Pulmonary Circulation

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RESEARCH ARTICLE OPEN ACCESS

Lung Transplant Outcomes in Patients With Preoperative Catheterization Indicating Group 2 Pulmonary Hypertension

Víctor M. Mora-Cuesta[1,2,3] | Amaya Martínez-Meñaca[1,2,3] | David Iturbe-Fernández[1,2,3] | Sandra Tello-Mena[1,2] | Sheila Izquierdo-Cuervo[1,2] | Tamara García-Camarero[4] | Aritz Gil-Ongay[4] | Pilar Alonso-Lecue[3] | José M Cifrián-Martínez[1,2,3] | Diego Agustín Rodríguez-Chiaradia[5,6] | Pilar Escribano-Subías[2,7,8,9] | Esther Barreiro[5,10,11]

[1]Respiratory Department, Marqués de Valdecilla University Hospital, Santander, Spain | [2]ERN-LUNG (European Reference Network on rare respiratory diseases), Frankfurt, Germany | [3]Valdecilla Research Institute (IDIVAL), Santander, Spain | [4]Cardiology Department, Marqués de Valdecilla University Hospital, Santander, Spain | [5]Pulmonology Department, Hospital del Mar, Barcelona, Spain | [6]Centro de Investigación en Red de Enfermedades Respiratorias (CIBERES), Instituto de Salud Carlos III (ISCIII), Barcelona, Spain | [7]Cardiology Department, Hospital Universitario Doce de Octubre, Madrid, Spain | [8]Centro de Investigación Biomédica en Red de Enfermedades Cardiovasculares (CIBERCV), Instituto de Salud Carlos III (ISCIII), Madrid, Spain | [9]Facultad de Medicina, Universidad Complutense de Madrid, Madrid, Spain | [10]Muscle Wasting and Cachexia in Chronic Respiratory Diseases and Lung Cancer Research Group, Hospital del Mar Research Institute (IMIM), Barcelona, Spain | [11]Department of Medicine and Life Sciences (MELIS), Universitat Pompeu Fabra, Barcelona, Spain

Correspondence: Víctor M. Mora-Cuesta (vmoracuesta@gmail.com)

Received: 5 February 2025 | **Revised:** 22 May 2025 | **Accepted:** 27 May 2025

Funding: The authors received no specific funding for this work.

Keywords: lung transplantation | primary graft dysfunction | pulmonary hypertension

ABSTRACT

Lung transplantation (LT) is a well-established therapeutic option for patients with advanced chronic respiratory diseases. This study aims to assess the prevalence and clinical impact of Group 2 pulmonary hypertension (PHg2) in LT recipients, comparing it with Group 3 pulmonary hypertension (PHg3). This retrospective cohort study analyzed LT recipients from 2015 to 2024 at a single center. Patients were categorized into three groups based on hemodynamic measurements: no PH, PHg2, and PHg3. Hemodynamic data were acquired via right heart catheterization. Perioperative complications, including primary graft dysfunction (PGD), and long-term survival were compared across the groups. Of the 412 LT recipients, 40 (10.9%) were diagnosed with PHg2, while 62.5% had PHg3. Statistical analysis revealed no significant differences in perioperative outcomes, including the incidence of PGD, between patients with PHg2 and those with PHg3. Additionally, there were no differences in long-term survival between the groups. Within the PHg2 subgroup, patients with isolated PHg2 and those with combined PHg2 exhibited similar post-transplant outcomes. PHg2 is identified in a notable fraction of LT recipients, yet it does not appear to adversely affect perioperative complications or long-term survival when compared to PHg3 or patients without PH. These findings suggest that PHg2, despite its prevalence, does not significantly alter transplant outcomes. Future multicenter studies are needed to further explore the impact of subtle left ventricular dysfunction on LT results.

Abbreviations: 6MWT, six minutes walking test; CO, cardiac output; COPD, chronic obstructive pulmonary disease; ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit; ILD, interstitial lung disease; ISHLT, International Society for Heart and Lung Transplantation; LAS, lung allocation score; LT, lung transplantation; mPAP, mean pulmonary arterial pressure; PGD, primary graft dysfunction; PH, pulmonary hypertension; PWP, pulmonary wedge pressure; RAP, right atrial pressure; RHC, right heart catheterization.

The authors Víctor M. Mora-Cuesta and Amaya Martínez-Meñaca have the same degree of contribution and share the first authorship

1 | Introduction

Lung transplantation (LT) is a well-established treatment option for patients with advanced chronic respiratory diseases who have significant quality of life limitations and poor life expectancy. Over the years, improved short- and long-term survival outcomes of LT have led to more flexible acceptance criteria for potential candidates [1, 2]. Consequently, the age of LT recipients has increased, along with a higher cardiovascular burden in these patients.

Pulmonary hypertension (PH) is a common comorbidity among LT candidates, with the most frequent type being associated with respiratory diseases or group 3 (PHg3) [3]. Although it is common, it usually manifests as mild PH, and it remains unclear whether it implies a higher risk of perioperative LT complications. Some studies suggest a greater need for ECMO, more bleeding, and more primary graft dysfunction, among other complications, while others have not reported this association [4–7].

On the other hand, PH associated with left heart disease or group 2 (PHg2) is the most common type of PH in the general population and is closely related to cardiovascular risk factors [8, 9]. From all the causes leading to PHg2, severe valvular abnormalities or left ventricular dysfunctions are unlikely to be found among patients listed for LT, as they generally represent a contraindication. However, other common forms of PHg2 are secondary to conditions that may go unnoticed, such as diastolic dysfunction or heart failure with preserved ejection fraction. Unlike PHg3, which usually resolves after LT due to the reversal of hypoxemia, the underlying mechanisms for PHg2 may persist after LT, potentially impacting long-term outcomes. It should be noted that the cardiopulmonary phenotype has also been described, in which heart failure and respiratory diseases coexist [10].

Due to the increased flexibility in selecting lung transplant candidates, with recipients being older and having more cardiovascular risk factors, a higher frequency of PHg2 could be expected, and its impact on post-transplant outcomes remains unknown. The aim of this study was to assess the prevalence of PHg2 in LT recipients, compare perioperative complications between patients with PHg2 and those with PHg3, and evaluate the long-term survival of patients with PHg2 after LT.

2 | Methods

Patients receiving an LT throughout the years 2015–2024 were recruited for the purpose of the study at a single reference center (Hospital Universitario Marqués de Valdecilla, Santander, Spain). The inclusion criteria were having undergone right heart catheterization during the pre-lung transplant evaluation and having all the necessary hemodynamic variables available to define the different study groups: mPAP, PWP, and PVR. For patients with more than one pre-transplant catheterization, the one closest to the transplant was selected. Patients with pulmonary arterial hypertension (PAH) and retransplantations were excluded.

The main study groups were defined as follows [8]:

1. Control group (No PH): patients with mPAP ≤ 20 mmHg.
2. PHg2: patients with mPAP > 20 mmHg + PWP > 15 mmHg. These were further divided into two groups:
   - Isolated PHg2: those with mPAP > 20 mmHg + PWP > 15 mmHg + PVR ≤ 2 Wood units.
   - Combined PHg2: those with mPAP > 20 mmHg + PWP > 15 mmHg + PVR > 2 Wood units.
3. PHg3: patients with mPAP > 20 mmHg + PWP ≤ 15 mmHg + PVR > 2 Wood units, in patients with lung parenchymal disease documented by chest CT and with significant impairment in pulmonary function tests.

In addition to demographic variables, cardiovascular risk factors at the time of listing for LT were included. Variables related to the immediate postoperative period of transplantation were also recorded. The characteristics of the donors were also recorded. Primary graft dysfunction was defined and graded according to ISHLT criteria [11]. The presence of post-transplant acute cellular rejection was defined and graded according to the ISHLT Working Formulation [12]. A long-term follow-up was conducted to assess the survival of the different pulmonary hypertension groups.

All patients routinely undergo an annual echocardiogram as part of the pre-transplant evaluation. Those in whom structural heart disease is suspected are referred to a cardiology specialist for further evaluation with appropriate diagnostic tests. At our center, as part of the pre-transplant evaluation, all patients undergo right heart catheterization. Those over 50 years old, with cardiovascular risk factors, or a smoking history of more than 10 pack-years are also routinely evaluated with coronary angiography. All catheterizations were performed in the supine position by the same team of hemodynamic specialists from a specialized pulmonary hypertension center. The zero-reference level is routinely set at the mid-thoracic level, which generally corresponds to the location of the left atrium. All measurements, including the PWP, are taken at the end of expiration (without breath-holding maneuvers). Due to potential intrathoracic pressure changes in these patients with respiratory diseases, the recorded values are the average of 3–4 respiratory cycles. Over the years, cardiac output has been measured using different methods: in the early years of the study period, it was assessed using the direct Fick method, whereas in recent years it has been measured by thermodilution. No vasoreactivity testing was performed in any case. The use of diuretics at the time of catheterization was not recorded. However, if the patient was taking them, routine clinical practice does not involve altering the usual medication at the time of catheterization. No volume overload tests were performed in any case. Routine catheterizations were not performed after lung transplantation, although the reasons for performing right heart catheterizations after the transplant were reviewed in selected cases.

For patients meeting PHg2 criteria, no different donor selection was used, nor was a different anesthetic, operative, or post-operative management applied. For patients with PHg2, the echocardiogram closest to the time of pre-transplant

catheterization was reviewed, as well as documented episodes of heart failure after the transplant and the need for hospitalization due to heart failure. Additionally, the use of diuretics beyond the first 3 months after the transplant was analyzed in all study groups. Patients with PHg2 were referred to the cardiology department and medically managed with diuretics and treatment of comorbidities, although specific treatment details for each case were not documented.

The study was approved by the Cantabria Ethics and Research Committee (CEIm) with the study code 2024.221. Due to the retrospective nature of the study and the loss of follow-up for some patients, the ethics committee granted a waiver of informed consent.

2.1 | Statistics

IBM SPSS Statistics 20 software was used for statistical analysis. For continuous variables, mean values +/− standard deviations were presented for those with a normal distribution, while medians and interquartile ranges (P25–P75) were shown for those without a normal distribution. Categorical variables were presented as frequencies and percentages.

The Smirnov–Kolmogorov test was used to determine if continuous quantitative variables followed a normal distribution. The ANOVA test was used to compare the means of three independent groups to determine if there were significant differences among them for normally distributed variables, and the Kruskal–Wallis test for non-normally distributed variables. The Student's *t*-test was used to determine if there was a significant difference between the means of two groups, and the Mann–Whitney–Wilcoxon test for non-normally distributed variables. The χ^2 test was applied to determine if there was a significant association between categorical variables.

The Kaplan–Meier analysis was used to estimate the survival function, and the log-rank test was used to compare survival curves of two or more groups.

A statistically significant relationship was considered at a p value ≤ 0.05.

3 | Results

Among 412 lung transplants performed during the study period, 29 patients were excluded due to the lack of necessary hemodynamic variables to establish the study groups, and another 15 patients with PAH were also excluded (Figure 1). The majority of the patients (62.5%) met the criteria for PHg3, and 40 (10.9%) patients met the criteria for PHg2.

Table 1 describes the baseline characteristics of all patients, categorized into subgroups. Patients with PHg2 had a higher BMI compared to the others (26.08 ± 3.33 vs. 24.11 ± 3.78 vs. 24.94 ± 3.30 kg/m^2; $p = 0.008$). Regarding the etiology of the respiratory disease, there was a higher proportion of COPD among patients with PHg2 and ILD in the PHg3 group. Among cardiovascular risk factors, there were no differences in the frequency of arterial hypertension or diabetes, but a significantly higher frequency of dyslipidemia was observed among patients with PHg3. There were no significant differences in the frequency of coronary lesions or LAS scores. A higher PaO2 was observed among patients without PH. No differences were found in the characteristics of the donors among the different groups (Supporting Information S1: Table S1).

When comparing only the hemodynamic characteristics of patients with PHg2 and PHg3, patients with PHg2 had a higher RAP [12 (8–15) vs. 8 (6–10); $p < 0.001$] and mPAP [28.5 (26–34.75) vs. 26 (23–30); $p < 0.001$], and lower PVR [2.32

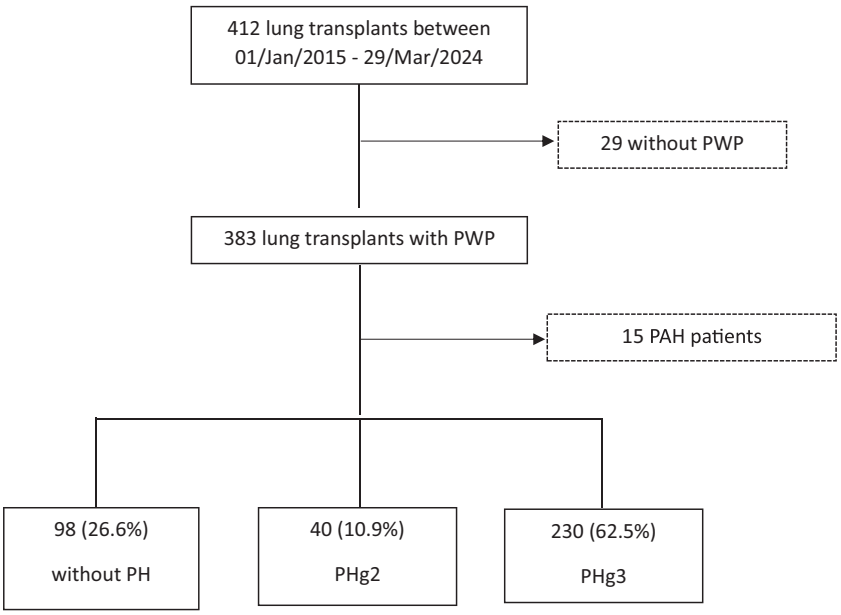

FIGURE 1 | Flowchart of the patients included in the study. Abbreviations: PAH = pulmonary arterial hypertension; PH = pulmonary hypertension; PHg2 = pulmonary hypertension group 2; PHg3 = pulmonary hypertension group 3; PWP = pulmonary wedge pressure.

TABLE 1 | Baseline characteristics.

Baseline					
	All	**No PH**	**PHg2**	**PHg3**	***p***
N	368	98 (26.6%)	40 (10.9%)	230 (62.5%)	—
Gender					0.148
Male	235 (63.9%)	55 (56.1%)	25 (62.5%)	155 (67.4%)	
Female	133 (36.1%)	43 (43.9%)	15 (37.5%)	75 (32.6%)	
BMI (kg/m^2)	24.85 ± 3.47	24.11 ± 3.78	26.08 ± 3.33	24.94 ± 3.30	0.008
Lung disease					0.023
COPD	142 (38.6%)	29 (29.6%)	22 (55.0%)	91 (39.6%)	
ILD	179 (48.6%)	61 (62.2%)	15 (37.5%)	103 (44.8%)	
Bronchiectasis	23 (6.2%)	4 (4.1%)	2 (5.0%)	17 (7.4%)	
Other	24 (6.5%)	4 (4.1%)	1 (2.5%)	19 (8.3%)	
Age (years)	60.48 (55.30–63.56)	60.03 (52.85–62.65)	59.78 (53.71–62.51)	60.70 (56.05–63.90)	0.089
Arterial hypertension	85 (23.1%)	18 (18.4%)	10 (25.0%)	57 (24.8%)	0.431
No treatment	11 (12.9%)	2 (11.1%)	4 (40.0%)	5 (8.8%)	0.024
ACE inhibitors	25 (29.4%)	5 (27.8%)	2 (20.0%)	18 (31.6%)	0.749
CCBs	10 (11.8%)	2 (11.1%)	2 (20.0%)	6 (10.5%)	0.689
Thiazides	15 (17.6%)	2 (11.1%)	1 (10.0%)	12 (21.1%)	0.500
β-blockers	7 (8.2%)	1 (5.6%)	1 (10.0%)	5 (8.8%)	0.890
ARBs	38 (44.7%)	8 (44.4%)	4 (40.0%)	26 (45.6%)	0.947
Loop diuretics	12 (14.1%)	1 (5.6%)	3 (30.0%)	8 (14.0%)	0.205
Diabetes	35 (9.5%)	4 (4.1%)	6 (15.0%)	25 (10.9%)	0.072
Only insulin	14 (40.0%)	1 (25.0%)	5 (83.3%)	8 (32.0%)	0.057
Oral antidiabetics	16 (45.7%)	3 (75.0%)	1 (16.7%)	12 (48.0%)	0.176
Insulin + oral antidiabetics	5 (14.3%)	0 (0.0%)	0 (0.0%)	5 (20.0%)	0.311
Dyslipidemia	140 (38.0%)	29 (29.6%)	12 (30.0%)	99 (43.0%)	0.039
No treatment	38 (27.1%)	7 (24.1%)	2 (16.7%)	29 (29.3%)	0.598
Statins	101 (72.1%)	21 (72.4%)	10 (83.3%)	70 (70.7%)	0.654
Ezetimibe	5 (3.6%)	0 (0.0%)	1 (8.3%)	4 (4.0%)	0.381
Fenofibrate	4 (2.9%)	1 (3.4%)	0 (0.0%)	3 (3.0%)	0.819
Former smoker	304 (82.6%)	75 (76.5%)	36 (90.0%)	193 (83.9%)	0.116
Accumulated consumption (pack-year)	35 (20–50)	30 (20–50)	40 (27.75–57.75)	38 (20–50)	0.347
RAP (mmHg)	7 (5–10)	5 (4–7)	12 (8–15)	8 (6–10)	< 0.001
mPAP (mmHg)	24.2 (20–29)	18 (16–20)	28.5 (26– 34.75)	26 (23–30)	< 0.001
PWP (mmHg)	12 (10–14)	10 (7–12)	17.5 (16–20.75)	12 (10–14)	< 0.001
Cardiac output (L/min)	5 (4.33–5.8)	4.76 (4.31–5.5)	4.85 (4.3–5.6)	5.15 (4.38– 5.9)	0.134
Cardiac index ($L/min/m^2$)	2.88 ± 0.66	2.88 ± 0.57	2.82 ± 0.62	2.89 ± 0.70	0.862
PVR (wood Units)	2.44 (1.72–3.39)	1.49 (1.08–2.19)	2.32 (1.58–3.15)	2.85 (2.26–3.67)	< 0.001
Coronary lesions	49 (15.1%)	12 (14.3%)	7 (19.4%)	30 (14.6%)	0.738
PaO_2 (mmHg)	59.84 ± 9.08	62.07 ± 9.47	59.56 ± 8.26	59.02 ± 8.94	0.042
6MWT (m)	375.56 ± 95.11	380.33 ± 100.14	345.03 ± 96.03	378.56 ± 92.32	0.118
Creatinine (mg/dL)	0.75 ± 0.18	0.72 ± 0.16	0.74 ± 0.21	0.75 ± 0.18	0.400
LAS	33.47 (31.81–35.65)	33.81 (32.63–36.26)	33.64 (31.46–35.07)	33.08 (31.64–35.70)	0.431

(Continues)

TABLE 1 | (Continued)

Baseline	All	No PH	PHg2	PHg3	*p*
PFT's					
COPD	142 (38.6%)				—
FEV1 (mL)	692.9 ± 298.5	621.8 ± 210.9	648.2 ± 198.9	725.6 ± 335.9	0.205
FEV1 (%)	24.7 ± 10.6	21.5 ± 6.9	24.5 ± 6.5	25.7 ± 12.1	0.181
FVC (mL)	2326.4 ± 798.9	2266.4 ± 779.4	2041.3 ± 761.1	2413.8 ± 804.2	0.132
FVC (%)	64.8 ± 18.1	61.4 ± 18.6	62.4 ± 20.5	66.5 ± 17.3	0.341
DLCO (%)	26.7 ± 11.4	28.6 ± 10.6	23.6 ± 6.9	27.0 ± 13.1	0.666
ILD	179 (48.6%)				—
FEV1 (mL)	1632.1 ± 598.5	1468.7 ± 570.1	1797.8 ± 533.2	1706.3 ± 607.3	0.026
FEV1 (%)	55.3 ± 16.9	49.3 ± 16.6	58.1 ± 18.5	58.4 ± 16.1	0.003
FVC (mL)	1979.2 ± 739.2	1776.4 ± 734.2	2199.3 ± 614.8	2069.4 ± 737.3	0.024
FVC (%)	52.8 ± 16.9	47.1 ± 16.6	56. ± 16.7	55.7 ± 16.4	0.005
DLCO (%)	22.7 ± 7.15	24.9 ± 6.8	21.4 ± 5.6	21.8 ± 7.4	0.079

Abberviations: 6MWT = six minutes walking test; ACE = Angiotensin-Converting Enzyme; ARBs = Angiotensin II Receptor Blockers; BMI = body mass index; CCBs = Calcium channel blockers; COPD = chronic obstructive pulmonary disease; DLCO = Diffusing Capacity of the Lung for Carbon Monoxide; FEV_1 = Forced Expiratory Volume in 1 s; FVC = Forced Vital Capacity; ILD = interstitial lung disease; LAS = lung allocation score; mPAP = mean pulmonary arterial pressure; PaO2 = arterial pressure of oxygen; PFT = Pulmonary Function Test; PH = pulmonary hypertension; PHg2 = pulmonary hypertension group 2; PHg3 = pulmonary hypertension group 3; PWP: pulmonary wedge pressure; PVR = pulmonary vascular resistance; RAP = right atrial pressure.

TABLE 2 | Surgery and postoperative outcomes.

Surgery and postoperative outcomes	All	No PH	PHg2	PHg3	*p*
N	368	98 (26.6%)	40 (10.9%)	230 (62.5%)	—
Type of transplant					0.294
Single lung	60 (16.3%)	20 (20.4%)	4 (10.0%)	36 (15.7%)	
Double lung	308 (83.7%)	78 (79.6%)	36 (90.0%)	194 (84.3%)	
Transfusions during surgery	100 (27.2%)	26 (26.5%)	13 (32.5%)	61 (26.5%)	0.725
Packed red blood cells	1 (1–3)	2 (1–3)	2 (1–4)	1 (1–2.5)	0.464
ECMO during surgery	29 (7.9%)	6 (6.1%)	5 (12.5%)	18 (7.8%)	0.451
PGD	92 (25.1%)	27 (27.6%)	12 (30.0%)	53 (23.1%)	0.524
Surgical reintervention	17 (6.7%)	3 (4.4%)	1 (4.3%)	13 (8.0%)	0.549
Tracheostomy	20 (5.4%)	5 (5.1%)	3 (7.55)	12 (5.2%)	0.832
Acute rejection	122 (35.0%)	33 (34.7%)	15 (40.5%)	74 (34.1%)	0.749
On ventilation (days)	1 (1–2)	1 (1–2)	1 (1–2)	1 (1–2)	0.899
ICU stay (days)	4 (3–6)	4 (3–6)	4.5 (3–6.25)	4 (3–6)	0.447
Length of stay (days)	23 (20–30)	22 (20–27)	26 (22– 34)	23 (20– 30)	0.109
Need for diuretics at any time after the transplant	192 (52.2%)	44 (44.9%)	26 (65.0%)	122 (53.0%)	0.091
Need for diuretics at any time beyond 90 days post-transplant	177 (48.1%)	40 (40.8%)	23 (57.5%)	114 (49.6%)	0.158

Abbreviations: ECMO = extracorporeal membrane oxygenation; ICU = intensive care unit; PH = pulmonary hypertension; PHg2 = pulmonary hypertension group 2; PHg3 = pulmonary hypertension group 3; PGD = primary graft dysfunction.

(1.58–3.15) vs. 2.85 (2.26–3.67); $p = 0.007$] (Supporting Information S1: Table S2).

Table 2 describes all variables related to LT and the immediate postoperative period, showing no significant differences between the three groups.

Out of the 40 patients with PHg2, 18 (45%) fulfilled hemodynamic criteria for isolated PHg2 while 22 (55%) had criteria for combined PHg2 (Table 3). Among the baseline characteristics, significant differences were found only in hemodynamic variables, with a higher mPAP among patients with combined PHg2 (28.33 ± 7.9 vs. 33.81 ± 7.5; $p = 0.031$), a higher cardiac

TABLE 3 | Baseline characteristics and postoperative outcomes in PHg2.

	All	Isolated PHg2	Combined PHg2	*p*
N	40 (100%)	18 (45.0%)	22 (55.0%)	—
Gender				0.436
Male	25 (62.5%)	12 (66.7%)	13 (59.1%)	
Female	15 (37.5%)	6 (33.3%)	9 (40.9%)	
BMI (kg/m^2)	26.09 ± 3.33	25.23 ± 3.63	26.78 ± 2.95	0.143
Lung disease				0.750
COPD	22 (55.0%)	11 (61.1%)	11 (50.0%)	
ILD	15 (37.5%)	6 (33.3%)	9 (40.9%)	
Bronchiectasis	2 (5.0%)	1 (5.6%)	1 (4.5%)	
Other	1 (2.5%)	0 (0.0%)	1 (4.5%)	
Age (years)	57.36 ± 7.89	57.45 ± 9.62	57.62 ± 6.81	0.949
Arterial hypertension	10 (25.0%)	4 (22.2%)	6 (27.3%)	0.503
Diabetes	6 (15.0%)	4 (22.2%)	2 (9.1%)	0.238
Dyslipidemia	12 (30.0%)	6 (33.3%)	6 (27.3%)	0.471
Former smoker	4 (10.0%)	2 (11.1%)	2 (9.1%)	0.617
Accumulated consumption (pack-year)	41.56 ± 23.75	43.18 ± 27.12	40.25 ± 21.30	0.718
RAP (mmHg)	11.45 ± 4.10	11 ± 3.35	11.80 ± 4.67	0.553
mPAP (mmHg)	31.35 ± 8.07	28.33 ± 7.9	33.81 ± 7.5	0.031
PWP (mmHg)	17.5 (16–20.75)	18 (16.75–21)	17 (16–20.25)	0.437
Cardiac output (L/min)	5.03 ± 1.09	5.58 ± 0.88	4.69 ± 1.07	0.018
Cardiac index ($L/min/m^2$)	2.82 ± 0.62	3.04 ± 0.65	2.67 ± 0.57	0.128
PVR (wood units)	2.27 (1.5–3)	1.4 (1.2–1.8)	2.86 (2.29–3.78)	< 0.001
Coronary lesions	7 (19.4%)	4 (25.0%)	3 (15.0%)	0.369
PaO_2 (mmHg)	59.56 ± 8.25	59.03 ± 8.19	60.01 ± 8.50	0.739
6MWT (m)	345.03 ± 96.03	330.82 ± 79.30	357.1 ± 108.82	0.414
Creatinine (mg/dL)	0.74 ± 0.21	0.71 ± 0.19	0.76 ± 0.23	0.440
LAS	33.07 (32.31–34.84)	33.06 (33.25–34.96)	33.19 (32.38–34.74)	0.641
Type of transplant				0.383
Single lung	4 (10%)	1 5.6%)	3 (13.6%)	
Double lung	36 (90.0%)	17 (94.4%)	19 (86.4%)	
Transfusions during surgery	13 (32.5%)	5 (27.8%)	8 (36.4%)	0.408
Packed red blood cells	2 (1–4)	4 (2–11)	1 (1–2)	0.065
ECMO during surgery	5 (12.5%)	2 (11.1%)	3 (13.6%)	0.598
PGD	12 (30.0%)	5 (27.8%)	7 (31.8%)	0.529
Surgical reintervention	1 (4.3%)	1 (9.1%)	0 (0.0%)	0.478
Tracheostomy	3 (7.5%)	3 (16.7%)	0 (0.0%)	0.083
Acute rejection	15 (40.5%)	6 (37.5%)	9 (42.9%)	0.505
On ventilation (days)	1 (1–2)	1 (1–2)	1 (1–2)	0.891
ICU stay (days)	4.5 (3–6.25)	5 (4–10)	4 (3–5.5)	0.060
Length of stay (days)	26 (22–34)	26.5 (22–34)	26 (21.5–33.25)	0.863

(Continues)

TABLE 3 | (Continued)

	All	Isolated PHg2	Combined PHg2	*p*
Need for diuretics at any time after the transplant	26 (65.0%)	12 (66.7%)	14 (63.6%)	0.554
Need for diuretics at any time beyond 90 days post-transplant	23 (57.5%)	10 (55.6%)	13 (59.1%)	0.538

Abbreviations: 6MWT = 6 min walking test; BMI = body mass index; COPD = chronic obstructive pulmonary disease; ECMO = extracorporeal membrane oxygenation; ICU = intensive care unit; ILD = interstitial lung disease; mPAP = mean pulmonary arterial pressure; PaO2 = arterial pressure of oxygen; LAS = lung allocation score; PGD = primary graft dysfunction; PH = pulmonary hypertension; PHg2 = pulmonary hypertension group 2; PHg3 = pulmonary hypertension group 3; PVR = pulmonary vascular resistance; PWP: pulmonary wedge pressure; RAP = right atrial pressure.

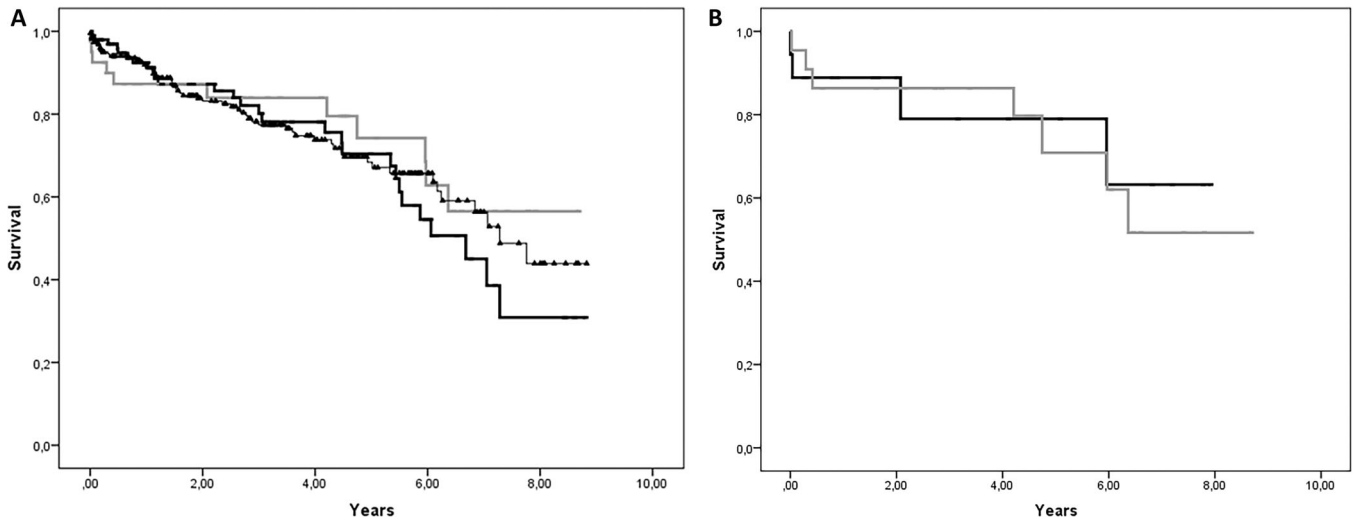

FIGURE 2 | (A) Survival of the different study groups after transplantation. (B) Survival of the different PHg2 groups after transplantation.

output in isolated PHg2 (5.58 ± 0.88 vs. 4.69 ± 1.07; $p = 0.018$), and lower PVR in the isolated group [1.4 (1.2–1.8) vs. 2.86 (2.29–3.78); $p < 0.001$]. No differences were found in any postoperative variables studied between the two groups.

Of the 40 patients with PHg2, in the pre-transplant echocardiogram, none showed evidence of systolic dysfunction, cava vein dilation, or significant valvular abnormalities; 10 patients had findings consistent with diastolic dysfunction, and one patient had a mild pericardial effusion. Among the patients with PHg2, four died in the immediate postoperative period following the transplant. Of the remaining 36 patients who were discharged, 6 (16.7%) were diagnosed with heart failure, and 5 (13.9%) required hospital readmission.

Only three right heart catheterizations were performed after the transplant: one in a patient with pre-transplant PHg2 presenting refractory heart failure after transplant, which confirmed the persistence of isolated postcapillary PHg2; another in a patient with precapillary pulmonary hypertension due to a recurrence of Langerhans cell histiocytosis; and finally, one in a patient with significant stenosis of the left arterial anastomosis, although no significant pressure gradient across the stenosis was observed.

There were no significant differences in post-transplant survival between the main study groups (Figure 2A). Among patients with PHg2, no differences were found between isolated and combined PHg2 (Figure 2B).

4 | Discussion

Our results highlight that PHg2 is present in up to 10.9% of patients who ultimately undergo lung transplantation. No significant variations were observed in perioperative complications or post-transplant survival between PHg2 and PHg3 patients. Additionally, within the PHg2 group, isolated and combined PHg2 did not show differences in postoperative outcomes.

Despite PHg2 being the most common type in the general population, we expected to find a higher frequency of PHg3 in this selected group of patients with advanced respiratory diseases. Furthermore, due to the strict selection of LT recipients, it is likely that a large group of patients with PHg2 were previously excluded, as left heart disease is considered a contraindication. Nonetheless, there is very little evidence regarding the frequency of PHg2 in LT recipients, and the available data shows a higher incidence than the one found in our cohort. A 2019 study by Li et al. reported a frequency of 32% at the University of Alberta [13], similar to the 28% found by Yadlapati et al. in a 2013 study at the University of Los Angeles [14]. The differences in the frequency of PHg2 with the two mentioned studies may relate to methodological issues such as study design, as the Li et al. analysis primarily focused on the risk of PGD. Although there are no apparent differences in cardiovascular risk factors such as arterial hypertension (24% for Li et al. 21% for Yadlapati et al. and 23.1% in our series), age (our recipients are actually older), or diabetes (12% in Yadlapati et al. and 9.5% in our cohort), both cohorts include transplants from

significantly older eras (2004–2016 and 2000–2009) than ours (2015–2024). The fact that they are older cohorts means that LAS is absent from their results, making this variable noncomparable.

There are several ways in which left ventricular dysfunction can lead to the development of PHg2. However, as previously mentioned, in patients who are considered for a lung transplant, the causes of PH group 2 are likely related to subtle left ventricular changes, as severe dysfunctions and valvulopathies would be considered unsuitable for transplantation. One of the most common causes of PHg2, which often goes unnoticed, is left ventricular diastolic dysfunction, where a decrease in myocardial relaxation leads to an increase in left ventricular end-diastolic pressure. Diastolic failure can be attributed to two reasons: one is heart failure with preserved ejection fraction, more commonly associated with older age and cardiovascular risk factors such as obesity, systemic arterial hypertension, diabetes, dyslipidemia, coronary artery disease, or arrhythmias; the other is due to a mechanism of ventricular interdependence in cases of significant precapillary PH, where right ventricular dilation can lead to impaired left ventricular filling [15]. Although our study found no significant differences in cardiovascular risk factors, it is likely that the underlying mechanism is due to heart failure with preserved ejection fraction, as patients with PAH (usually with more severe PH) were excluded and the severity of PH found in both PHg2 and PHg3 were mild (mPAP 24.2 mmHg and PVR 2.44 Wood units).

Another challenge in studying left ventricular diastolic dysfunction is the diagnostic method. To date, most studies have used echocardiography to assess this condition. However, echocardiography is prone to variations in interpretation based on the observer's experience [15]. Additionally, in LT candidates, echocardiographic assessment is even more complicated due to frequently poor acoustic windows, especially in COPD patients. Furthermore, there is no clear consensus on what the cardiogenic evaluation of LT candidates should be: some centers perform right heart catheterization in all cases, while others only do so in patients with suspected significant PH detected by echocardiography [16–18].

Moreover, there are some controversies regarding the current definition of PHg2. While the normal PAWP is below 12 mmHg, a definition with PAWP > 15 mmHg is being used due to limitations in the measurement. An uncertainty zone between 12 and 18 mmHg has been described, where below 12 mmHg, the probability that PH is precapillary is high, while in patients with PAWP > 18 mmHg, it is highly likely to be postcapillary. In this uncertainty zone, in addition to the pressure measurement itself, clinical history, risk factors, history of pulmonary edema, echocardiographic or MRI variables, and even response to volume overload or exercise should be considered when there is doubt about the etiology [19, 20]. That is, interpreting invasive haemodynamics should be done in the context of the clinical picture and other diagnostic investigations.

No significant differences were found in any relevant variables during surgery and the immediate postoperative period of LT. One of the most relevant variables, normally a study objective, is PGD. Although the mechanisms responsible for PGD are multiple, PH has always been debated as a potential risk factor, with some studies demonstrating it as a risk factor, while others have not found this association [3]. This same controversy extends to PHg2, as the Li et al. study did show a higher frequency of grade 3 PGD at 48 and 72 h among patients with diastolic dysfunction, while in Yadlapati et al. study, this association was not found [14]. In our cohort, a PGD incidence similar to that described in the literature (around 36–37%) was evidenced, with no significant differences between patients with PHg2 compared to those with PHg3 or those without PH. One of the main problems in studying PGD is that it is subject to observer subjectivity and requires experience in radiological evaluation of newly lung transplanted patients. Additionally, many factors related to PGD development extend beyond merely vascular issues, such as ischemia times, preservation methods, surgical times, transfusion needs, use of extracorporeal circulation, or donor and recipient-related factors.

Despite left ventricular dysfunction, even in asymptomatic patients (most likely attributable to undetected diastolic dysfunction), being associated with a worse prognosis, our series found similar long-term survival outcomes when compared to patients without PH or those with PHg3. However, it is important to note that the patients identified as PHg2 in our study might also have some degree of PHg3 due to advanced respiratory pathology. It is difficult to quantify the extent of PH from each condition, but it is possible that a combination of both, as described in the cardiopulmonary phenotype in the COMPERA registry, could lead to a worse prognosis [10].

As little information is available, the results encountered in the study are of interest and may help generate further hypotheses. Despite the relevant findings, a few limitations are to be considered. Firstly, we did not include echocardiographic or MRI variables, as these tests are typically performed at the candidate's originating hospitals, leading to widespread dispersion of the received information. Additionally, there was no precise definition of left heart disease available, so each case was studied individually with the help of Cardiology specialists. Furthermore, as this is a retrospective study, regular records of BNP or NT-proBNP levels were not available for all groups, either before or after the transplant. However, we plan to incorporate it as part of the pre-transplant evaluation in light of these results. Lastly, as mentioned at the beginning of the discussion, there is a significant selection bias, as only patients already transplanted were included, excluding those with absolute contraindications due to left ventricular alterations or those with a sum of risk factors for poor outcomes. It should also be noted that the study has certain strengths, as being conducted at a single center with extensive experience in PH allows for thorough hemodynamic evaluation in LT candidates (greater accuracy and fewer complications have been demonstrated in units with high levels of experience); moreover, there is uniformity in the interpretation of subjective variables such as PGD or candidate selection itself; and finally, it includes a cohort of patients from a recent LT era where candidate selection adheres to current ISHLT recommendations.

In patients receiving an LT, PHg2 was present in 10.9%, and no significant differences in perioperative complications or long-

term survival were observed compared to patients with PHg3 or without PH. These findings suggest that while PHg2 is relatively common, it does not adversely impact immediate or long-term outcomes in LT. Future research should focus on larger, multicenter studies to further investigate the impact of subtle left ventricular dysfunction in better understanding the effects of PHg2 on transplant outcomes.

Author Contributions

Conceptualization, Methodology, and Formal analysis: Víctor M. Mora-Cuesta and Amaya Martínez-Meñaca. Investigation: Víctor M. Mora-Cuesta, Amaya Martínez-Meñaca, David Iturbe-Fernández, Sandra Tello-Mena, Sheila Izquierdo-Cuervo, Aritz Gil-Ongay, and Tamara García-Camarero. Writing – original draft preparation: Víctor M. Mora-Cuesta and Amaya Martínez-Meñaca. Writing – review and editing: David Iturbe-Fernández, Aritz Gil-Ongay, Tamara García-Camarero, José M. Cifrián-Martínez, Esther Barreiro-Portela, Diego A. Rodríguez Chiaradia, and Pilar Escribano-Subías. Supervision: José M. Cifrián-Martínez, Esther Barreiro-Portela, and Pilar Escribano-Subías. Project administration: Pilar Alonso-Lecue.

Acknowledgments

The authors have nothing to report.

Ethics Statement

This study was approved by the Drug Research Ethics Committee of Cantabria (Spain) and coordinated by the Valdecilla Research Institute (IDIVAL, Instituto de Investigación Valdecilla), with protocol code 2024.221.

Consent

The ethics committee approved the waiver of informed consent for the conduct of this study due to its retrospective nature and the inability to obtain consent from all included subjects.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further enquiries can be directed to the corresponding author.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.