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Pulmonary Endarterectomy: Risk Factors for Early and Late Mortality

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Abstract:
Background
Pulmonary endarterectomy is a potentially curative treatment option for chronic thromboembolic pulmonary hypertension (CTEPH). This study aimed to identify predictors of short- and long-term outcomes after pulmonary endarterectomy for CTEPH patients, including age.
Methods
Patients who underwent surgery between March 2014 and January 2024 were included in the study. Perioperative and follow-up data were retrospectively studied, including age, in-hospital mortality, one- and five-year survival, and the length of intensive care unit and hospital stays after pulmonary endarterectomy.
Results
In total, 834 consecutive patients (mean age 51±15.3 years) underwent pulmonary endarterectomy and were included in the analysis. The in-hospital mortality rate was 7.8% (n = 65), while overall mortality rates at one and five years were 10.6% and 11.3%, respectively. The in-hospital mortality rate was 6.7% for patients < 70 years compared to 12.4% for patients ≥70 years (p=0.029). In the multivariate analysis of mortality, age (p=0.007), and length of intensive care unit stay (p= 0.028) emerged as independent predictors of in-hospital mortality, while the Charlson Comorbidity Index (p<0.001) and six-minute walk distance (p=0.005) were also significant predictors of one-year survival.
Conclusion Despite higher short-term mortality rates, pulmonary endarterectomy was feasible and well tolerated among elderly patients. Despite surgical advancements, careful patient selection remains crucial, particularly in the presence of comorbidities. Significant clinical and hemodynamic improvements were observed, along with favorable long-term survival outcomes.

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Conclusion Despite higher short-term mortality rates, pulmonary endarterectomy was feasible and well tolerated among elderly patients. Despite surgical advancements, careful patient selection remains crucial, particularly in the presence of comorbidities.

Significant clinical and hemodynamic improvements were observed, along with favorable long-term survival outcomes.

Keywords: geriatrics (includes early), pulmonary embolism, pulmonary vascular resistance/hypertension

Introduction

Chronic thromboembolic pulmonary hypertension (CTEPH) is recognized as a distinct subtype of pulmonary hypertension (PH) Although minimally invasive or noninvasive therapies have shown clinical benefits, including improved survival, pulmonary endarterectomy (PEA) remains treatment of choice for CTEPH [3]. PEA is a challenging surgical procedure requiring cardiopulmonary bypass and deep hypothermic circulatory arrest, which aims to remove chronic thromboembolic material, generally resulting in favorable long-term outcomes [4]. While an estimated two-thirds of global CTEPH cases are deemed eligible for surgery, current guidelines emphasize the importance of evaluation and treatment at specialized expert centers [5-7]. In these centers, in-hospital mortality rates range from 3.5% to 7.4% [8].

Patients diagnosed with CTEPH undergoing PEA surgery range in age from 18 to 84 years [6, 9, 10]. However, recent reports indicate an increasing frequency of CTEPH in older patients [5, 10, 11]. Interestingly, guidelines suggest that mortality and morbidity rates remain acceptable, even in older age groups [12-14]. However, there is a paucity of specific data on PEA outcomes in the elderly CTEPH population.

Hence, this study aims to identify predictors of short- and long-term outcomes after PEA in CTEPH patients, with a particular focus on patient’s age.

Material and Methods

Study design

We conducted a retrospective cohort study at a tertiary university-affiliated center specializing in CTEPH in Turkey. [15]

Patients

Between March 2014 and January 2024, 834 consecutive patients underwent PEA at our center. Following three months of adequate anticoagulation treatment, CTEPH was diagnosed based on the presence of mismatched perfusion defects in radioisotopic ventilation perfusion (V/Q) scans. The diagnosis was then confirmed by a computed tomography pulmonary angiogram (CTPA) and right heart catheterization (RHC). Right atrial pressure, pulmonary artery pressure, and pulmonary wedge pressure were measured with RHC. Cardiac output (CO) and cardiac index (CI) were determined by thermodilution, and pulmonary vascular resistance (PVR) was calculated. Pulmonary hypertension was defined as a mean pulmonary arterial pressure (mPAP) greater than >20 mmHg at rest.

Data Collection

Prospectively collected data were entered into a database, and the study was carried out retrospectively. Baseline characteristics, perioperative data, and post-operative assessment results were obtained from patients' files and the database for the study. Echocardiography was performed according to our previous reports [15]. Briefly, right atrial and ventricular function was assessed, and the degree of functional tricuspid regurgitation was reported as trivial, mild, or severe. Other preoperative tests included the six-min walking test (6MWD), pulmonary function tests, forced expiratory volume in one second (FEV_1), duplex scanning of the lower extremities, and arterial blood gas tests. Surgical candidates over 45 years of age underwent routine coronary angiography. The Charlson Comorbidity Index was calculated preoperatively. Patients were categorized as having proximal or distal disease based on the anatomical localization of thrombus in the pulmonary artery. Proximal disease is defined as fibrotic obstructions located in the main and lobar parts of the pulmonary artery, while lesions located in the segmental and subsegmental branches of the pulmonary artery are referred to as distal disease [3].

Complications were evaluated, and the duration of both in-hospital and intensive care unit (ICU) stays was recorded. Postoperative pulmonary artery pressure, cardiac index and pulmonary vascular resistance were measured after sternal closure. Operative mortality was defined as death in the hospital or within 30 days of surgery. Deterioration in the World Health Organization (WHO) functional class was identified by a decline of at least one class relative to the best class attained after surgery. Repeat RHC was performed when patients experienced deterioration in WHO functional class or remained in functional class III after PEA.

Decision for Surgery

Given the critical importance of meticulous patient selection for PEA surgery, a thorough evaluation for the procedure was conducted by a multidisciplinary team, including expert PEA surgeons, pulmonologists, cardiologists, rheumatologists, and radiologists specialized in CTEPH.

Surgery

All patients underwent PEA as described previously [15]. Anesthetic management and pulmonary catheterization protocols were all managed in a standard manner, with the operation was performed in deep hypothermia (20°C) under circulatory arrest. The endarterectomy started at the proximal part of the artery and proceeded to the subsegmental branches in each lobe to facilitate complete clearance of the pulmonary vascular tree.

All patients were followed at three and six months. They were classified functionally according to the WHO functional class and assessed with a 6MWD and echocardiogram at each follow-up visit.

Ethics

This study received approval from the local ethics committee (number 09.2018.091).

Statistics

Descriptive statistics were used to characterize patient attributes, with nonparametric continuous variables presented as the median and interquartile range and parametric continuous variables as mean ± standard deviation. Categorical variables were expressed as counts and percentages when applicable. Group differences were analyzed using the chi-square test, t-test, and Mann–Whitney U test, while Spearman's correlation was used for assessing associations. Multivariate logistic analysis, incorporating a forward stepwise likelihood test, was performed to evaluate mortality. Cox regression analysis was performed to assess overall mortality. All analyses were conducted using IBM SPSS Statistics 29 (Chicago, Illinois).

Results

Patient Demographics

A total of 834 consecutive patients (422 males, 50.6% and 412 females,49.4%) who underwent PEA for CTEPH at our center were included in the analysis. The mean age of the cohort was 51 ± 15.3 years. Demographics of the patients are shown in Table 1. Among the cohort studied, there were 65 in-hospital deaths (7.8%), with a mean age of 56.4 ± 14.6 years. Comparisons between non-survivors and survivors in terms of in-hospital mortality are presented in Table 1. Significant differences were observed in various parameters, including age (56.4±14.6 vs 50.9±15.3 years, $p=0.006$), Charlson Comorbidity Index (2 [IQR, 1–2.5] vs 0 [IQR, 0–1], $p < 0.001$), albumin level (3.4 ±0.3 vs 3.5±0.2 g/dL, p=0.001), FEV_1 (1.7 [IQR, 1.2–2.2) vs 2.3 (IQR, 1.7–2.9) /L, p < 0.001), six-minute walking distance (222 [IQR, 0–330] vs 291 [IQR,145–390] meters, p=0.002), pulmonary vascular resistance (795.1±415.2 vs 662.6±400.3 dynes/s/cm^{-5}, p=0.019), cardiac index (2.28±0.88 vs 2.47±1.09 L/min/m^2, p=0.036), pH-specific treatment (17, 25.8% vs 83, 10.9%, p=0.001), cardio-pulmonary bypass time (248 [IQR, 207–308] vs 193 [IQR, 173–222] min, p<0.001), total circulatory arrest time (28 [IQR, 20–37] vs 21 [IQR, 16–28] min, p<0.001), and the presence of concomitant surgery (19, 29.2% vs 115, 15%, p=0.004) between non-survivors and survivors.

Concomitant surgery was performed in 134 (16.1%) patients. We have previously reported our 56 patients who underwent PEA with additional cardiac surgery [17]. The most common concomitant surgeries included cardiopulmonary bypass graft (CABG) (n=32), atrial septal defect (ASD) closure, or patent foramen ovale (PFO). Additional surgeries included simultaneous ASD or PFO closure with valve surgery (n=9), lung resection (n=6), CABG and valve surgery (n=3), thyroidectomy (n=3), and abdominal surgery (n=2). There was no difference between the groups according to the type of surgery.

Main outcomes in hospital

In the postoperative period, survivors showed a tendency toward early extubation, with a median of one day (IQR, 1–1) compared to two days (IQR, 1–2) for non-survivors (p < 0.001). They also had shorter lengths of stay in the ICU, with a median stay of three days (IQR, 2-5) versus 6.5 days (IQR, 3–11) for non-survivors (p<0.01), and a reduced incidence of perioperative complications (3.4% and 35.9%, respectively; p<0.001). Additionally, non-survivors demonstrated higher PVR levels, with mean values of 289.1±135.6 dyns.s.cm^{-5} compared to 256.6±181.9 dynes.s.cm^{-5} for survivors (p=0.02) (Table 2).

Complications in survivors included a need for extracorporeal membrane oxygenation (ECMO) (n=15 1.9%), airway bleeding (n=6, 0.8%), and pericardial tamponade necessitated surgery (n=3, 0.4%). In non-survivors, the complications were a need for ECMO (n=20, 30.7%) and airway bleeding (n=4, 6.1%). In terms of perioperative complications, no difference was observed between the groups. Patients with perioperative complications had higher preoperative mean pulmonary arterial pressure (48.5±13.6 vs 43.4±15.8 mmHg, p<0.053) and pulmonary vascular resistance (809.3±474.9 vs 649.2±392.2 dyns.s.cm^{-5}, p=0.047). However, this effect was not observed in the regression analysis. No differences in hemodynamic outcomes were observed between the groups with RHC before hospital discharge.

Mortality

Overall, the in-hospital mortality rate was 7.8% (n=65), one-year mortality was 10.6% (n=87), and five-year mortality was 11.3% (n=96) for the whole cohort. The causes of early mortality were sepsis (n=22), hemoptysis (n=11), right heart failure (n=9), pericardial tamponade (n=6), reperfusion injury (n=5), massive pulmonary embolism (n=3), acute coronary syndrome (n=2), sudden cardiac arrest secondary to arrhythmia (n=2), intracranial bleeding (n=1), extra-thoracic bleeding (n=2), hypoxic brain injury (n=1), and disseminated intravascular coagulation (n=1).

The cut-off value for age was set as 70 years to analyze the impact of the patient's age on the outcome of PEA. The in-hospital mortality rate was 12.4% in the older group compared to 6.7% in the younger group (Kaplan–Mayer analysis, p=0.029) (Figure 1). Furthermore, considering patients surviving the operation, patients under 70 years of age had one-year survival rates of 97.3%, three-year survival rates of 97.1%, and five-year survival rates of 96%, compared to 92.9%, 92.9%, and 86.2%, respectively, for those over 70 years of age (p=0.004).

In the multivariate analysis of mortality, age (OR 1.1, 95% CI 1.02–1.20, p=0.007) and ICU stay (OR 1.1, 95% CI 1.01–1.19, p=0.028) were independent predictors of in-hospital mortality. In addition, Cox regression analysis was performed to assess one-year survival. The Charlson comorbidity index, albumin level, 6MWD test, concomitant surgery, preoperative pulmonary vascular resistance, and age over 70 were included in the analysis. Only the Charlson Comorbidity Index and 6MWD test distance were found to be associated with one-year survival [HR:1.99 (1.50 – 2.26) p<0.001, HR:0.99 (0.996 – 0.999) p:0.005 respectively] (Table 3).

Discussion

The present study aimed to identify predictors of both short- and long-term outcomes following PEA. The main findings were as follows: (1) Increased in-hospital mortality rates were observed among patients ≥70 years undergoing PEA; (2) There was a positive correlation between prolonged ICU stay and in-hospital mortality; and (3) Higher Charlson Comorbidity Index scores and reduced 6MWD were associated with 1-year survival.

Pulmonary endarterectomy is the treatment of choice ~~still the definitive curative treatment~~ for patients with CTEPH. It is typically conducted at specialized reference centers worldwide and has notably low mortality rates (<5%) [6,8]. Reported data from high-volume centers and international global registries indicate a positive correlation between center experience and operability rates [6,16]. Moreover, data from well-known high-volume centers show that advanced age alone is not a contraindication to surgery [5,7-9,12, 18-21]. Vistarini et al. [9] reported a 30-day mortality rate of 5.1% for patients under 70 years of age and 9.1% for those over 70 years of age, without a statistically significant difference. However, Tscholl et al. [22] reported that age is an independent risk factor of 30-day hospital mortality in PEA patients. Similarly, Ogino et al. [23] reported significantly higher mortality rates in patients aged 60 and above. Notably, in our study, there were 138 patients (16.5%) aged 70 and older, with six patients aged 80 and above. We also observed significantly higher mortality rates for patients ≥70 years of age following PEA. Studies that have failed to identify age as a risk factor have often categorized age groups within specific timeframes, which may have contributed to the observed variations.

Among our patient cohort, 16.1% (n=134) underwent concomitant surgeries. As the experience level of both the center and the surgeon grows, there is a tendency to undertake more challenging cases. Consequently, there is an increasing need for a comprehensive approach to CTEPH patients that extends beyond age considerations and encompassed accompanying comorbidities and pathologies requiring additional surgical interventions. Multidisciplinary management of older surgical patients has been recommended. [17].

An additional critical consideration is the ethnic diversity observed among the patients in our study. While the majority came from our country, approximately 12% were referred from nearby Middle Eastern and Turkic republics. It is noteworthy that studies indicating the insignificance of age predominantly originate from European centers. Discrepancies in racial backgrounds, variations in performance conditioning, and diverse levels of frailty among older patients could impact mortality rates within older age groups. According to data from the World Health Organization, life expectancy is reported as 82.9 years in Italy, 81.7 years in Germany, and 81.4 years in England, whereas it is only 78.4 years in Turkey. [24].

In our study, length of ICU stay was found to be a predictor of 30-day mortality, consistent with similar findings reported in the literature [9, 19, 23]. The Charlson Comorbidity Index was identified as an independent risk factor for one-year survival, as in previous studies [8, 25]. Furthermore, our results showed that 6MWD was a long-term mortality risk factor. The 6MWD test can serve as an indicator for patients with compromised hemodynamics and diminished functional capacity, often associated with advanced age, and our findings are consistent with those of previous reports [20].

Reported in-hospital mortality rates range from 1.3% to 24%, regardless of case volume [26]. In this study, the in-hospital mortality rate was 7.8%, and the overall mortality rates at one and five years ere 10.6% and 11.3%, respectively. These results are comparable to those reported in the literature [25,26].

Although univariate analysis showed that complications were correlated with mortality, this relationship was not supported by multivariate analysis. No direct effect of pulmonary hemodynamics on mortality was observed. Although, postoperative PVR > 500 dyn.s.cm^{-5} has been identified as a critical indicator for in-hospital mortality after pulmonary endarterectomy, postoperative PVR in the intensive care unit stratifies mortality rates, with PVR > 500 dyn·s·cm^{-5} associated with a mortality rate of 10.3%, compared to 0.9% for PVR < 500 dyn·s·cm^{-5} [8]. Since, pulmonary vascular resistance improved significantly from 795.1 to 289.1 dyn.s.cm^{-5} in non-survivors and from 662.6 to 256.6 dyn.s.cm^{-5} in survivors, after surgery, our study did not establish a direct effect of pulmonary hemodynamics on mortality. Our findings suggest that while pre-operative hemodynamic parameters are linked to complications, this association diminished in multivariate analysis. This underscores the importance of vigilant postoperative management of PVR to mitigate the risk of mortality. Future studies should further investigate strategies to manage and optimize PVR levels postoperatively to improve patient outcomes.

Some limitations of our study should be noted, including its retrospective and single-center design, data loss, the lack of an additional functional evaluation for older patients, and the exclusion of postoperative functional and hemodynamic data during follow-up.

Conclusion

In conclusion, our study highlights advanced age and prolonged ICU length of stay as independent risk factors for in-hospital mortality while elevated Charlson Comorbidity Index and reduced 6MWD values signify a poorer prognosis and increased one-year mortality. Despite the increasing number of CTEPH patients and the improved experience of surgical centers, careful patient selection for surgery is crucial, particularly considering advanced age and the presence of comorbid conditions, to effectively mitigate mortality risks.

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Figure 1. Kaplan–Meier curves for survival after pulmonary endarterectomy, dichotomized by age

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Table 1. Demographics of patients.

	All n=834	30 days mortality Non-Survivor n=65	Survivor n= 769	p-values
Age, years, mean (SD)	51.4 (15.3)	56.4 (14.6)	50.9 (15.3)	**0.006**†
Female, n (%)	412 (49.5)	33 (50.8)	379 (49.3)	0.899‡
Current or ex-smoker, n (%)	50 (6.3)	4 (6.3)	45 (6.2)	0.456‡
BMI, kg/m^2 mean (SD)	28.5 (5.5)	27.7 (5.3)	28.6 (5.5)	0.280†
CCI, median (IQR)	0 (0 – 1)	2 (1 – 2.5)	0 (0 – 1)	**<0.001**†
CAD, n (%)	30 (4)	4 (6.3)	26 (3.8)	0.308‡
Vasculitis/Behçet's disease, n (%)	59 (7.2)	4 (6.8)	55 (7.3)	1‡
DVT, n (%)	119 (14.8)	7(10.8)	112(15.2)	0.443‡
Albumin, g/dL, mean (SD)	3.5 (0.2)	3.4 (0.3)	3.5 (0.2)	**0.001**†
FEV$_1$, L, median (IQR)	2.24 (1.7 – 2.9)	1.7 (1.2 – 2.2)	2,3 (1.7 – 2.9)	**<0.001**†
FEV$_1$/FVC, %, median (IQR)	84 (76 – 96)	82 (72 – 92)	85 (76 – 96)	0.251†
WHO Classification, n (%)				
II	59 (7.1)	6 (9.2)	53 (6.9)	0.403‡
III	586 (70.5)	41(63.1)	545 (71.1)	
IV	186 (22.4)	18 (27.7)	168 (21.9)	
6MWD, m, median (IQR)	285 (125 – 389)	222 (0 – 330)	291 (145–390)	**0.002**†
mPAP, mmHg, mean (SD)	44.5 (16.2)	46.1 (16.1)	44.3 (16.2)	0.419†
PVR, dynes.sec.cm^{-5}, mean (SD)	672.1 (402.4)	795.1 (415.2)	662.6 (400.3)	**0.019**†
CI, L/min/m^2, mean (SD)	2.46 (1.08)	2.28 (0.88)	2.47 (1.09)	**0.036**†
PH specific treatment, n (%)	100 (12)	17 (25.8)	83 (10.9)	**0.001**‡
Type of disease, distal, n (%)	232 (37.6)	20 (39.2)	212 (37.5)	0.880‡
Operative parameters				
CCT, min, median (IQR)	29 (6 – 52)	34 (8 - 64)	29 (6 – 51)	0.073†
CPBT, min, median (IQR)	195 (175 – 230)	248 (207 – 308)	193 (173 – 222)	**<0.001**†
TCAT, min, median (IQR)	21 (16 – 28)	28 (20 – 37)	21 (16 – 28)	**<0.001**†

Concomitant Surgery, n (%)		134 (16.1)	19 (29.2)	115 (15)	**0,004**
	CABG	32 (26.7)	6 (40)	26 (24.8)	0,661‡
	ASD/PFO closure	32 (26.7)	4 (26.7)	28 (26.7)	
	Atrial thrombus or mass removal	18 (15)	1 (6.7)	17 (16.2)	
	Valve surgery	15 (12.5)	1 (6.7)	14 (13.3)	
	Other	23 (19.2)	3 (20)	20 (19)	

ASD: Atrial Septal Defect; BMI: Body Mass Index; CAD: Coronary Artery Disease; CABG: Coronary Artery Bypass Graft; CCI: Charlson Comorbidity Index; CI: Cardiac Index; CCT: Cross-Clamp Time; CPBT: Cardio-Pulmonary Bypass Time; DVT: Deep Vein Thrombosis; 6MWD: 6-Minute Walking Distance; FEV_1: Forced Expiratory Volume in 1 second; FEV_1/FVC: Forced Expiratory Volume in 1 Second over Forced Vital Capacity; mPAP: mean Pulmonary Artery Pressure; PFO: Patent Foramen Ovale; PH: Pulmonary Hypertension; PVR: Pulmonary Vascular Resistance; TCAT: Total Circulatory Arrest Time; WHO: World Health Organization; †: Mann–Whitney U Test, ‡: Chi-Square Test

Table 2: Postoperative outcomes of patients.

	All n=834	**30 days mortality**		**p-values**
		Non-survivors n=65	**Survivors n=769**	
mPAP, mmHg, mean (SD)	28.1 (9.8)	30.6 (11.1)	28.1 (9.7)	0.155†
PVR, dyns.s.cm^{-5}, mean (SD)	258.2 (179.9)	289.1 (135.6)	256.6 (181.9)	**0.02†**
Time to extubation, day, median	1 (1 – 1)	2 (1 – 2)	1 (1 – 1)	**<0.001†**

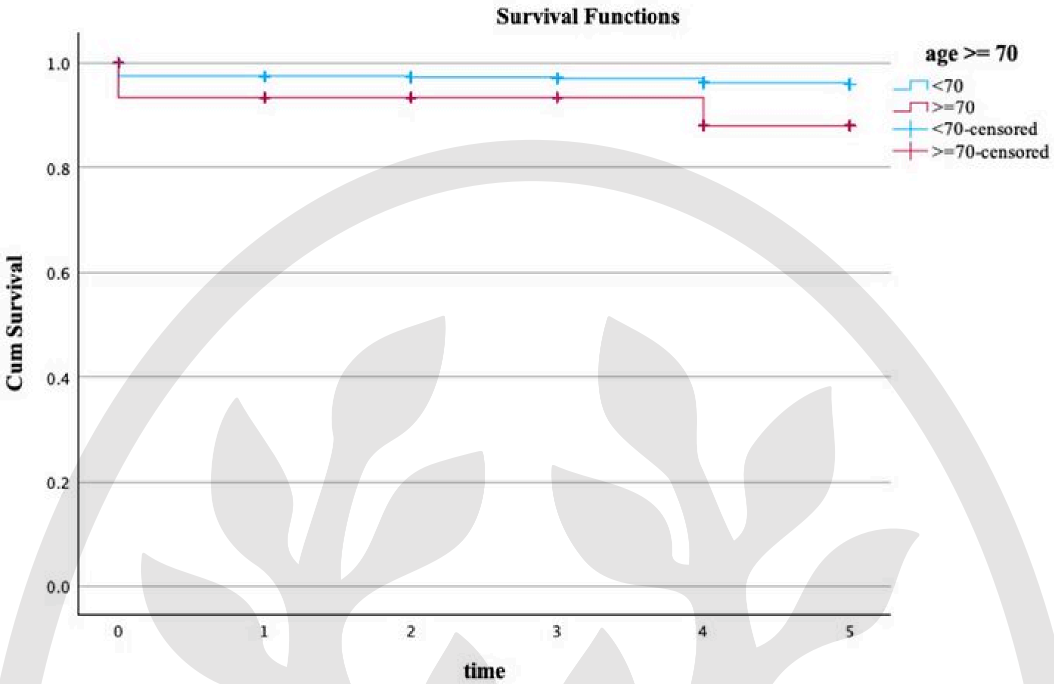
(IQR)				
ICU stay, day, median (IQR)	3 (2 – 5)	6.5 (3 – 11)	3 (2 – 5)	**0.01**†
Hospital stays, day, median (IQR)	10 (8 – 13)	9 (5 – 19)	10 (8 – 13)	0.663†
Peri-operative complication, n (%)	48 (5.9)	23 (35.9)	25 (3.4)	**<0.001**‡

ICU: Intensive Care Unit; mPAP: mean Pulmonary Artery Pressure; PVR: Pulmonary Vascular Resistance; †: Mann–Whitney U Test, ‡: Chi-Square Test

Table 3. Multivariate logistic regression analysis of factors associated with 30-day and 1-year mortality.

	unadjusted			adjusted		
	OR	**95% CI**	**p values**	**OR**	**95% CI**	**p-values**
			30 Days Mortality			
Age, years (year)	1.02	1.01 – 1,04	0.007	1.1	1.02 – 1.20	0.007
ICU stay (day)	1.08	1.02– 1.15	0.015	1.1	1.01 – 1.19	0.028
			1 Year Mortality			
Charlson Comorbidity Index	2.17	1.77 – 2.65	<0.001	2.97	1.60 – 5.53	<0.001
6MWD	0.99	0.996- 0.999	<0.001	0.99	0.98 – 0.99	0.005

ICU: Intensive Care Unit; 6MWD: 6-Minute Walking Distance, OR: Odds Ratio; 95% CI: 95% Confidence Interval



Number at risk		1-year	2-year	3-year	4-year	5-year
<70 years	663	579	498	417	358	297
>70 years	106	89	72	63	52	35