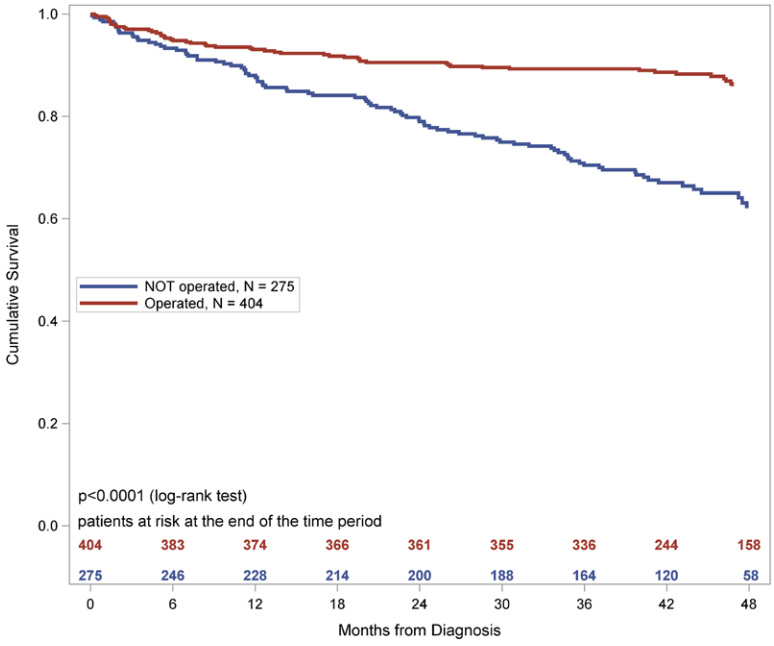

Figure 1. Kaplan–Meier estimates of survival from date of diagnosis in operated and not-operated CTEPH patients. CTEPH indicates chronic thromboembolic pulmonary hypertension.

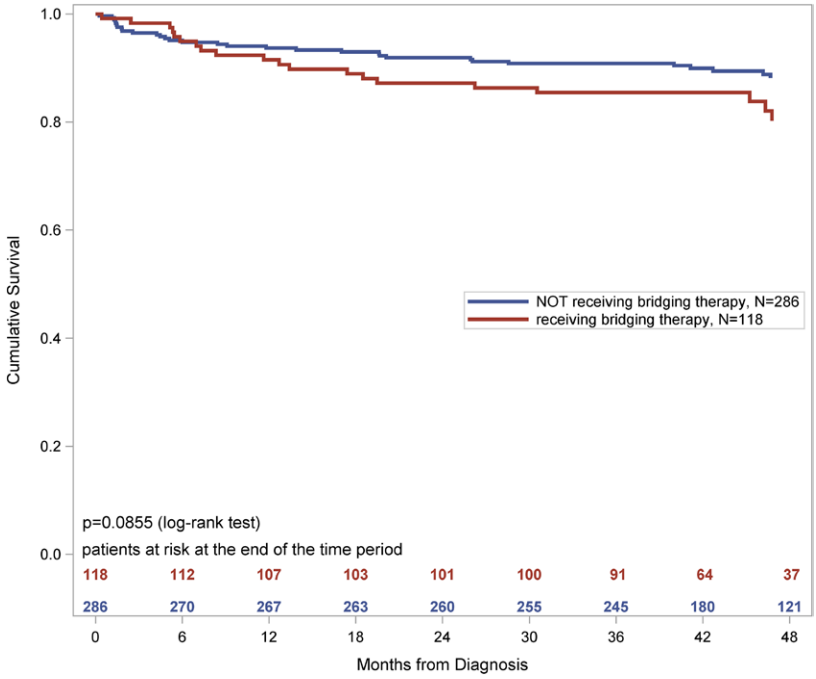

Figure 2. Kaplan–Meier estimates of survival from date of diagnosis in operated patients, stratified by whether they received bridging therapy to PEA. PEA indicates pulmonary endarterectomy.

important predictor of death in both groups, increasing mortality by 4 to 5 times (HR, 4.16; 95% CI, 1.49–11.62; *P*=0.0065 and HR, 4.76; 95% CI, 1.76–12.88; *P*=0.0021, respectively) in comparison with NYHA class I to II patients. Other correlates were increased RAP (HR, 1.34; 95% CI, 0.95–1.90; *P*=0.0992 and HR, 1.50; 95% CI, 1.20–1.88; *P*=0.0004), and a history of cancer (HR, 3.02; 95% CI, 1.36–6.69; *P*=0.0065 and HR, 2.15; 95% CI, 1.18–3.94; *P*=0.0129).

Global Analysis of the Overall Population (Operated and Not-Operated Patients)

When considering the whole patient cohort, PEA was the strongest independent predictor of survival (HR, 0.37; 95% CI, 0.24–0.58; *P*<0.0001; Table 5). Other independent risks factors were age, NYHA class, RAP and history of cancer, left heart failure or left systolic/diastolic ventricular dysfunction, and dialysis-dependent renal failure.

Discussion

The present multicenter registry represents the largest prospectively collected contemporary population of newly diagnosed CTEPH patients with long-term follow-up, including operated and not-operated cases. The main finding is that operated patients have a significantly better long-term survival than not-operated patients, despite similar hemodynamic

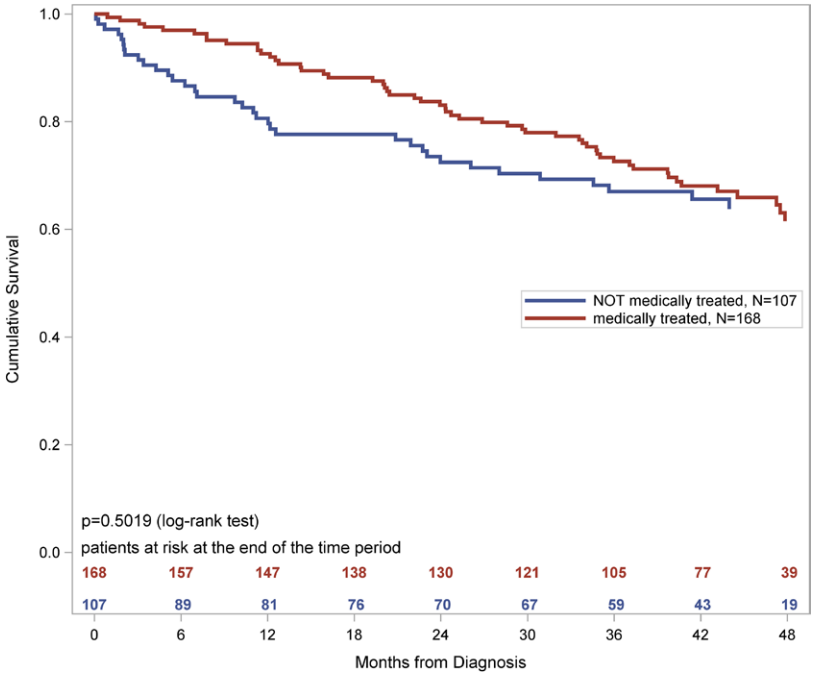

Figure 3. Kaplan–Meier estimates of survival from date of diagnosis in not-operated, medically treated and not-treated CTEPH patients (at any time). CTEPH indicates chronic thromboembolic pulmonary hypertension.

Table 4. Independent Correlates of Mortality for Operated and Not-Operated Patients

	Operated (n=346)			Not-Operated (n=219)		
Covariate	HR	95% CI	*P* Value	HR	95% CI	*P* Value
NYHA class III vs I–II				2.43	1.00–5.89	0.0489
NYHA class IV vs I–II	4.16	1.49–11.62	0.0065	4.76	1.76–12.88	0.0021
RAP	1.34	0.95–1.90	0.0992	1.50	1.20–1.88	0.0004
PAP	0.67	0.47–0.94	0.0226			
History of acute VTE	0.48	0.24–0.97	0.0413			
History of cancer	3.02	1.36–6.69	0.0065	2.15	1.18–3.94	0.0129
Coronary disease/myocardial infarction	–			1.81	1.00–3.28	0.0492
CHF or LV dysfunction	–			1.98	1.02–3.83	0.0440
Dialysis-dependent renal failure	11.52	1.42–93.48	0.0221	–		
COPD	–			2.14	1.22–3.73	0.0075
PAH-targeted therapy started at diagnosis	2.62	1.30–5.28	0.0072	–	–	–
Postoperative PH	3.66	1.72–7.82	0.0008	–	–	–
All other complications	3.82	1.72–8.51	0.0010	–	–	–
Additional cardiac procedure	3.10	1.54–6.24	0.0015	–	–	–

Cox multivariable analysis of operated and not-operated patients, separately. CHF indicates congestive heart failure; CI, confidence interval; COPD, chronic obstructive pulmonary disease; HR, hazard ratio; LV, left ventricle; NYHA, New York Heart Association; PAH, pulmonary arterial hypertension; PAP, pulmonary artery pressure; PH, pulmonary hypertension; RAP, right atrial pressure; and VTE, venous thromboembolism

severity at diagnosis, confirming that the prognosis following PEA is excellent in well-selected patients.

Operated Patients

PEA is the therapy of choice for CTEPH.[30] It consists in removing all thrombotic endoluminal material, neointima, and few elastic lamellae from the inner layers of the tunica media of pulmonary arteries using a surgical approach.[31] Under optimal conditions, including experienced centers and selected patients, PEA can be performed with low perioperative mortality, with improvements in hemodynamics, symptoms, and survival.[7,32] According to the current CTEPH registry, PEA can be performed in most CTEPH patients (60%) with 4.7% in-hospital mortality. The present multicenter registry also shows a 3-year survival of 89% in operated patients, which has to be compared with 81%[8] and 76%[9] 3-year survival rates reported 15 and 8 years ago in 2 large single-center cohorts. It suggests that the technique, presumably also general patient care, have improved over time and that PEA can be performed safely in experienced European centers.

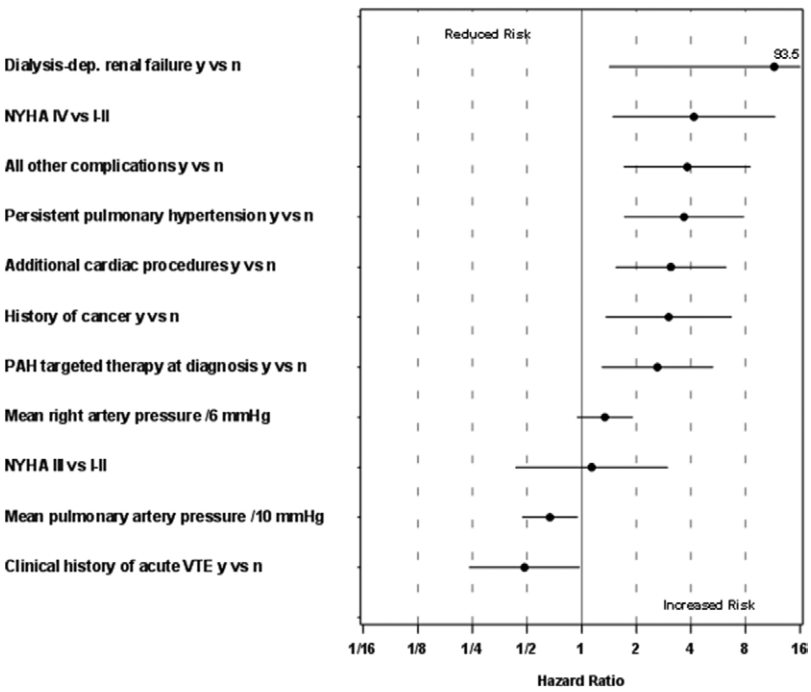

Figure 4. Hazard ratios and 95% confidence limits for risk factors of death in operated patients identified by multivariable analysis. n indicates no; NYHA, New York Heart Association functional class; PAH, pulmonary arterial hypertension; VTE, venous thromboembolism; and y, yes.

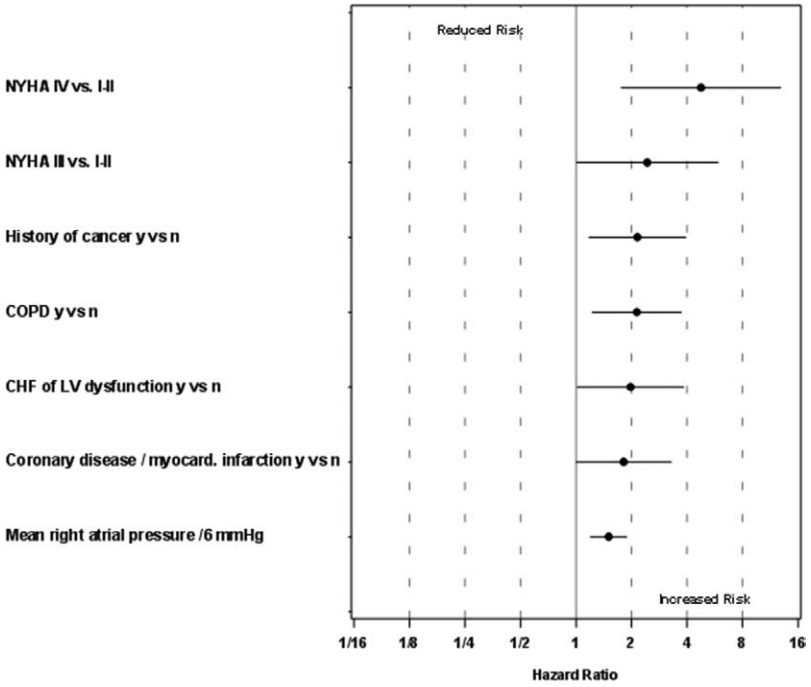

Figure 5. Hazard ratios and 95% confidence limits for risk factors of death in not-operated patients identified by multivariable analysis. CHF indicates congestive heart failure; COPD, chronic obstructive pulmonary disease; LV, left ventricular; n, no; NYHA, New York Heart Association functional class; and y, yes.

Surprisingly, the number of PEAs performed per center did not appear as a determinant of improved long-term survival in the multivariable analysis (Table 4). However, in the smallest centers performing <10 PEAs per year, the mortality, both in-hospital and at long term, was 2-fold higher than in centers with a larger volume of surgery (Table 6). The absence of a difference between intermediate-size centers and high-volume centers could be related to the fact that the largest centers operate on more high-risk patients.

According to the multivariable analysis, bridging therapy with PAH-targeted drugs, in nearly one-third of the operated patients, increased the risk of death. Possible explanations are: (1) delayed PEA because of the start of medical therapy, as suggested by a retrospective analysis from the San Diego PEA center[19] and by the longer time from CTEPH diagnosis to PEA in the current registry (Table 2); (2) possible effects of PAH-targeted therapies on the properties of chronic thromboembolic material making surgery more difficult[7]; and (3) most importantly, the strictly observational nature of the registry with medical therapy started more often in patients with more severe hemodynamics (Table 2). In any case, the registry data tend to discourage the use of bridging therapy in operable patients.

Table 5. Multivariable Correlates of Mortality for All Patients

	HR Risk factor		
	HR	95% CI	*P* Value
PEA performed, yes vs no	0.37	0.24–0.58	<0.0001
Age, /10 y	1.27	1.05–1.53	0.0142
NYHA class			
III vs I/II	1.24	0.61–2.56	0.55
IV vs I/II	2.81	1.25–6.28	0.0118
RAP, /6 mm Hg	1.38	1.14–1.67	0.0011
History of cancer, yes vs no	2.04	1.23–3.39	0.0059
CHF or LV systolic/diastolic dysfunction, yes vs no	2.16	1.20–3.87	0.0097
Dialysis-dependent renal failure, yes vs no	13.32	1.79–99.17	0.0115

Multivariable analysis including PEA in all CTEPH patients. CHF indicates congestive heart failure; CI, confidence interval; CTEPH, chronic thromboembolic pulmonary hypertension; HR, hazard ratio; LV, left ventricle; NYHA, New York Heart Association; PEA, pulmonary endarterectomy; and RAP, right atrial pressure.

Among the other factors influencing mortality in operated patients, operative complications, postoperative pulmonary hypertension, additional cardiac procedures performed concomitantly with the PEA, and a history of cancer were observed in 46%, 17%, 15%, and 12% of the patients, respectively, and increased mortality by 3-fold. In contrast, a history of acute VTE was observed in 80% of patients and reduced mortality by half.

Preoperative placement of an inferior vena cava filter to prevent embolic recurrences in the postoperative period and later, which was initially recommended for PEA,[4] was progressively abandoned by an increasing number of centers. This is now supported by the registry data showing that the presence of an inferior vena cava filter in 40% of the patients did not influence long-term survival.

Regarding timing and patient selection for PEA, the current registry shows that neither the delay between symptoms and PEA, neither between most recent pulmonary embolism and PEA, nor between CTEPH diagnosis and PEA were related to survival (Table I in the online only Data Supplement). As a consequence, an ideal time frame to perform PEA in patients with CTEPH does not seem to exist. Our data suggest a more cautious approach to surgery in patients with high NYHA class, high RAP, a history of cancer, and dialysis-dependent renal failure (risk of death increased by a factor 11.5) and a reduced risk in patients with a history of acute VTE. However, we cannot derive recommendations for patient selection

Table 6. Center Expertise and PEA Survival (Based on Centers' Data From 2004 to 2006)

	1–10	11–50	>50	All
Number of PEA centers, n (%)	5 (33.3)	8 (53.3)	2 (13.3)	15
Number of PEAs, n (%)	57 (14.1)	201 (49.9)	145 (36.0)	403
Number of PEAs per center	12 (3–20)	22 (2–62)	73 (46–99)	18 (2–99)
Death, n (%)				
In-hospital	5 (8.8)	9 (4.5)	5 (3.4)	19 (4.7)
1-y	9 (15.8)	14 (7.0)	12 (8.3)	35 (8.7)
3-y	10 (17.5)	17 (8.5)	16 (11.0)	43 (10.7)
Moved centers for follow-up, n (%)	1 (1.8)	13 (6.5)	77 (53.1)	91 (22.6)

1–10, 11–50, >50 correspond to the number of PEAs performed per year. Differences in mortality are nonsignificant. Fisher exact 2×3 tests give P=0.25, 0.12, and 0.14 for in-hospital, 1-, and 3-year mortality, respectively. PEA indicates pulmonary endarterectomy.

for PEA because these prognostic factors would also have affected survival if patients were not operated on.

Not-Operated Patients

In our registry not-operated patients represented only 40% of the overall cohort. They were quite different from the operated patients (older, more female, more distal angiographic abnormalities). In comparison with operated patients, survival at 3 years was only 70% versus 89%, despite similar severity regarding functional class and hemodynamics at diagnosis. This is, however, still better than the reported outcome of patients with idiopathic PAH, with 1-, 2-, and 3-year survivals of 86%, 70%, and 55%, respectively.[33]

The main determinants of survival were functional class, RAP, and the presence of comorbidities such as cancer, coronary disease, left heart failure, and chronic obstructive pulmonary disease, observed in 16%, 15%, 9%, and 13% of the patients, respectively.

All not-operated patients received anticoagulation and 61% received PAH-targeted therapy. Surprisingly, the survival of medically treated patients was not improved in comparison with untreated patients, which could have been related to their worse functional and hemodynamic profile at diagnosis. However, the multivariable analysis also did not show any benefit of medical therapy. It is noteworthy that PAH-targeted drugs were used off-label because the efficacy of endothelin receptor antagonist and phosphodiesterase-5 inhibitor had not been proven in CTEPH by randomized controlled trials. These drugs were not available in all countries and for all patients, and patients with less severe CTEPH were not treated. Riociguat, the first drug approved for inoperable CTEPH, on the basis of a short-term randomized controlled trial,[6] was not yet available during the registry data collection.

Limitations

Surgical and medical treatment approaches for CTEPH cannot be formally compared because they target different populations, the operable patients with surgically accessible disease and the inoperable patients. Of a total of 679 patients, overlap of these patient populations occurred in only 38 patients, deemed operable, but who refused surgery. It was beyond the scope of current registry to come up with standardized operability criteria through extensive imaging analyses.

Peripheral vascular disease, stroke, arrhythmia, cognitive/psychiatric diseases, and mild to moderate renal failure, all of which are independent correlates of mortality in unselected populations, could have affected survival in the current population. Unfortunately, these data were not collected.

Conclusions

This is the first multicenter, international prospective registry to provide long-term outcome data in CTEPH, with at least 3-year follow up. Globally, operated patients had a better survival than not-operated patients (89% versus 70% at 3 years), corresponding to a 67% lower risk of death (HR, 0.33, Table 5). A substantial number of operated and not-operated patients were treated with PAH-targeted therapy, which failed to be an independent, favorable prognostic factor. However, medically treated patients were sicker than patients who did not receive medical treatment, precluding strong statements on the effects of PAH-targeted therapy in CTEPH. In addition, patients were treated off-label with endothelin receptor antagonist or phosphodiesterase-5 inhibitor, and the long-term effects of the recently approved drug need to be further evaluated.

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CLINICAL PERSPECTIVE

Chronic thromboembolic pulmonary hypertension, a rare complication of acute pulmonary embolism, is characterized by fibrothrombotic obstructions of large pulmonary arteries combined with small-vessel arteriopathy. A European registry was set up in 27 centers to evaluate long-term outcome and outcome predictors in operated and not-operated patients. Six hundred seventy-nine newly diagnosed patients were prospectively included over a 24-month period. Estimated survival at 3 years was 89% in operated patients and only 70% in not-operated patients. In both operated and not-operated patients, pulmonary arterial hypertension–targeted therapy did not affect survival estimates. Mortality was associated with New York Heart Association functional class, right atrial pressure, and a history of cancer. Additional predictors of mortality were bridging therapy with pulmonary arterial hypertension–targeted drugs, postoperative pulmonary hypertension, surgical complications, and additional cardiac procedures in operated patients, and comorbidities such as coronary disease, left heart failure, and chronic obstructive pulmonary disease in not-operated patients. This article shows that the long-term prognosis of operated patients is nowadays excellent and better than the outcome of not-operated patients. We thereby demonstrate that turning down a patient for surgery is predicting poor survival and support the recommendation that an experienced chronic thromboembolic pulmonary hypertension team should assess operability before medical treatment is considered, even obtaining a second opinion from a more experienced chronic thromboembolic pulmonary hypertension center in cases of borderline operability.

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