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Overlap and correlation of reperfusion lung injury with postoperative pneumonia following pulmonary thromboendarterectomy: incidence, characteristics, and outcomes in chronic thromboembolic pulmonary hypertension



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Abstract

Chronic thromboembolic pulmonary hypertension (CTEPH) can be treated with pulmonary thromboendarterectomy (PTE) which may lead to reperfusion lung injury (RPLI) and postoperative pneumonia. We aimed to describe the incidence, diagnostic characteristics, and clinical outcomes of post-PTE pneumonia compared to RPLI. A retrospective study involving CTEPH subjects who underwent PTE at a large referral center was conducted. Data included demographics, hemodynamics, microbiologic diagnostics, and clinical outcomes. Post-PTE pneumonia was diagnosed based on documentation, signs/symptoms, or microbiologic sampling within seven days of surgery. Among 75 PTE subjects, 21 (28%) had RPLI, and 18 (24%) had post-PTE pneumonia. Of those with RPLI, 48% had pneumonia, suggesting overlap. Eight of 75 (11%) subjects underwent bronchoscopic sampling, and five (63%) samples yielded positive results indicative of infection. Subjects with post-PTE pneumonia and RPLI had longer hospital and ICU lengths of stay and mechanical ventilation duration than either group alone. Post-PTE pneumonia is prevalent and overlaps with RPLI in CTEPH subjects. The study highlights the importance of systematic evaluation and early detection of pneumonia in subjects with RPLI post-PTE. Timely diagnosis and management of pneumonia may improve outcomes. Further research is needed to understand risk factors and develop preventive strategies for post-PTE pneumonia.

Keywords Chronic thromboembolic pulmonary hypertension (CTEPH), Pulmonary thromboendarterectomy (PTE), Reperfusion lung injury (RPLI), Postoperative pneumonia, Outcome assessment

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Background

Chronic thromboembolic pulmonary hypertension (CTEPH) is a potentially life-threatening condition that can result in right ventricular failure and mortality if left untreated [1]. While the precise etiology remains unclear, established risk factors encompass recurrent embolic events, right ventricular dysfunction, acute pulmonary embolism (PE), and idiopathic PE [2-4]. The incidence of CTEPH ranges from 0.1 to 9.1% within two years of symptomatic PE, with a reported general population incidence of 3 to 30 per million [3, 5]. The gold standard treatment for CTEPH is pulmonary thromboendarterectomy (PTE), yielding favorable outcomes in symptomatic relief and long-term survival [1, 6]. However, PTE is linked to complications including postoperative bleeding, residual pulmonary hypertension, extended postoperative mechanical ventilation, prolonged ICU length of stay, and reperfusion lung injury (RPLI) [7]. RPLI, which can occur in up to 40-50% of cases, is characterized by a high permeability edema resulting in hypoxemia and radiographic opacities in reperfused areas of the lung [8, 9]. This significantly affects patient outcomes, prolonging mechanical ventilation and increasing ICU and hospital stays due to the associated inflammatory response and respiratory complications [10]. Given the correlation between RPLI and post-PTE outcomes, timely diagnosis and effective management of pneumonia in RPLI patients is crucial to mitigate additional adverse effects on patient outcomes.

While pneumonia after cardiac surgery is well described in the literature with reported rates of 2–10% among cardiac surgery patients, postoperative pneumonia following PTE is less well understood [9, 11-13]. There is a limited body of literature, without clear definition or distinctions among subjects with RPLI, indicating the rates of postoperative pneumonia following PTE which range from 12–17% [14, 15]. Unique features of this highly specialized surgery may predispose patients to increased risk of postoperative pneumonia. Transesophageal echocardiography (TEE) is performed during surgery in which the probe remains in place for the duration of surgery. Data has shown an association between TEEassociated micro-aspiration and increased incidence of ventilator-associated pneumonia (VAP) [16]. Unique to PTE, intraoperative bronchoscopy to assess for airway hemorrhage is also performed, in which bronchoscopy is associated with developing complications such as pneumonia [17]. Patients are intubated for the duration of surgery and are typically extubated on postoperative day one, though may remain intubated for longer which may pose a risk for postoperative VAP. The endothelial injury caused by pulmonary endarterectomy surgery may disrupt the normal pulmonary vasculature and compromise the integrity of the alveolar epithelial lining, potentially leading to impaired antibiotic penetration and reduced concentration within the epithelial lining fluid. These alterations in the local microenvironment may compromise immune surveillance, thereby contributing to potential challenges in effectively combating respiratory infections. Importantly, the same vascular insult likely provides the physiologic basis underlying reperfusion lung injury.

Although RPLI and postoperative pneumonia may present with similar clinical features (e.g. hypoxemia, radiographic opacities), the latter complication is not as well described following PTE. This study aims to describe the incidence of suspected/confirmed post-PTE pneumonia compared to RPLI, assess the diagnostic and clinical characteristics, and evaluate the outcomes of these groups.

Methods

Study design and setting

We conducted a retrospective observational study of subjects treated for chronic thromboembolic pulmonary hypertension with pulmonary thromboendarterectomy at Northwestern Memorial Hospital (NMH), a 943-bed academic medical center, between May 2016 and December 2022. This study received approval from the Northwestern University Institutional Review Board (IRB) STU00009959. All patients provided informed written consent for the presentation and publication of their study data, adhering to ethical standards in accordance with the Declaration of Helsinki. As this study involved standard clinical procedures and assessments without an experimental treatment protocol, it did not require registration with a public clinical trials registry.

CTEPH registry

Through the establishment of the Chronic Thromboembolic Disease program at Northwestern Memorial Hospital, a research registry of CTEPH and Venous thromboembolic disease (VTED) subjects was created. These subjects were approached for enrollment, and if consented, clinical phenotypic information was gathered. During the study period 94 subjects were eligible for inclusion and 75 consented (80%).

Definitions

As previously defined, RPLI was characterized as the presence of radiographic infiltrates in the region of endarterectomized tissue and hypoxemia (saturation < 88%) within 48–72 h following PTE, without an alternative explanation (PNA, bleeding, atelectasis) [18, 19]. Aligned with the Agency for Healthcare Research and Quality (AHRQ) that defines hospital acquired pneumonia, postoperative pneumonia was defined based on documentation, signs/symptoms (e.g. fever, leukocytosis, infiltrates on chest x-ray in regions of non-endarterectomized lung), and/or confirmative microbiologic diagnostic sampling within seven days following PTE. Microbiologically confirmed pneumonia was defined as a positive culture from a lower respiratory tract specimen with a quantitative threshold of $\geq 10^4$ cfu/mL.²⁰

Perioperative care

The standard perioperative care for patients undergoing PTE involves administering prophylactic vancomycin and cefazolin for 48 h. Post-operative steroid use is not recommended, nor used, for preventing RPLI. During the study period, intubated patients received routine oral care, including chlorhexidine gluconate (CHG) rinses. Routine subglottic or endotracheal suctioning was not advocated for unless clinically necessary. When endotracheal suctioning was required, a closed-loop suction device was utilized. In cases where pulmonary infection was suspected, microbiological sampling was recommended, either through bronchoscopic or nonbronchoscopic alveolar lavage. However, routine collection of endotracheal aspirates and sputum cultures did not occur. Post-extubation respiratory support, including the use of high-flow nasal canula or non-invasive positive pressure ventilation, was at the discretion of the treating physicians. There is no standardized protocol to routinely favor or avoid these modalities. The management of reperfusion lung edema followed standard supportive measures, including oxygen supplementation, diuresis, and judicious use of positive end expiratory pressure.

Microbiologic diagnostics

Lower respiratory tract specimens including bronchoscopic and non-bronchoscopic bronchoalveolar lavage (BAL, NBBAL) were incubated in the WASP[®] instrument (bioMérieux, Marcy-l'Étoile, France) with a first read at 18 h. Clinicians ordered the BioFire[®] FilmArray[®] Pneumonia (PN) Panel (bioMérieux, Marcy-l'Étoile, France) for rapid results, which were run regardless of culture growth (March 2020 onwards). If culture growth was observed, the specimens were Gram stained and isolated by plating onto MacConkey or blood agar with a first plate read at 18–24 h.

Antimicrobial susceptibility testing was performed using the Vitek[®] 2 instrument. The overall turnaround time of species identification was 24 h from culture growth and 48–72 h from culture growth for antimicrobial susceptibility.

Data collection

Baseline demographic, clinical, hemodynamic, and comorbidity data for each subject in the study were collected. We assessed hospital and ICU courses, clinical signs and symptoms of RPLI and pneumonia, antimicrobial use, microbiologic sampling, and subject outcomes through electronic medical record (EMR) chart review. We also recorded historical data on pneumonia in the six months prior PTE.

Primary and secondary outcomes

The primary outcomes of interest were diagnoses of RPLI and post-PTE pneumonia. The secondary outcomes, comparing the select groups of (1) normal post PTE, (2) Post PTE PNA (+), (3) Post PTE RPLI (+), and (4) Post PTE RPLI (+) & PNA (+), include hospital length of stay (LOS), ICU LOS, mechanical ventilation (MV) duration, and mean white blood cell (WBC) count on postoperative day one.

Data analysis

We summarized continuous variables as means with standard deviations and categorical variables as numbers and percentages. Comparisons among groups were conducted using Mann-Whitney's U-Test for continuous variables and Fischer's Exact Test for categorical variables. We conducted a Kruskal-Wallis test to assess the equality of medians across the four groups. Post-hoc analysis for pairwise comparisons was performed using Dunn's test for multiple comparisons. Statistical significance was defined as p-values less than 0.05. Data analysis was performed using R Studio Version 4.3.1.

Results

During the study period, subjects had a median followup of 670 days (318-1,389). The study population had a median age of 56 years and were majority female (60%). The median body mass index (BMI) was 33 (28-40). The majority (93%) identified as non-Hispanic. Four (5%) subjects had a history of pneumonia (PNA) within the six months before PTE surgery, two of which developed post-operative PNA (Tables 1 and 2). The cohort had hemodynamics suggestive of moderate to severe CTEPH, with mean pulmonary arterial pressure (mPA) of 45.7 mmHg (± 12) and mean pulmonary vascular resistance (PVR) of 610.5 dynes/sec/cm⁵ (\pm 336). The average New York Heart Association (NYHA) Functional Class was III, with an average six-minute walk distance of 311 ± 176 m. Operative characteristics, including circulatory arrest times, and cardiopulmonary bypass times are included in Table 1, and are not different among the groups.

Of the 75 subjects who underwent PTE, 21 (28%) subjects were found to have documented cases of RPLI with a median onset of two days following PTE surgery. Additionally, 18 of 75 (24%) of the total cohort of subjects, or 10 of 21 (48%) of those with RPLI, were diagnosed with PNA (Fig. 1). Microbiologically confirmed PNA was diagnosed at a median onset of five days post-PTE. Of the total cohort of subjects, eight of 75 (11%) underwent

Table 1 Baseline, operative, and Post-Operative characteristics of the study population (n = 75)

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Interf Interf Interf Interf Interf Outh within a year of PTE 23 (50.7) 5 (23.8) 5 (27.8) Interf Outh within a year of PTE 23 (50.7) 2 (95.) 1 (56.) Interf Obstructive Sleep Apnea (05A) 27 (36.0) 7 (33.3) 6 (33.3) Interf Diabetes Mellita, Type II (DMII) 13 (17.3) 3 (14.3) 3 (6.7) Interf Cerebrovascular Accident (CVA) 7 (93.3) 1 (48) 1 (56.) Interf Chronic (bottructive Pulmonang Disease 29 (20.7) 5 (23.8) 6 (33.3) Annemia Annemia 32 (42.7) 8 (38.1) 8 (44.4) Interf CHTPE Comorbidities Interf Interf Interf Interf Splenectorny 3 (40.0) 1 (48) 1 (56.) Interf Ventriculatiat (W3 Shunt 1 (1.3) 0 (0.0) 0 (0.0) Interf Provenos Thromboembolism (VTE) 3 0 29 29 Interf Stati Sta	Never	42 (56 0)	13 (61 9)	12 (66 7)	
Juli before ayear of PTE 23 (507) 1 (130) 5 (27.8) Current 5 (6.7) 2 (9.5) 1 (6.6) Obstructive Sleep Apnea (OSA) 27 (36.0) 7 (33.3) 3 (16.7) Current 5 (6.7) 2 (9.5) 1 (6.6) Obstructive Sleep Apnea (OSA) 27 (36.0) 7 (33.3) 3 (16.7) Chronic Kolmonary Disease 19 (25.3) 5 (23.8) 5 (23.8) 5 (23.8) Cerebrovascular Accident (CVA) 23 (60.7) 5 (23.8) 6 (33.3)	Ouit within a year of PTE	5 (6 7)	1 (4 8)	0 (0 0)	
Sam Source year on the second secon	Quit within a year of PTE	23 (30 7)	5 (23.8)	5 (27.8)	
Current 5 (0.7) 2 (5.7) (5.0) Obstructive Sleep Apnea (OSA) 2 (360) 7 (33) 6 (33.3) Diabetes Wellfus, Type II (DMII) 13 (17.3) 3 (14.3) 3 (16.7) Chronic Obstructive Pulmonary Disease 19 (25.3) 5 (23.8) 5 (27.8) Cerebroxisoutive Accident (CMA) 7 (9.3) 1 (48) 1 (5.6) Chronic Mark Accident (CMA) 2 (3 (0.7) 5 (23.8) 6 (33.3) Anemia 3 (24.27) 8 (8.8).1) 8 (44.4) CEPH Comorbidities 1 (48) 1 (5.6) CEPH Comorbidities 1 (13) 0 (0.0) 0 (0.0) Prior Venous Thromboembolism (VTE) 6 (8.1) 1 (8.65.7) 1 (47.78) Obesity 9 (46.9) 11 (13) 0 (0.0) 1 (47.78) Obesity 9 (46.9) 2 (25.433.37) 2 (24.40) 2 (29.440.87) SINP 2 (25.433.7) 2 (25.440.87) 3 (3 ± 1.4.5) 1 (2 ± 6.63) Proceed byritory Molume, (FU) 7 (4 ± 1.44) 8 09 ± 8.2 1 ± 1.1.5 1 ± 1.5		5 (6 7)	2 (0 5)	1 (5.6)	
Chand Mare allely Applied (CSM) 2 (-000) 7 (3-3.0) 6 (3-3.7) Chronic Obstructive Pulmonary Disease 19 (25.3) 5 (23.8) 5 (27.8) Cerebrvascular Accident (CM) 7 (9.3) 1 (4.8) 1 (5.6) Chronic Obstructive Pulmonary Disease 19 (25.3) 8 (38.1) 8 (44.4) Cerebrvascular Accident (CM) 23 (0.7) 8 (38.1) 8 (44.4) Chronic Kidney Disease (CKD) 23 (0.7) 8 (38.1) 8 (44.4) Chronic Kidney Disease (CKD) 3 (4.0) 1 (4.8) 1 (5.6) Splenectomy 3 (4.0) 1 (4.8) 1 (5.6) Ventriculoatrial (VM) Shunt 1 (1.3) 0 (0.0) 0 (0.0) Prior Venous Thromboembolism (VTE) 61 (81.3) 18 (85.7) 1 (7.7.8) Obesity 3/0 2.9 2.9 Chrical Risk Assessments 11.176 2.84 ± 180 2.89 ± 186 SNP 2.0 2.9 2.9 4.4000 2.9 Ortored Expiratory Volume (FEV) 3/1 ± 176 2.8 ± 1.2 2.8 ± 1.2 2.8 ± 1.2 <t< td=""><td>Obstructive Sleep Append (OSA)</td><td>27 (26 0)</td><td>2 (9.3) 7 (22 2)</td><td>6 (22 2)</td><td></td></t<>	Obstructive Sleep Append (OSA)	27 (26 0)	2 (9.3) 7 (22 2)	6 (22 2)	
Dabbets Memilos, type ILCMII 15 (17.3) 3 (14.3) 5 (17.3) 5 (17.3) Chronic Obstructive Pulmonary Disease [925.3) 5 (23.8) 5 (27.8) - Chronic Kidney Disease (CKD) 23 (30.7) 5 (23.8) 6 (33.3) - Anemia 23 (30.7) 5 (23.8) 6 (33.3) - Anemia 24 (27) 8 (38.1) 8 (44.4) - Splenectomy 6 (80.0) 4 (19.0) 1 (5.6) - Splenectomy 3 (40.0) 1 (4.8) 1 (5.6) - Splenectomy 6 (80.1) 18 (85.7) 1 (7.7) - Obesity 0 (0.0) 0 (0.0) - - Obesity 0 (40.2) 7 (7.8) - - Obesity 0 (42.7) 296 ±408.7 39.6 ±456.8 - Splenetomy 3.0 29 29 - - Othersity (Proton Tests (PTS) 20.2 ±33.7 329.6 ±408.7 39.6 ±456.8 - - Spreedivital Capacity (FUC) 79.8 ±14.0 <td>Dishataa Mallitua Turaa II (DAIII)</td> <td>27 (30.0)</td> <td>7 (33.3)</td> <td>0 (33.3)</td> <td></td>	Dishataa Mallitua Turaa II (DAIII)	27 (30.0)	7 (33.3)	0 (33.3)	
Chronic Closificative Fundman 2 bisease (9 (2s.3) 5 (2s.3) 5 (2s.4)	Change of the structure of the second of the	13 (17.3)	3 (14.3)	3 (10.7)	
Cerebory 1(4.3) 1(4.3) 1(4.3) 1(4.3) Chronic Kidney Disease (CKD) 2(307) 5(38) 6(3.3) - Anemia 32 (42.7) 8(38.1) 8(44.4) - CTEPH Comorbiditis - - - - - Antiphospholipid Syndrome (APLS) 6(8.0) 1(4.8) 1(5.6) - - Splenectomy 3(4.0) 1(4.8) 1(5.6) - <t< td=""><td>Chronic Obstructive Pulmonary Disease</td><td>19 (25.3)</td><td>5 (23.8)</td><td>5 (27.8)</td><td></td></t<>	Chronic Obstructive Pulmonary Disease	19 (25.3)	5 (23.8)	5 (27.8)	
Chronic Kidney Disease (LKD) 23 (30./ 5 (23.8) 6 (33.3) Anemia 32 (42.7) 8 (31.) 8 (44.4) CTEPH Comobidities Antiphospholipid Syndrome (APLS) 6 (80.) 1 (49.0) 1 (5.6) Splenectomy 3 (40.) 1 (48.3) 1 (5.6) Ventriculoatrial (VA) Shunt 1 (1.3) 0 (0.0) 0 (0.0) Ventriculoatrial (VA) Shunt 1 (1.3) 1 (85.7) 1 4 (77.8) Obesty 0 (29.0) 7 (38.9) 1 (7.8) Obesty 30 2.9 2.9 GMWD 311±176 284±180 289±186 Pulmonary Function Tests (PFTs) 794±14.4 80.9±12.6 51±19.2 VC/FEV, ratio 0.7 0.73 51±19.2 VC/FEV, ratio 0.7 0.73 21±1.2 Paredexpriatory Volume, (FEV) 74±14.4 <t< td=""><td>Cerebrovascular Accident (CVA)</td><td>/ (9.3)</td><td>I (4.8)</td><td>I (5.6)</td><td></td></t<>	Cerebrovascular Accident (CVA)	/ (9.3)	I (4.8)	I (5.6)	
Anemia S2(4.7) 8 (81) 8 (44.4) CTEPH Comobidities C	Chronic Kidney Disease (CKD)	23 (30.7)	5 (23.8)	6 (33.3)	
CTEPI comorbidities Antiphospholipid Syndrome (APLS) 6 (8.0, 4 (19.0, 1 (5.6) Splenectomy 3 (4.0, 1 (4.8) 1 (5.6) Ventriculoatrial (VA) Shunt 1 (1.3) 0 (0.0, 0 (0.0, Prior Venous Thromboembolism (VTE) 61 (81.3) 18 (85.7) 14 (77.8) Obesity 0 (42.9) 18 (85.7) 14 (77.8) CIlnical Risk Assessments	Anemia	32 (42.7)	8 (38.1)	8 (44.4)	
Antiphospholipid syndrome (APLS) 6 (8,0) 1 (9,0) 1 (5.6) Splenectomy 3 (4.0) 1 (4.8) 1 (5.6) Ventriculoatrial (VA) Shunt 1 (1.3) 0 (0.0) 0.0) Prior Venous Thromboembolism (VTE) 61 (81.3) 18 (85.7) 14 (77.8) Obesity 7 (8.9) 7 (3.8) 7 (3.8) Clinical Risk Assessments	CTEPH Comorbidities				
Splenctomy3(4.0)1(4.8)1(5.6)Ventriculoatrial (VA) Shunt1(1.3)0(0.0)0(0.0)Prior Venous Thromboembolism (VTE)61 (81.3)18 (85.7)14 (77.8)Obesity47 (62.7)9 (42.9)7 (38.9)Clinical Risk Assessments738.9WTH AF C30292.9GMWD311 ± 176284 ± 18.029.9 ± 18.6BNP252.6 ± 33.7.7329.6 ± 408.7399.6 ± 456.8Forced Vtal Capacity (FVC)79.8 ± 14.07.9 ± 11.280.3 ± 14.5Forced Expiratory Volume, (FEV ₁)74.4 ± 14.480.9 ± 8.27.5 ± ± 19.2FVC/FEV, ratio0.730.73Total Lung Capacity (TLC)87.0 ± 16.44.9 ± 1.25.7 ± 18.3Proced Expiratory Volume, (FEV ₁)10.2 ± 6.011.3 ± 5.310.2 ± 4.6Preoperative Hemodynamics11.2 ± 5.015.0 ± 5.417.8 ± 5.6Vertory Capillary Wedge Pressure (mPAP)45.8 ± 12.014.4 ± 9.344.2 ± 12.6Pulmonary Actery Pressure (mPAP)12.7 ± 5.015.0 ± 5.7 ± 17.9 ± 2.417.9 ± 9.4Pulmonary Vacular Resistance (FVR)12.4 ± 5.015.0 ± 5.7 ± 6.63.1 ± 5.6Cardiac Index (C)0.4 ± 15.310.2 ± 4.65.8 ± 6.65.8 ± 6.6Operative CharacteristicV12.4 ± 5.61.5 ± 5.7 ± 6.61.4 ± 9.8Pulmonary Vacular Resistance (FVR)5.3 ± 6.65.8 ± 6.75.7 ± 5.9 ± 6.65.8 ± 6.6Cardiac Index (C)2.7 ± 4.5	Antiphospholipid Syndrome (APLS)	6 (8.0)	4 (19.0)	1 (5.6)	
Ventriculatial (VA) Shunt 1 (1.3) 0 (0.0) 0 (0.0) Prior Venous Thromboembolism (VTE) 6 (81.3) 18 (85.7) 14 (77.8) Obesity 7 (82.7) 9 (42.9) 7 (38.9) Clinical Risk Assessments	Splenectomy	3 (4.0)	1 (4.8)	1 (5.6)	
Prior Venous Thromboembolism (VTE) 61 (81.3) 18 (85.7) 14 (77.8) Obesity 9 (62.9) 7 (38.9) 7 Clinical Risk Assessments . . . NYHA FC 3.0 2.9 2.9 . 6MWD 311±176 284±180 289±186 . BNP 252.6±333.7 329.6±408.7 39.96±456.8 . Pulmoary Function Tests (PFTs) Forced Vital Capacity (FVC) 79.8±14.0 79.7±11.2 80.3±14.5 . Forced Expiratory Volume, (FEV ₁) 74.4±14.4 80.9±8.2 75.1±19.2 . FVC/FEV ₁ ratio 0.73 0.77 0.73 . . DLCO 64.4±17.6 62.3±23.9 57.2±18.3 . Preoperative Hemodynamics Verteo Coll 63.4±0.2 44.4±3.3 44.2±1.26 . Pulmonary Artery Pressure (mRAP) 10.2±6.0 11.3±5.3 10.2±6.0 . Pulmo	Ventriculoatrial (VA) Shunt	1 (1.3)	0 (0.0)	0 (0.0)	
Obesity 47 (62.7) 9 (42.9) 7 (38.9) Clinical Risk Assessments	Prior Venous Thromboembolism (VTE)	61 (81.3)	18 (85.7)	14 (77.8)	
Clinical Risk Assessments Sint Service S	Obesity	47 (62.7)	9 (42.9)	7 (38.9)	
NYHA FC 30 29 29 6MWD 311±176 284±180 289±186 BNP 256±333.7 390±408.7 390±156.8 Pulmonary Function Tests (PFTs) 79.7±11.2 80.3±14.55 30.3±14.55 Forced Vital Capacity (FVC) 79.8±14.0 80.9±8.2 75.1±19.2 V Forced Expiratory Volume ₁ (FEV ₁) 74.4±14.4 80.9±8.2 75.1±19.2 V FVC/FEV ₁ ratio 0.73 0.77 0.73 V V Total Lung Capacity (TLC) 87.0±16.4 4.9±1.2 4.9±1.2 V DLCO 0.74 1.3±5.3 10.2±4.6 V V Mean Right Atrial Pressure (mRAP) 10.2±6.0 11.3±5.3 10.2±4.6 V Pulmonary Attery Pressure (mPAP) 12.7±5.0 15.0±5.4 17.8±5.6 V Pulmonary Vascular Resistance (PVR) 10.5±3.36 562.2±2.32 51.9±2.48 V Pupothermic Nadir* 17.4±0.9 17.0±0.9 17.4±1.0 0.40 0.40 Total Operative Time* (min)	Clinical Risk Assessments				
6MWD 311±76 284±180 289±186 BNP 252.6±333.7 329.6±408.7 399.6±456.8 Pulmonary Function Tests (PFTs) 79.2±11.2 80.3±14.5 ************************************	NYHA FC	3.0	2.9	2.9	
BNP252.6 ± 333.7329.6 ± 408.7399.6 ± 456.8Pulmonary Function Tests (PFTs)Forced Vtal Capacity (FVC)79.8 ± 14.079.7 ± 11.280.3 ± 14.5Forced Expiratory Volume ₁ (FEV ₁)74.4 ± 14.480.9 ± 8.275.1 ± 19.2FVC/FEV ₁ ratio0.730.770.73Total Lung Capacity (TLC)87.0 ± 16.44.9 ± 1.24.9 ± 1.2DLCO64.4 ± 17.662.3 ± 2.3.952.2 ± 18.3Preperative HemodynamicsMean Right Atrial Pressure (mRAP)10.2 ± 6.011.3 ± 5.310.2 ± 4.6Mean Pulmonary Artery Pressure (mPAP)25.4 ± 12.044.4 ± 9.344.2 ± 12.6Pulmonary Capillary Wedge Pressure (PCWP)12.7 ± 5.015.0 ± 5.417.8 ± 5.6Cardia Index (CI)2.3 ± 0.62.2 ± 0.72.6 ± 0.71.9 ± 4.6Pulmonary Artery Pressure (PCWP)2.3 ± 0.62.2 ± 0.72.6 ± 0.7Pulmonary Capillary Wedge Pressure (PCWP)3.4 ± 0.41.7 ± 1.00.40Cardia Index (CI)2.3 ± 0.62.2 ± 0.72.6 ± 0.7Pulmonary Astery Eressure (PCWP)1.7 ± 0.91.7 ± 1.00.40Total Operative Time (min)54.8 ± 62.157.8 ± 67.654.3 ± 60.40.58Circulatory Arrest Time (min)44.5 ± 12.340.7 ± 1.30.425.7 ± 40.70.70Cardio pulmonary Bypass Time (min)2.3 ± 43.521.5 ± 42.72.5 ± 42.70.704.2 ± 9.80.52Cardiopulmonary Bypass Time (min)44.6 ± 13.241.5 ± 42.72.5 ± 44.70.70 <td>6MWD</td> <td>311±176</td> <td>284 ± 180</td> <td>289±186</td> <td></td>	6MWD	311±176	284 ± 180	289±186	
Pulmonary Function Tests (PFTs) 98 ± 1.0 97.2 ± 1.2 80.3 ± 1.4.5 Forced Expiratory Volume, (FEV,) 74.4 ± 1.4.4 80.9 ± 8.2 75.1 ± 1.9.2 - FVC/FEV, ratio 0.73 0.77 0.73 - - Total Lung Capacity (FLC) 87.0 ± 1.64 9.9 ± 1.2 - - - Total Lung Capacity (TLC) 87.0 ± 1.64 0.2 ± 2.0 0.2 ± 2.0 - <td>BNP</td> <td>252.6±333.7</td> <td>329.6 ± 408.7</td> <td>399.6 ± 456.8</td> <td></td>	BNP	252.6±333.7	329.6 ± 408.7	399.6 ± 456.8	
Forced Vital Capacity (FVC) 79.8±14.0 79.7±11.2 80.3±14.5 Forced Expiratory Volume ₁ (FEV ₁) 74.4±14.4 80.9±8.2 75.1±19.2 FVC/FEV ₁ ratio 0.73 0.77 0.73 Total Lung Capacity (TLC) 87.0±16.4 .9±1.2 .4±1.3 DLCO 62.3±23.9 57.2±18.3 Presentive Hemodynamics Mean Right Atrial Pressure (mRAP) 10.2±6.0 11.3±5.3 10.2±4.6 Mean Pulmonary Artery Pressure (mPAP) 45.8±12.0 44.4±9.3 44.2±12.6 Pulmonary Capillary Wedge Pressure (PCWP) 12.7±5.0 15.0±5.4 17.8±5.6 Cardiac Index (Cl) 2.3±0.6 2.2±0.7 2.6±0.7 Pulmonary Vascular Resistance (PVR) 610.5±336 562.2±232 517.9±248 Uppothermic Nadir* 17.4±0.9 17.0±0.9 17.4±1.0 0.40 Total Operative Time* (min) 44.5±12.3 46.7±13.2 44.2±9.8 0.52 Carcidopulmonary Bypass Time (min) 273.1±43.5 281.5±42.7 79.9±46.7 0.70	Pulmonary Function Tests (PFTs)				
Forced Expiratory Volume_1(FEV_1) 74.4 ± 14.4 80.9 ± 8.2 75.1 ± 19.2 FVC/FEV_1 ratio 0.73 0.77 0.73 Total Lung Capacity (TLC) 87.0 ± 16.4 4.9 ± 1.2 4.9 ± 1.2 DLCO 64.4 ± 17.6 62.3 ± 23.9 57.2 ± 18.3 Preoperative Hemodynamics Wean Right Atrial Pressure (mRAP) 10.2 ± 6.0 11.3 ± 5.3 10.2 ± 4.6 Mean Pulmonary Artery Pressure (mPAP) 45.8 ± 12.0 44.4 ± 9.3 44.2 ± 12.6 Pulmonary Capillary Wedge Pressure (PCWP) 12.7 ± 5.0 15.0 ± 5.4 17.8 ± 5.6 Cardiac Index (CI) 2.3 ± 0.6 2.2 ± 0.7 2.6 ± 0.7 1.9 ± 0.9 Pulmonary Vascular Resistance (PVR) 10.5 ± 366 562.2 ± 322 51.7 ± 2.48 1.9 ± 0.9 Hypothermic Nadir* 17.4 ± 0.9 17.4 ± 0.9 17.4 ± 0.9 0.40 Total Operative Time* (min) 544.8 ± 62.1 557.8 ± 67.6 543 ± 60.4 0.58 Circulatory Arrest Time (min) 44.5 ± 12.3 40.7 ± 1.3 0.52 52 52 57.9 ± 4.6.7 0.70 Additional Operative Procedure, n (%) 34.63.3 10.4(7.7) 75.9 ± 4.	Forced Vital Capacity (FVC)	79.8 ± 14.0	79.7±11.2	80.3 ± 14.5	
FVC/FEV1 ratio 0.73 0.77 0.73	Forced Expiratory Volume ₁ (FEV ₁)	74.4±14.4	80.9 ± 8.2	75.1±19.2	
Total Lung Capacity (TLC) 87.0 ± 16.4 4.9 ± 1.2 4.9 ± 1.2 DLCO 64.4 ± 17.6 62.3 ± 23.9 57.2 ± 18.3 Preoperative Hemodynamics 10.2 ± 6.0 11.3 ± 5.3 10.2 ± 4.6 Mean Right Atrial Pressure (mRAP) 45.8 ± 12.0 44.4 ± 9.3 44.2 ± 12.6 Pulmonary Artery Pressure (PCWP) 12.7 ± 5.0 15.0 ± 5.4 17.8 ± 5.6 Cardiac Index (Cl) 2.3 ± 0.6 2.2 ± 0.7 2.6 ± 0.7 Pulmonary Vascular Resistance (PVR) 610.5 ± 336 562.2 ± 232 517.9 ± 248 Hypothermic Nadir* 17.4 ± 0.9 17.0 ± 0.9 17.4 ± 1.0 0.40 Total Operative Time (min) 544.8 ± 62.1 557.8 ± 67.6 543 ± 60.4 0.58 Circulatory Arrest Time (min) 44.5 ± 12.3 46.7 ± 13.2 44.2 ± 9.8 0.52 Cardiopulmonary Bypass Time (min) 273.1 ± 43.5 281.5 ± 42.7 75.9 ± 46.7 0.70 Additional Operative Procedure, n(%) 34 (45.3) 10 (47.7) 7 (38.9) 0.52 Additional Operative Procedure, n(RAP) 80.55 88 (6.4) 9.6 (7.6) 0.75	FVC/FEV ₁ ratio	0.73	0.77	0.73	
DLCO 64.4 ± 17.6 62.3 ± 23.9 57.2 ± 18.3 Properative Hemodynamics Mean Right Atrial Pressure (mRAP) 10.2 ± 6.0 11.3 ± 5.3 10.2 ± 4.6 Mean Pulmonary Artery Pressure (mPAP) 45.8 ± 12.0 44.4 ± 9.3 44.2 ± 12.6 Pulmonary Capillary Wedge Pressure (PCWP) 12.7 ± 5.0 15.0 ± 5.4 17.8 ± 5.6 Cardiac Index (Cl) 2.3 ± 0.6 2.2 ± 0.7 2.6 ± 0.7 Pulmonary Vascular Resistance (PVR) 610.5 ± 336 562.2 ± 232 517.9 ± 248 Mypothermic Nadir* 17.4 ± 0.9 17.0 ± 0.9 17.4 ± 1.0 0.40 Total Operative Time* (min) 544.8 ± 62.1 557.8 ± 67.6 543 ± 60.4 0.58 Circulatory Arrest Time (min) 44.5 ± 12.3 46.7 ± 13.2 44.2 ± 9.8 0.52 Cardiopulmonary Bypass Time (min) 273.1 ± 43.5 281.5 ± 42.7 75.9 ± 46.7 0.70 Additional Operative Procedure, n (%) 34 (45.3) 10 (47.7) 7 (38.9) 0.52 Maen Right Atrial Pressure (mRAP) 80 (5.5) 88 (6.4) 9.6 (7.6) 0.75	Total Lung Capacity (TLC)	87.0 ± 16.4	4.9±1.2	4.9±1.2	
Preoperative Hemodynamics 10.2 ± 6.0 11.3 ± 5.3 10.2 ± 4.6 Mean Right Atrial Pressure (mRAP) 45.8 ± 12.0 44.4 ± 9.3 44.2 ± 12.6 Pulmonary Capillary Wedge Pressure (PCWP) 12.7 ± 5.0 15.0 ± 5.4 17.8 ± 5.6 Cardiac Index (CI) 2.3 ± 0.6 2.2 ± 0.7 2.6 ± 0.7 17.9 ± 4.8 Pulmonary Vascular Resistance (PVR) 610.5 ± 336 562.2 ± 232 51.7 ± 24.8 17.9 ± 4.8 Operative Characteristics r r r 17.4 ± 0.9 17.0 ± 0.9 17.4 ± 1.0 0.40 Total Operative Time* (min) 544.8 ± 62.1 557.8 ± 67.6 543.8 ± 60.4 0.58 Circulatory Arrest Time (min) 244.5 ± 1.2.3 46.7 ± 13.2 42.2 ± 9.8 0.52 Cardiopulmonary Bypass Time (min) 273.1 ± 43.5 281.5 ± 42.7 275.9 ± 46.7 0.70 Additional Operative Procedure, n(%) 34 (45.3) 10 (47.7) 7 (38.9) 0.75 Mean Right Atrial Pressure (mRAP) 80 (5.5) 88 (6.4) 9.6 (7.6) 0.75 Mean Pulmonary Artery Pressure (mPAP) 30.3 (12.5) 34.7 (14.1) 40.6 (15.4) 0.77	DLCO	64.4±17.6	62.3±23.9	57.2±18.3	
Mean Right Atrial Pressure (mRAP) 10.2 ± 6.0 11.3 ± 5.3 10.2 ± 4.6 Mean Pulmonary Artery Pressure (mPAP) 45.8 ± 12.0 44.4 ± 9.3 44.2 ± 12.6 Pulmonary Capillary Wedge Pressure (PCWP) 12.7 ± 5.0 15.0 ± 5.4 17.8 ± 5.6 Cardiac Index (CI) 2.3 ± 0.6 2.2 ± 0.7 2.6 ± 0.7 Pulmonary Vascular Resistance (PVR) 610.5 ± 336 562.2 ± 232 517.9 ± 248 Prealue Prealue Prealue Operative Characteristics Prealue Hypothermic Nadir* 17.4 ± 0.9 17.0 ± 0.9 17.4 ± 1.0 0.40 Total Operative Time* (min) 544.8 ± 62.1 557.8 ± 67.6 543 ± 60.4 0.58 Circulatory Arrest Time (min) 44.5 ± 12.3 46.7 ± 13.2 44.2 ± 9.8 0.52 Cardiopulmonary Bypass Time (min) 273.1 ± 43.5 281.5 ± 42.7 275.9 ± 46.7 0.70 Additional Operative Procedure, n (%) 34 (45.3) 10 (47.7) 7 (38.9) 0.75 Postoperative Hemodynamics S8.0 (5.5) 8.8	Preoperative Hemodynamics				
Mean Pulmonary Artery Pressure (mPAP) 45.8 ± 12.0 44.4 ± 9.3 44.2 ± 12.6 Pulmonary Capillary Wedge Pressure (PCWP) 12.7 ± 5.0 15.0 ± 5.4 17.8 ± 5.6 Cardiac Index (Cl) 2.3 ± 0.6 2.2 ± 0.7 2.6 ± 0.7 Pulmonary Vascular Resistance (PVR) 610.5 ± 336 562.2 ± 232 517.9 ± 248 Operative Characteristics v p-value Hypothermic Nadir* 17.4 ± 0.9 17.0 ± 0.9 17.4 ± 1.0 0.40 Total Operative Time* (min) 544.8 ± 62.1 557.8 ± 67.6 543 ± 60.4 0.58 Circulatory Arrest Time (min) 44.5 ± 12.3 46.7 ± 13.2 44.2 ± 9.8 0.52 Cardiopulmonary Bypass Time (min) 273.1 ± 43.5 281.5 ± 42.7 7.5 9 ± 46.7 0.70 Additional Operative Procedure, n (%) 34 (45.3) 10 (47.7) 7 (38.9) 0.75 Mean Right Atrial Pressure (mRAP) 8.0 (5.5) 8.8 (6.4) 9.6 (7.6) 0.75 Mean Pulmonary Artery Pressure (mPAP) 30.3 (12.5) 34.7 (14.1) 40.6 (15.4) 0.77	Mean Right Atrial Pressure (mRAP)	10.2±6.0	11.3±5.3	10.2±4.6	
Pulmonary Capillary Wedge Pressure (PCWP) 12.7±5.0 15.0±5.4 17.8±5.6 Cardiac Index (Cl) 2.3±0.6 2.2±0.7 2.6±0.7 Pulmonary Vascular Resistance (PVR) 610.5±336 562.2±322 517.9±248 p-value Operative Characteristics p-value Hypothermic Nadir* 17.4±0.9 17.0±0.9 17.4±1.0 0.40 Total Operative Time* (min) 544.8±62.1 557.8±67.6 543±60.4 0.58 Circulatory Arrest Time (min) 44.5±12.3 46.7±13.2 44.2±9.8 0.52 Cardiopulmonary Bypass Time (min) 273.1±43.5 281.5±42.7 275.9±46.7 0.70 Additional Operative Procedure, n (%) 34 (45.3) 10 (47.7) 7 (38.9) 0.75 Postoperative Hemodynamics Mean Right Atrial Pressure (mRAP) 8.0 (5.5) 8.8 (6.4) 9.6 (7.6) 0.75 Mean Pulmonary Artery Pressure (mPAP) 30.3 (12.5) 34.7 (14.1) 40.6 (15.4) 0.27	Mean Pulmonary Artery Pressure (mPAP)	45.8±12.0	44.4±9.3	44.2±12.6	
Cardiac Index (CI) 2.3±0.6 2.2±0.7 2.6±0.7 Pulmonary Vascular Resistance (PVR) 610.5±336 562.2±232 517.9±248 Operative Characteristics p-value Hypothermic Nadir* 17.4±0.9 17.0±0.9 17.4±1.0 0.40 Total Operative Time* (min) 544.8±62.1 557.8±67.6 543±60.4 0.58 Circulatory Arrest Time (min) 44.5±12.3 46.7±13.2 44.2±9.8 0.52 Cardiopulmonary Bypass Time (min) 273.1±43.5 281.5±42.7 275.9±46.7 0.70 Additional Operative Procedure, n (%) 34 (45.3) 10 (47.7) 7 (38.9) 0.75 Postoperative Hemodynamics s.0 (5.5) 8.8 (6.4) 9.6 (7.6) 0.75 Mean Right Atrial Pressure (mRAP) 30.3 (12.5) 34.7 (14.1) 40.6 (15.4) 0.27	Pulmonary Capillary Wedge Pressure (PCWP)	12.7±5.0	15.0 ± 5.4	17.8±5.6	
Pulmonary Vascular Resistance (PVR) 610.5 ± 336 562.2 ± 232 517.9 ± 248 Operative Characteristics	Cardiac Index (CI)	2.3±0.6	2.2 ± 0.7	2.6±0.7	
Operative Characteristics p-value Hypothermic Nadir* 17.4±0.9 17.0±0.9 17.4±1.0 0.40 Total Operative Time* (min) 544.8±62.1 557.8±67.6 543±60.4 0.58 Circulatory Arrest Time (min) 44.5±12.3 46.7±13.2 44.2±9.8 0.52 Cardiopulmonary Bypass Time (min) 273.1±43.5 281.5±42.7 275.9±46.7 0.70 Additional Operative Procedure, n (%) 34 (45.3) 10 (47.7) 7 (38.9) 0.75 Postoperative Hemodynamics Kean Right Atrial Pressure (mRAP) 8.0 (5.5) 8.8 (6.4) 9.6 (7.6) 0.75 Mean Pulmonary Artery Pressure (mPAP) 30.3 (12.5) 34.7 (14.1) 40.6 (15.4) 0.27	Pulmonary Vascular Resistance (PVR)	610.5 ± 336	562.2 ± 232	517.9±248	
Hypothermic Nadir*17.4±0.917.0±0.917.4±1.00.40Total Operative Time* (min)544.8±62.1557.8±67.6543±60.40.58Circulatory Arrest Time (min)44.5±12.346.7±13.244.2±9.80.52Cardiopulmonary Bypass Time (min)273.1±43.5281.5±42.7275.9±46.70.70Additional Operative Procedure, n (%)34 (45.3)10 (47.7)7 (38.9)0.75Postoperative HemodynamicsMean Right Atrial Pressure (mRAP)8.0 (5.5)8.8 (6.4)9.6 (7.6)0.75Mean Pulmonary Artery Pressure (mPAP)30.3 (12.5)34.7 (14.1)40.6 (15.4)0.27	Operative Characteristics				p-value
Y 544.8 ± 62.1 557.8 ± 67.6 543 ± 60.4 0.58 Circulatory Arrest Time (min) 44.5 ± 12.3 46.7 ± 13.2 44.2 ± 9.8 0.52 Cardiopulmonary Bypass Time (min) 273.1 ± 43.5 281.5 ± 42.7 275.9 ± 46.7 0.70 Additional Operative Procedure, n (%) 34 (45.3) 10 (47.7) 7 (38.9) 0.75 Postoperative Hemodynamics Nean Right Atrial Pressure (mRAP) 8.0 (5.5) 8.8 (6.4) 9.6 (7.6) 0.75 Mean Pulmonary Artery Pressure (mPAP) 30.3 (12.5) 34.7 (14.1) 40.6 (15.4) 0.27	Hypothermic Nadir*	17.4 ± 0.9	17.0±0.9	17.4±1.0	0.40
Circulatory Arrest Time (min) 44.5±12.3 46.7±13.2 44.2±9.8 0.52 Cardiopulmonary Bypass Time (min) 273.1±43.5 281.5±42.7 275.9±46.7 0.70 Additional Operative Procedure, n (%) 34 (45.3) 10 (47.7) 7 (38.9) 0.75 Postoperative Hemodynamics Mean Right Atrial Pressure (mRAP) 8.0 (5.5) 8.8 (6.4) 9.6 (7.6) 0.75 Mean Pulmonary Artery Pressure (mPAP) 30.3 (12.5) 34.7 (14.1) 40.6 (15.4) 0.27	Total Operative Time* (min)	544.8±62.1	557.8±67.6	543 ± 60.4	0.58
Cardiopulmonary Bypass Time (min) 273.1±43.5 281.5±42.7 275.9±46.7 0.70 Additional Operative Procedure, n (%) 34 (45.3) 10 (47.7) 7 (38.9) 0.75 Postoperative Hemodynamics Mean Right Atrial Pressure (mRAP) 8.0 (5.5) 8.8 (6.4) 9.6 (7.6) 0.75 Mean Pulmonary Artery Pressure (mPAP) 30.3 (12.5) 34.7 (14.1) 40.6 (15.4) 0.27	Circulatory Arrest Time (min)	44.5 + 12.3	46.7 + 13.2	44.2 + 9.8	0.52
Additional Operative Procedure, n (%) 34 (45.3) 10 (47.7) 7 (38.9) 0.75 Postoperative Hemodynamics Mean Right Atrial Pressure (mRAP) 8.0 (5.5) 8.8 (6.4) 9.6 (7.6) 0.75 Mean Pulmonary Artery Pressure (mPAP) 30.3 (12.5) 34.7 (14.1) 40.6 (15.4) 0.27	Cardiopulmonary Bypass Time (min)	273.1 ± 43.5	281.5+42.7	275.9+46.7	0.70
Postoperative Hemodynamics 8.0 (5.5) 8.8 (6.4) 9.6 (7.6) 0.75 Mean Pulmonary Artery Pressure (mPAP) 30.3 (12.5) 34.7 (14.1) 40.6 (15.4) 0.27	Additional Operative Procedure. n (%)	34 (45.3)	10 (47.7)	7 (38.9)	0.75
Mean Right Atrial Pressure (mRAP) 8.0 (5.5) 8.8 (6.4) 9.6 (7.6) 0.75 Mean Pulmonary Artery Pressure (mPAP) 30.3 (12.5) 34.7 (14.1) 40.6 (15.4) 0.27	Postoperative Hemodynamics		,	(,)	
Mean Pulmonary Artery Pressure (mPAP) 30.3 (12.5) 34.7 (14.1) 40.6 (15.4) 0.27	Mean Right Atrial Pressure (mRAP)	8.0 (5.5)	8.8 (6.4)	9.6 (7.6)	0.75
	Mean Pulmonary Artery Pressure (mPAP)	30.3 (12.5)	34,7 (14.1)	40.6 (15.4)	0.27

Table 1 (continued)

	Total Cohort (n=75)	RPLI (n=21)	PNA (n = 18)	
Pulmonary Capillary Wedge Pressure (PCWP)	12.5 (6.7)	13.4 (6.8)	12.4 (8.5)	0.71
Cardiac Index (CI)	2.6 (0.5)	2.5 (0.5)	2.4 (0.4)	0.75
Pulmonary Vascular Resistance (PVR)	3.5 (2.2)	4.5 (2.8)	6.0 (2.8)	0.13
Postoperative Complications				
Airway Hemorrhage	4 (5.3)	1 (4.8)	2 (11.1)	0.59
Extracorporeal Membrane Oxygenation (ECMO)	5 (6.7)	3 (14.3)	4 (22.2)	0.68

Data are summarized as mean (standard deviation) or number (percentage)

Abbreviations: IQR, interquartile range; BMI, body mass index; PNA, pneumonia; PTE, pulmonary thromboendarterectomy; CTEPH, chronic thromboembolic pulmonary hypertension; APLS, antiphospholipid syndrome; VA, ventriculoatrial; VTE, venous thromboembolism; mRAP; mPAP, mean pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; CI, cardiac index; SD, standard deviation; PVR, pulmonary vascular resistance; NYHA, New York Heart Association; FC, functional class; 6MWD, 6-minute walk distance; BNP, B-type natriuretic peptide; FVC, forced vital capacity; FEV₁, forced expiratory volume at 1 s; TLC, total lung capacity; DLCO, diffusing capacity of lungs for carbon monoxide

*Data is incomplete for some subjects

 Table 2
 Microbiologic data for subjects with diagnoses of RPLI,

 PNA, and microbiologically confirmed PNA

RPLI (+)	
Rate of Documented RPLI, n (%) (total cohort)	21 (28.0)
History of PNA in prior 180 days, n (%)	2 (9.5)
Time between PTE and RPLI (days), median (IQR)	2 (1,3)
PNA (+)	
Rate of Documented PNA, n (%) (total cohort)	18 (24.0)
History of PNA in prior 180 days, n (%)	2 (11.1)
Rate of Microbiologically Confirmed PNA, n (%) (total cohort)	5 (6.7)
Time between PTE and PNA, median (IQR)	5 (3,5)
Diagnostic Sampling	
Rate of Diagnostic Sampling Performed, n (%)	8 (10.7)
Rate of Positive BAL/NBBAL*, n (%)	5 (62.5)
Haemophilus parainfluenzae, n (%)	1 (20.0)
Pseudomonas aeruginosa, n (%)	2 (40.0)
Staphylococcus aureus, n (%)	2 (40.0)
Methicillin-resistant Staphylococcus aureus (MRSA), n (%)	1 (50.0)
Postoperative Antibiotics in Post-PTE PNA Subjects	
Postoperative Antibiotics, n (%)	
Cefepime	3 (60.0)
Ceftriaxone	1 (20.0)
Piperacillin-tazobactam	1 (20.0)
Vancomycin	1 (20.0)
Duration of Antibiotics in Days, median (IQR)	7.5
	(2.5,8.8)

Abbreviations: RPLI, reperfusion lung injury; PNA, pneumonia; PTE, pulmonary thromboendarterectomy; IQR, interquartile range; BAL, bronchoscopic bronchoalveolar lavage; NBBAL, non-bronchoscopic bronchoalveolar lavage; MRSA, methicillin-resistant *Staphylococcus aureus*

*Subjects may have had more than one organism isolated

bronchoscopic sampling (seven (87%) BAL, one (13%) non-bronchoscopic BAL), and five (63%) of these samples yielded positive results indicative of infection (Table 2). There were no significant differences with regard to operative characteristics (i.e.: operative time, circulatory arrest time, cardiopulmonary bypass time, hypothermic nadir), post-operative hemodynamics, airway

hemorrhage, or ECMO use (Table 1). Overall, 48 of 75 (64%) of subjects were free of either RPLI or PNA, and neither RPLI nor PNA resulted in a 30-day mortality.

Subjects with post-PTE PNA received antibiotic treatment for an average duration of 7.5 days. The most commonly isolated causative organisms in post-PTE pneumonia cases were *Staphylococcus aureus* (40%) and *Pseudomonas aeruginosa* (40%). No viral infections were identified. Cefepime was the most commonly used antimicrobial agent to treat pneumonia in this cohort (60%).

Comparison between normal post PTE, Post PTE PNA (+), Post PTE RPLI (+), and Post PTE RPLI (+) & PNA (+) groups revealed several significant findings. Median duration of ICU and hospital length of stay among the RPLI (+) & PNA (+) (12.5 days (10.3, 21.8) and 27.0 days (17.5, 32.0), respectively) was significantly higher than in either RPLI (+) & PNA (-) (4.0 days (3.0, 6.0) and 7.0 days (6.5, 9.5), respectively) or RPLI (-) & PNA (+) (5.0 days (3.0, 7.0) and 10.5 days (7.8, 17.5), respectively) alone (Table 3). Median duration of MV among the RPLI (+) & PNA (+) cohort (5.5 days (3.0, 7.0)) was significantly higher than in either RPLI (+) & PNA (-) (1 day, (1.0, 1.0)) or RPLI (-) & PNA (+) (1.5 days (1.0, 2.3)) cohorts alone. There was a significant difference in groups with regard hospital and ICU length of stay, and duration of mechanical ventilation (H = 20.27, df = 3, p-value 0.000), but not with regard to WBC on post-operative day one (H = 1.19, H)df = 3, p-value 0.76). Post-hoc analysis indicated that the combined group of Post PTE RPLI (+) & PNA (+) subjects had longer hospital and ICU LOS, and duration of mechanical ventilation as compared to normal post PTE and post PTE RPLI (+) only subjects. (Fig. 2).

Discussion

Among subjects who underwent PTE, a notable proportion (24%) were diagnosed with PNA, with a median onset of five days in microbiologically confirmed PNA following surgery. Importantly, within the cohort of subjects with RPLI, 48% were also diagnosed with PNA



Fig. 1 Characteristics of total cohort (n=75) including a breakdown of subjects with and without RPLI, subjects with and without PNA, and subjects with microbiologically confirmed PNA from the RPLI (+) group and 1 subject with microbiologically confirmed PNA from the RPLI (-) group

Table 3 Outcomes (n = 75)

Outcome, me- dian (IQR)	RPLI (-) & PNA (-) (<i>n</i> = 46)	RPLI (-) & PNA (+) (n=8)	RPLI (+) & PNA (-) (<i>n</i> = 11)	RPLI (+) & PNA (+) (<i>n</i> =10)
Length of Stay (LOS), days				
Hospital LOS	7.5 (6.0, 10.0)	10.5 (7.8, 17.5)	7.0 (6.5, 9.5)	27.0 (17.5, 32)
ICU LOS	3.0 (2.0, 4.0)	5.0 (3.0, 7.0)	4.0 (3.0, 6.0)	12.5 (10.3, 21.8)
MV Duration (days)	1.0 (1.0, 1.0)	1.5 (1.0, 2.3)	1.0 (1.0, 1.0)	5.5 (3.0, 7.0)

Abbreviations: IQR, interquartile range; LOS, length of stay; ICU, intensive care unit; MV, mechanical ventilation

and 40% of these had microbiologically confirmed PNA based on bronchoscopic sampling, highlighting the overlap and potential correlation between RPLI and PNA in this population. Significant distinctions emerged among post-PTE groups, highlighting notably poorer outcomes in the combined Post PTE RPLI (+) & PNA (+) group as compared to either group alone. The combined Post PTE RPLI (+) & PNA (+) group had considerably prolonged hospital and ICU length of stays. The Post PTE RPLI (+) & PNA (+) group had significantly longer duration of MV than either positive group alone (RPLI (+) & PNA (-) or RPLI (-) & PNA (+)) suggesting MV duration may correlate with prolonged length of stay in the Post PTE RPLI (+) & PNA (+) group. Notably, the duration of MV among the RPLI (-) & PNA (-) group is similar to both the RPLI (+) & PNA (-) and RPLI (-) & PNA (+) groups, suggesting RPLI as a cause of prolonged MV may not entirely account for the prolonged MV in the RPLI (+) & PNA (+) group (Fig. 2). This is the first study to highlight concurrent rates of both RPLI and PNA, using clinically relevant definitions similar to prior published studies, that demonstrates implications on clinical outcomes that have meaningful impact on patient centered care [9].

The presence of RPLI may predispose patients to a higher risk of developing PNA, possibly due to compromised lung function and impaired clearance of pathogens. The use of TEE during surgery, with the known association of micro aspiration and increased incidence of VAP, combined with the duration of surgery may predispose to increased frequency of post-operative PNA. Intraoperative bronchoscopy, performed to assess bronchial bleeding, may introduce pathogens into the respiratory tract, contributing to the development of PNA. Further, owing to the type of surgery, endothelial compromise, injury, and inflammation may result in altered immune surveillance, epithelial lining fluid penetration of antibiotics, and warrant further study.

Subjects diagnosed with post-PTE PNA received antibiotic treatment for an average duration of 7.5 days, as compared to the standard 48 h of periprocedural prophylaxis. The most frequently isolated causative organisms in cases of post-PTE PNA were Staphylococcus aureus and Pseudomonas aeruginosa. This is consistent with historical data, implicating Staphylococcus aureus (especially methicillin-resistant Staphylococcus aureus [MRSA]) and Gram-negative bacilli such as Pseudomonas aeruginosa as leading microbial causes of nosocomial pneumonia associated with significant morbidity and mortality [20, 21]. These findings emphasize the importance of appropriate antibiotic coverage against these pathogens in the management of PNA following PTE. The identification of specific causative organisms warrants further investigation in larger cohorts of post-PTE subjects to determine if routine periprocedural antimicrobial prophylaxis



Fig. 2 Subject outcomes related to ICU LOS, hospital LOS, and MV duration

should be modified to target these pathogens more effectively.

It is important to acknowledge several limitations of this study. First, our study represents a single center, albeit large volume, experience. This may limit the generalizability of our findings to other institutions. Secondly, the retrospective nature of the study design introduces the possibility of selection bias and incomplete data collection. Additionally, the lack of systematic evaluation for PNA in all subjects may have led to underdiagnosis or missed cases. The rate of PNA may also have been overestimated as there was not a microbiologic confirmation in many cases diagnosed as PNA. Furthermore, clinical anchoring bias on a diagnosis of RPLI may have prevented systematic evaluation for PNA (i.e. microbiologic sampling) and delay in appropriate care. Future prospective studies involving multiple centers with a standardized approach to diagnosing and monitoring PNA following PTE would provide more robust evidence and help overcome these limitations.

In light of the overlap and correlation between RPLI and PNA and poor outcomes observed in our study, clinicians may consider a more systemic evaluation for PNA when managing patients with RPLI. The high prevalence of positive cultures in subjects who underwent bronchoscopy underscores the importance of actively investigating for concurrent pulmonary infections in these critically ill individuals. The timely diagnosis and appropriate management of PNA in patients with RPLI are crucial to mitigate the potential adverse effects on patient outcomes.

Conclusion

In conclusion, our study highlights the incidence of PNA in subjects undergoing PTE for CTEPH and its correlation with RPLI. A considerable portion of PTE subjects, particularly those with RPLI, experienced PNA, leading to substantially poorer post-operative outcomes. This correlation emphasizes the need for a comprehensive and vigilant approach in the evaluation, early detection, and management of PNA in patients with RPLI post-PTE. Future studies should aim to further elucidate the underlying mechanisms and risk factors associated with post-PTE PNA, evaluate the efficacy of preventive strategies, and target interventions aimed to reduce the incidence and impact of PNA in this patient population.

Abbreviations

BAL	Bronchoscopic bronchoalveolar lavage
BMI	Body mass index
CTEPH	Chronic thromboembolic pulmonary hypertension
EMR	Electronic medical record
ICU	Intensive care unit
IRB	Institutional review board
LOS	Length of stay
MDR	Multidrug-resistant
mPA	Mean pulmonary arterial pressure
MRSA	Methicillin-resistant Staphylococcus aureus
MV	Mechanical ventilation
NBBAL	Non-bronchoscopic bronchalveolar lavage
NMH	Northwestern Memorial Hospital
NYHA	New York Heart Association
PE	Pulmonary embolism
PNA	Pneumonia
PTE	Pulmonary thromboendarterectomy
PVR	Pulmonary vascular resistance
RPLI	Reperfusion lung injury
TEE	Transesophageal echocardiography

VAP	Ventilator-associated pneumonia
VTED	Venous thromboembolic disease
WBC	White blood cell
XDR	Extensively drug-resistant

Author contributions

SR and RM had full access to all of the data in the study and take responsibility for the integrity and the accuracy of the data analysis, development and writing of the manuscript. PR, JG, CQ, AS, MB, DS, SC, SM, and MC contributed substantially to the study design, data analysis and interpretation, and the writing of the manuscript.

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Data availability

The datasets used in the present study are available from the first author and corresponding authors on reasonable request.

Declarations

Ethics approval and consent to participate

This study received approval from the Northwestern University Institutional Review Board (IRB) STU0000959. All patients provided informed written consent for the presentation and publication of their study data, adhering to ethical standards in accordance with the Declaration of Helsinki.

Clinical trial number

As this study involved standard clinical procedures and assessments without an experimental treatment protocol, it did not require registration with a public clinical trials registry.

Competing interests

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Ruben Mylvaganam reports a relationship with United Therapeutics Corporation Research and Development that includes: consulting or advisory. Michael Cuttica reports a relationship with United Therapeutics Corporation Research and Development that includes: consulting or advisory. Michael Cuttica reports a relationship with Janssen Pharmaceuticals Inc that includes: consulting or advisory. Michael Cuttica reports a relationship with Bayer Corporation that includes: consulting or advisory. Michael Cuttica reports a relationship with Insemd that includes: funding grants. Ruben Mylvaganam reports a relationship with Janssen Pharmaceuticals Inc that includes: funding grants. Daniel Schimmel reports a relationship with Penumbra Inc that includes: consulting or advisory, funding grants, and speaking and lecture fees. Daniel Schimmel reports a relationship with Inari Medical Inc that includes: consulting or advisory, funding grants, and speaking and lecture fees. Daniel Schimmel reports a relationship with Sanofi-Aventis US LLC that includes: funding grants. Daniel Schimmel reports a relationship with Boston Scientific Corp that includes: consulting or advisory and funding grants. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. The authors received no funding for this study. The authors declare that they have no financial interests or relationships that could be perceived as a conflict of interest regarding the publication of this manuscript.

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