Original Article

Lung transplantation for emphysema: only emphysema or something else?

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Background: Some studies have reviewed lung explants histology to determine the frequency of pretransplant non-identified neoplasms or explore its diagnostic correlation with a previous diagnosis of interstitial lung disease (ILD). This study aims to review the histopathology of explants from patients who underwent lung transplantation (LT).

Methods: A retrospective, single-center study that included patients who underwent LT for emphysema between 01 January 2011 and 31 October 2021. The control group was composed of patients with lung cancer who underwent a lung resection between 01 November 2011 and 31 December 2019 and had a previous diagnosis of chronic obstructive pulmonary disease (COPD) prior to lung resection surgery. A systematic review was performed of histological findings to compare the frequency of additional histological diagnoses.

Results: The study sample included 160 patients (43.8%) who received a lung transplant for emphysema and 205 patients with COPD and lung cancer treated surgically. Although the patients in the cancer group were significantly older and had more comorbidities and higher cumulative tobacco consumption, transplant recipients received an additional significative histologic diagnosis more frequently (58.1% *vs.* 12.7%; P<0.001) including ILD, pneumoconiosis and others.

Conclusions: Significant additional histological findings were more frequent in the group of lung transplant recipients with emphysema. Notably, these findings were not explained by tobacco use, and they were significantly more frequent in transplant recipients than in patients with a previous diagnosis of COPD and higher cumulative tobacco consumption but with a better respiratory functional status.

Keywords: Lung transplantation (LT); emphysema; interstitial lung disease (ILD)

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Introduction

Chronic obstructive pulmonary disease (COPD) used to be the primary indication for lung transplantation (LT). However, in recent times, interstitial lung disease (ILD) has surpassed COPD as the primary reason for LT (1-3).

COPD is defined by GOLD (Global Initiative for Chronic Obstructive Lung Disease) as a frequent, preventable, treatable entity characterized by persistent respiratory symptoms and progressive, irreversible airflow limitation secondary to airway and/or alveolar abnormalities. These abnormalities are generally caused by long-term exposure to toxic particles and gases (4). Chronic airflow obstruction is caused by a combination of parenchymal destruction and small airway disease. In our setting and in other Western countries, the etiology of this disease is exposure to tobacco smoke, which causes over 90% of cases. However, only a proportion (20–40%) of smokers ultimately develop COPD. Hence, individual predisposition must also play a role in the development of the disease. The only genetic risk factor identified to date is α1-antitrypsin deficiency. There are other less frequent etiologies, especially in developing countries, including exposure to toxic volatile agents and toxic occupational exposure (byssinosis, coniosis, swine farming, and popcorn manufacturing, among others) (5).

The most characteristic manifestation of COPD is emphysema. This complication affects the lung parenchyma causing an abnormal enlargement of airspaces distal to the terminal bronchioles as a result of the destruction of alveolar walls. This process does not generally involve significant fibrosis, although a fibrotic phenotype has been described in histological variants (6).

Highlight box

Key findings

- Significant additional histological findings were more frequent in the group of lung transplant recipients with emphysema.

What is known and what is new?

- Emphysema used to be the primary indication for lung transplantation.
- These additional histological findings were not explained by tobacco use.

What is the implication, and what should change now?

- It is necessary to explore other associated respiratory diseases in patients with emphysema who are candidates for lung transplantation.

Some studies have reviewed the histology of lung explants to determine the incidence of unknown neoplasms in pretransplant evaluation or assess diagnostic concordance in ILD, especially in idiopathic pulmonary fibrosis (IPF) (7-9). Rates of discrepancy due to minor (addition of a diagnosis secondary to the underlying disease) or major discrepancies (involving a change in the primary diagnosis of the patient) ranged from 10% to 20% (10-15). Many of these findings may have considerable implications not only at epidemiological but also at legal level, as in the case of pneumoconiosis.

To the best of our knowledge, this is the first systematic review of the histology of lung explants from lung transplant recipients (LTR) with COPD. It is worth mentioning that some of the studies mentioned included small subgroups of patients with emphysema. Compared to ILD, establishing a pretransplant diagnosis is less complex in COPD patients, since a pretransplant biopsy is not necessary.

This study aimed to examine the histology of explants from patients who underwent LT for COPD, assessing the presence of findings of clinical or diagnostic relevance. We present this article in accordance with the STROBE reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1160/rc).

Methods

A retrospective, descriptive, comparative study was performed including all LTR with COPD in Marqués de Valdecilla University Hospital during the 01 January 2011–31 October 2021 period. To be included as patients with COPD, all of them had to have obstructive ventilatory syndrome in spirometry (FEV_1/FVC <0.7) and radiological signs of emphysema in chest CT reported by a radiologist expert in thoracic radiology (according to our protocol, all patients should have at least an annual chest CT scan before transplant).

A control group was also included to determine whether the addition of histological diagnoses was more frequent in LTR with emphysema, as compared to non-transplanted COPD patients with lung histology available. The control group was composed of patients with lung cancer who underwent lung resection between 01 November 2011 and 31 December 2019 who received a diagnosis of COPD prior to surgery, and whose lung histology was available. Clinical data were extracted from the electronic medical records of the public health system of Cantabria, Spain.

A diagnosis was added based on the presence of

histological findings of a chronic pulmonary parenchymal disease unrelated to lesions caused by tobacco use. Thus, acute lung diseases (i.e., pulmonary thromboembolism or infectious complications) and tobacco-related lung diseases (respiratory bronchiolitis, desquamative interstitial pneumonia) were excluded. Likewise, obstructive pneumonia was excluded in the control group, since it was assumed to be directly related to compression exerted by the tumor.

The clinical variables assessed included: age at transplantation or surgery for neoplastic disease; sex; height; weight; cardiovascular risk factors (arterial hypertension, diabetes, hypercholesterolemia); history of smoking; α1-antitrypsin values; need for oxygen therapy; pulmonary hypertension; respiratory function tests; laboratory variables; status and time on follow-up. The BODE (Body mass index-Obstruction-Dyspnea-Exercise) scale and the Lung Allocation Score (LAS) were used to assess severity in the patient who received a lung transplant due to COPD.

In relation to patients with lung cancer treated surgically, variables included site of the tumor, staging, previous chemotherapy or induction radiotherapy, type of surgical approach, and type of resection performed.

With regard to LTR, variables were recorded in relation to the transplant process (type of transplant; use of induction), immediate postoperative period [duration of orotracheal intubation; intensive care unit (ICU) stay; hospital stay; primary graft dysfunction according to the ISHLT (International Society for Heart and Lung Transplantation) definition and graduation (16)], and variables related to long-term graft dysfunction based on ISHLT criteria (17) and survival.

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). 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 2021.395. Individual consent for this retrospective analysis was waived, in accordance with ethics committee approval.

Statistical analysis

Statistical analysis was performed with the IBM SPSS Statistics 20 software package.

Continuous quantitative variables were expressed as mean values ± standard deviations for normally distributed variables and as median and interquartile range (IQR) for non-normally distributed data. Categorical variables were expressed as frequencies and percentages.

The Kolmogorov-Smirnov test was used to assess normal distribution in continuous quantitative variables. Student's *t*-test was used to compare a quantitative variable with normal distribution and a qualitative variable. Non-normally distributed quantitative data were compared with qualitative data using Mann Whitney *U*-test. Chi-square test was used for comparison of qualitative variables. Kaplan-Meier curves with log-rank tests were used for analysis of mortality and time to chronic lung allograft dysfunction (CLAD). Univariate logistic regression analysis to predict the risk of added histological diagnoses was performed to estimate the odds ratio (OR) and 95% confidence interval (CI). A P value 0.05 was considered statistically significant.

Results

The study sample included a total of 365 patients, of whom 160 (43.8%) received a lung transplant for emphysema, and the remaining 205 (56.2%) were included in the control group. Of the 160 recipients with LT, 138 (86.3%) had COPD-related emphysema, whereas 22 (13.8%) had α1-antitrypsin deficiency.

Table 1 contains the clinical characteristics of patients prior to surgery (lung transplant or neoplasm resection).

Patients were predominantly male, especially in the control group, where they accounted for 86.8% of cases *vs.* 61.9% in the group of transplant recipients. A proportion of 98.9% of patients were smokers or former smokers, and only 4 (1.1%) were never-smokers (three received a transplant and one underwent surgery for cancer). Tobacco consumption was higher in the cancer group, with 50 (IQR, 40–70) packs-year, as compared to LTR, with a median of 40 (IQR, 30–60) packs-year (P<0.001).

Examination of explant histology

An examination of histopathological findings was performed in lung explants and lung resection specimens (*Table 2*). A total of 119 patients (32.6%) were found to have additional histological lesions concurrent to emphysema: 93/160 (58.1%) of LTR, and 26/205 (12.7%) controls (P<0.001). In addition to the added diagnoses, LTR more frequently had bronchiectasis, carcinoid tumorlets, and signs of pulmonary hypertension (P<0.001 for all variables).

Following explant examination, diagnosis was changed in four LTR (2.5%). Thus, after a multidisciplinary evaluation,

Table 1 Preoperative characteristics of two groups: LTR or surgical resection of lung cancer

Characteristics of patients	All	Transplant	Cancer surgery	P
N	365	160 (43.8)	205 (56.2)	–
Sex				<0.001
Male	277 (75.9)	99 (61.9)	178 (86.8)	
Female	88 (24.1)	61 (38.1)	27 (13.2)	
Age (years)	64.11±8.43	58.85±5.59	68.20±7.99	<0.001
Height (cm)	167.25±8.69	164.65±8.98	169.25±7.92	<0.001
Weight (kg)	70.25±13.59	66.70±11.55	78.39±14.48	<0.001
BMI (kg/m^2)	25.06 [22.34–28]	24.04 [22.14–27.07]	27.36 [24.82–30.48]	<0.001
HTN	143 (39.2)	30 (18.8)	113 (55.1)	<0.001
Dyslipidemia	150 (41.1)	43 (26.9)	107 (52.2)	<0.001
Diabetes	50 (13.7)	10 (6.3)	40 (19.5)	<0.001
Smoking				<0.001
Never-smoker	4 (1.1)	3 (1.9)	1 (0.5)	
Former smoker	302 (82.7)	157 (98.1)	145 (70.7)	
Active smoker	59 (16.2)	0 (0)	59 (28.8)	
Tobacco consumption (packs-year)	46.50 [35–60]	40 [30–60]	50 [40–70]	<0.001
α1-antitrypsin (mg/dL)	139 [109–154]	134.5 [102–155.5]	147 [142–153]	0.236
Need for O_2[†]				<0.001
Nocturnal	4 (1.1)	2 (1.3)	2 (1.0)	
At rest	140 (39.1)	140 (90.3)	0	
Exertion	6 (1.7)	6 (3.9)	0	
Not needed	208 (58.1)	7 (4.5)	201 (99.0)	
FVC (mL)	2,939.97±983.71	2,292.12±803.77	3,463.48±784.76	<0.001
FVC (%)	82.21±23.55	65.81±17.87	95.19±18.96	<0.001
FEV_1 (mL)	1,410 [670–2,000]	630 [510–797.5]	1,930 [1,630–2,360]	<0.001
FEV_1 (%)	43 [24–73]	23 [19.82–27.6]	71 [60–82]	<0.001
FEV_1/FVC	48 [31–61.64]	30 [26–35.5]	59.54 [51.86–65.87]	<0.001
DLCO (%)	43.4 [26.4–70]	32 [22.25–44.5]	75.2 [52.75–92.25]	<0.001
PaO_2 (mmHg)	59.51±9.18	56.99±8.11	67.91±7.46	<0.001
$PaCO_2$ (mmHg)	44.78±81.6	45.74±7.94	38.93±7.05	<0.001
Creatinine (mg/dL)	0.79 [0.65–0.93]	0.68 [0.57–0.80]	0.86 [0.74–1.02]	<0.001
Cholesterol (mg/dL)	189.73±42.98	195.18±42.21	176.84±42.33	0.003
Albumin (g/dL)	4.3 [4.1–4.5]	4.4 [4.2–4.6]	4.3 [4.1–4.4]	<0.001
CRP (mg/dL)	0.8 [0.4–1.7]	0.4 [0.4–1.27]	1.2 [0.5–3.5]	0.019
ESR (mm)	17 [8–31]	16 [7–29]	24 [11.5–43]	0.101
Fibrinogen (mg/dL)	417 [335–530]	417 [340–530]	417 [320.5–533.25]	0.72
Platelets (×10^3/μL)	230.000 [188.500–269.500]	230.000 [189.000–266.500]	229.000 [187.000–279.500]	0.832

[†], there are five and two missing values (lack of information) in the "Transplant" and "Cancer surgery" groups, respectively. Continuous quantitative variables are expressed as mean ± standard deviation for normally distributed variables and as median [interquartile range] for non-normally distributed data. Categorical variables were expressed as frequencies (percentages). LTR, lung transplant recipients; N, number; cm, centimeter; kg, kilogram; mg, milligram; BMI, body mass index; HTN, arterial hypertension; FVC, forced vital capacity; FEV_1, forced expiratory volume in the first second; DLCO, diffusing capacity for carbon monoxide; Pa, arterial pressure; O_2, oxygen; CO_2, carbon dioxide; mmHg, millimeters of mercury; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; μL, microliter; dL, deciliter; mL, milliliter.

Table 2 Histological findings in lung explants and lung resection specimens

Histological findings	All	Transplant	Cancer surgery	P
N	365	160	205	–
Adds diagnosis	119 (32.6)	93 (58.1)	26 (12.7)	<0.001
Bronchiectasis	61 (16.7)	49 (30.6)	12 (5.9)	<0.001
Carcinoid tumorlet	19 (5.2)	16 (10.0)	3 (1.5)	<0.001
Signs of pulmonary hypertension	13 (3.6)	12 (7.5)	1 (0.5)	<0.001

Categorical variables were expressed as frequencies (percentages). N, number.

Table 3 Diagnoses added after analysis of emphysema transplant recipients in absolute numbers (N) and as relative frequency with respect to the total of patients with some additional entity in this group (%)

Additional diagnoses	N	%
Subacute NSIP/OP with microgranulomas suggestive of hypersensitivity pneumonitis	29	31.2
Organized pneumonia	18	19.3
Pneumoconiosis	14	15.0
Cellular NSIP without further details	10	10.8
Non-necrotizing granulomatous pneumonia	7	7.5
Follicular bronchiolitis	5	5.4
Pulmonary capillary hemangiomatosis	3	3.2
Obliterative bronchiolitis	2	2.2
Langerhans cell histiocytosis	1	1.1
Cellular NSIP with capillaritis and alveolar hemorrhage suggestive of connective tissue disease (vasculitis)	1	1.1
Pleuroparenchymatous fibroelastosis	1	1.1
UIP	1	1.1
Obliterative bronchiolitis with areas of cellular NSIP	1	1.1

NSIP, nonspecific interstitial pneumonia; OP, organizing pneumonia; UIP, usual interstitial pneumonia.

diagnosis changed to IPF, sarcoidosis, pneumoconiosis and hypersensitivity pneumonitis.

Unexpected histological lesions concurrent to emphysema were found in 93 of the 160 transplant recipients (58.1%). *Table 3* describes histological findings in lung explants. Among the diagnoses added to the LTR group, the most frequent finding was a histological pattern of nonspecific interstitial pneumonia (NSIP), observed in 39 patients. Microgranulomas suggestive of chronic hypersensitivity pneumonitis occurred in 31.2%. Organized pneumonia was established in 19.3% of patients, whereas 15.0% had findings consistent with pneumoconiosis.

Among the 93 patients who received an additional diagnosis, only 14 (15.1%) had radiological alterations other than emphysema on the chest computed tomography (CT) before transplantation that could suggest other additional entities.

Among the 22 patients with a previous diagnosis of α1-antitrypsin deficiency, 8 of them had bronchiectasis in the explant (36.4%).

Seven of the 160 LTR (4.4%) had occult neoplasms: one multifocal lepidic adenocarcinoma, two non-keratinizing squamous cell carcinomas, and four *in situ* squamous cell carcinoma.

Histological review of lung resections

Among the 205 controls, only 26 (12.7%) received an

Table 4 Diagnoses added after analysis of the parenchyma of lung cancer operated patients with COPD in absolute numbers (N) and as relative frequency with respect to the total of patients with some additional entity in this group (%)

Additional diagnoses	N	%
Pneumoconiosis	8	30.8
Necrotizing granulomatous pneumonia	5	19.2
Non-necrotizing granulomatous pneumonia	2	7.7
ILD without further details	2	7.7
UIP	2	7.7
Lymphoma	2	7.7
Cellular NSIP without further details	1	3.8
Cellular NSIP with microgranulomas suggestive of hypersensitivity pneumonitis	1	3.8
Langerhans cell histiocytosis	1	3.8
Exogenous lipoid pneumonia	1	3.8
Organized pneumonia	1	3.8

COPD, chronic obstructive pulmonary disease; ILD, interstitial lung disease; UIP, usual interstitial pneumonia; NSIP, nonspecific interstitial pneumonia.

additional diagnosis based on the histological examination of lung parenchyma tissue. *Table 4* summarizes the entities found in histological analysis. As many as 30.8% (8 cases) had pneumoconiosis. Seven (26.9%) had granulomatous pneumonia, five of which were necrotizing and two non-necrotizing. The number of undiagnosed diffuse ILDs was negligible, with a case of usual interstitial pneumonia (UIP) (7.7%), cellular NSIP (7.7%) and ILD not specified (7.7%), respectively. Lung cancer-related data from the control group is shown in Table S1.

Course of LTR

A total of 156 LTR with histologically-confirmed emphysema were included in the binary logistic regression analysis (the four patients whose diagnosis was changed in the explant were excluded). None of the variables studied before transplantation was useful to identify patients at risk of having added histological findings (*Table 5*). No differences were observed either in the variables related to the immediate postoperative period after LT (*Table 6*), long-term survival (*Figure 1*) or CLAD (*Figure 2*), across recipients with emphysema, irrespectively whether they had received an additional diagnosis or not.

Discussion

To the best of our knowledge, this is the first study to review the histology of lungs explanted for emphysema, with a particular focus on additional histological findings. Diagnosis of lung explants have been reviewed in previous studies, although they included patients with different conditions, with a limited number of cases of emphysema. In addition, a control group was not used in these studies for comparative analysis.

Our study revealed that half of the patients who received a lung transplant for emphysema had other additional histological findings that were not attributable to tobacco use. Determining whether these findings were also frequent in other patients with emphysema is challenging, as a histological sample is not generally available in this entity. Thus, the control group of our study included lung cancer patients with a previous diagnosis of COPD and a lung resection specimen available. In this group, the frequency of additional diagnoses was significantly lower.

It is worth noting that there were significant differences in the characteristics of the patients included in the two groups. Lung cancer patients were older, had a higher body mass index, and more comorbidities (higher frequency of hypertension, dyslipidemia and diabetes). In addition, active smoking was more frequent in the group of patients with lung cancer treated surgically. This is not striking, since active smoking is an absolute contraindication for LT. Literature suggests that smoking duration alone provides stronger risk estimates of COPD than the composite index of pack-years (18), although we did not have this

Table 5 Binary logistic regression analysis for risk factors of added histological diagnoses among lung transplant recipients with histologically confirmed emphysema

Variables	OR	95% CI	P
Sex			
Male	Ref.	–	–
Female	0.845	0.441–1617	0.611
Type			
COPD	Ref.	–	–
Alfa-1 deficiency	0.765	0.301–1.943	0.573
Age (years)	0.975	0.022–1.032	0.383
BMI (kg/m^2)	0.989	0.898–1.089	0.821
HTN	1.076	0.483–2.400	0.857
Diabetes	1.096	0.294–4.010	0.901
Dyslipidemia	1.141	0.560–2.328	0.716
Smoking			
Never-smoker	Ref.	–	–
Former smoker	0.353	0.031–3.978	0.400
Tobacco consumption (packs-year)	1.003	0.989–1.018	0.642
α1-antitrypsin (mg/dL)	1.007	0.995–1.020	0.26
FVC (mL)	1.000	1.000–1.000	0.796
FVC (%)	0.998	0.980–1.015	0.784
FEV_1 (mL)	0.999	0.998–1.000	0.199
FEV_1 (%)	0.982	0.953–1.013	0.259
FEV_1/FVC	0.992	0.963–1.022	0.614
DLCO (%)	0.996	0.971–1.021	0.727
6-minute walking test (m)	1.001	0.997–1.004	0.700
Desaturation walk test (%)	1.009	0.969–1.050	0.676
PaO_2 (mmHg)	1.011	0.959–1.066	0.673
BODE	1.025	0.813–1.291	0.836
LAS score	0.628	0.375–1.051	0.077
Creatinine (mg/dL)	1.069	0.751–1.520	0.712
Cholesterol (mg/dL)	0.995	0.987–1.003	0.204
Albumin (g/dL)	0.836	0.360–1.943	0.677
CRP (mg/dL)	1.197	0.901–1.590	0.216
ESR (mm)	0.997	0.977–1.017	0.775
Fibrinogen (mg/dL)	0.998	0.996–1.001	0.261
Platelets (×10^3/μL)	1.000	1.000–1.000	0.547

Table 5 (*continued*)

Table 5 (*continued*)

Variables	OR	95% CI	P
IgG (mg/dL)	1.000	1.000–1.001	0.429
IgA (mg/dL)	0.999	0.996–1.001	0.330
IgM (mg/dL)	1.001	0.995–1.008	0.850
C3 (mg/dL)	0.998	0.987–1.008	0.684
C4 (mg/dL)	0.992	0.975–1.010	0.378
Coronary lesions	1.007	0.396–2.559	0.988
Pulmonary hypertension	1.302	0.605–2.801	0.499

OR, odds ratio; CI, confidence interval; COPD, chronic obstructive pulmonary disease; m, meter; kg, kilogram; BMI, body mass index; HTN, arterial hypertension; mg, milligram; dL, deciliter; FVC, forced vital capacity; mL, milliliter; FEV1, forced expiratory volume in the first second; DLCO, diffusing capacity for carbon monoxide; Pa, arterial pressure; O_2, oxygen; mmHg, millimeters of mercury; BODE, Body mass index-Obstruction-Dyspnea-Exercise; LAS, Lung Allocation Score; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; µL, microliter.

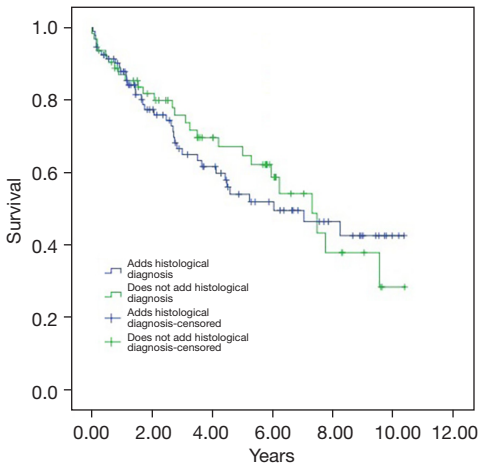
Table 6 Transplant-related variables in patients with and without additional histologic diagnosis

Post-transplant characteristics	All	Adds diagnosis	Does not add diagnosis	P
Intraoperative ECMO	9 (5.6)	7 (7.5)	2 (3.0)	0.207
PGD	26 (16.2)	18 (19.3)	8 (11.9)	0.234
Type of transplantation				0.413
Single lung	37 (23.7)	21 (22.6)	16 (25.4)	
Double lung	119 (76.3)	72 (77.4)	47 (74.6)	
Mechanical ventilation (days)	1 [1–1]	1 [1–1]	1 [1–1]	0.946
ICU stay (days)	4 [3–7]	4 [3–7]	4 [3–6.5]	0.536
Hospital stay (days)	26 [22–33]	26 [22–33.25]	26 [22–31]	0.736

Continuous quantitative variables are median [interquartile range] for non-normally distributed data. Categorical variables were expressed as frequencies (percentages). ECMO, extracorporeal membrane oxygenation; PGD, primary graft dysfunction; ICU, intensive care unit.

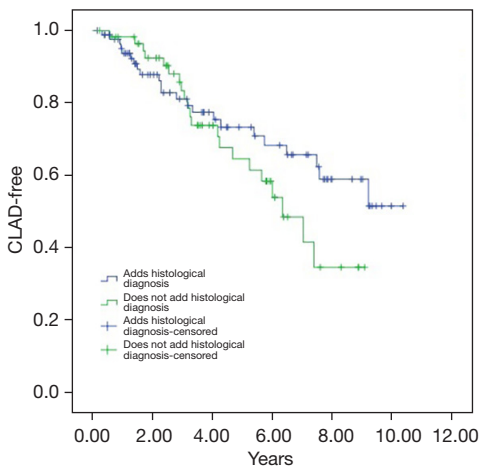
information in our patient series.

In addition, cancer patients showed a higher cumulative tobacco consumption. In contrast, although cancer patients had a previous diagnosis of COPD (as shown by the presence of moderate obstructive lung disease on respiratory function tests) and a higher cumulative tobacco use, the results of their respiratory function tests were significantly better than in recipients of a lung transplant due to emphysema. This finding is not surprising, as a poor pulmonary function is required for inclusion in the waiting list for a transplant. In addition, patients with lung cancer candidates for surgical resection are required to have a good functional status. It is striking that transplant recipients had poorer lung function despite having lower cumulative tobacco consumption, which is the main risk factor for emphysema in developed countries. Additionally, there were no differences between groups in α1-antitrypsin, which is the only known genetic factor predisposing to the development of emphysema. There are many factors that influence the development of emphysema (not well-known genetic susceptibility factors, age of initiation of smoking, type of tobacco consumption, duration of smoking, childhood development, environmental pollution, etc.) and there are many potential respiratory diseases other than emphysema that can be caused by tobacco. Therefore, the worse lung function of transplant candidate patients may be explained by a greater susceptibility to the development of emphysema and the development of other respiratory



Survival	1 year	3 years	5 years	10 years	P
Adds diagnosis	87.8%	66.6%	54%	42.6%	0.743
Does not add diagnosis	87.1%	75.8%	67.2%	28.5%	

Figure 1 Survival of emphysema transplant recipients based on the establishment or not of an additional diagnosis on explant analysis (P=0.743).



CLAD	1 year	3 years	5 years	10 years	P
Adds diagnosis	6.3%	18.9%	26.7%	48.4%	0.230
Does not add diagnosis	1.8%	16.6%	35.4%	–	

Figure 2 Percentage of emphysema transplant recipients who develop CLAD over time based on the presence/absence of an additional diagnosis (P=0.230). CLAD, chronic lung allograft dysfunction.

diseases caused by tobacco, or the confluence of emphysema with other entities not caused by smoking. but potentially aggravated by tobacco consumption.

Among the transplant patients, seven of them had some cancer in the explant. No changes were made in immunosuppression among patients with situ squamous cell carcinoma, and none of them recurred. For the other three cases (one multifocal lepidic adenocarcinoma, two non-keratinizing squamous cell carcinomas) all of them were stage IA, and in those cases, no changes were made to the immunosuppression regimen, and no patient had recurrences during follow-up. It is not entirely clear what is the correct approach to explant cancer in transplant patients. In our hospital, patients with stage I are closely monitored, but the immunosuppression regimen is not changed considering that the pneumonectomy has been curative (in fact, no case recurred without changing the usual immunosuppression protocol). For patients with stage II onwards, the dose of antimetabolite is reduced by half, the level of tacrolimus is reduced to the lowest possible range for the time of transplant, and if it is not inconvenient, from the third month after transplant the antimetabolite is changed by an mTOR inhibitor. Furthermore, these patients are followed up with positron emission tomography (PET) periodically from the 3rd month in search of potential pathological foci.

In both groups, only the additional histological findings that were not explained by their initial lung disease were selected. Otherwise said, in the group of LTR, the findings traditionally associated with tobacco use such as desquamative interstitial pneumonia or respiratory bronchiolitis, were excluded. In the group of cancer patients, diagnoses of tumor-induced obstructive pneumonia were excluded. This way, additional histological diagnoses were required to be based on new findings with a potential clinically relevant role in the course of lung disease.

It is worth noting that findings such as NSIP or the presence of microgranulomas suggestive of clinical entities such as chronic hypersensitivity pneumonitis, are histological patterns; therefore, these findings should not be considered clinical diagnoses. In terms of respiratory function, the poorer forced vital capacity exhibited by transplant recipients could be explained by the severity of their respiratory dysfunction. However, the disease identified is occasionally found in clinical entities that,

as it occurs with chronic hypersensitivity pneumonitis, manifest mixed respiratory syndromes. This may exacerbate obstructive pulmonary disease induced by emphysema.

Despite the fact that multiple clinical, analytical and functional variables were studied before transplantation, none of them was able to identify patients with a higher risk of having added histological findings in the explant of LTR.

The literature available on patients with emphysema is limited. In a study including 175 patients referred to a lung transplant unit for different entities, diagnosis of emphysema was confirmed upon review of explant histology in 32 out of 35 patients (91%). The remaining three cases were consistent with pneumoconiosis, asthma and diffuse alveolar damage with organized pneumonia (10). Recently, a study that included 4,361 patients from the COPDGene cohort showed that up to 5% of patients had findings suggestive of ILD on chest CT. These patients had poor quality of life, poorer functional capacity, greater oxygen requirement, increased risk of exacerbations, and worse survival than the 5% of patients with chest CT abnormalities that were not suggestive of ILD (19). Another study that evaluated three cohorts of patients (COPDGene, AGES-Reykjavik and Framingham Heart Study) showed that the pulmonary abnormalities found were associated with telomere shortening (20).

In relation to posttransplant follow-up, no significant differences were observed between LTR in immediate postoperative (primary graft dysfunction; duration of intubation; length of ICU and hospital stay) and long-term follow-up variables (time free of CLAD and survival) based on them having received an additional histologic diagnosis or not.

Although these findings are relevant, they should be taken with caution since our study has some limitations. Firstly, since it is a retrospective study, there was some missing data, which may reduce the statistical power of the study, and clinical records have a lack of data on work history and exposure to biomass degradation products or auto-immunity tests. Secondly, it is a single-center study. Further studies in other populations are necessary to confirm our findings, although most of our patients came from other geographical areas. Another limitation to the detection of histological findings is the size of specimens: in the transplant group, as most transplants were bilateral, the pathologist could analyze the entire two lungs. In contrast, in the lung resection group, samples of healthy parenchyma tissue were significantly smaller, since most were obtained from a lobectomy.

Conclusions

In summary, additional histological findings were more frequent in recipients of a lung transplant for emphysema which could not be explained by the consumption of tobacco. In addition, these findings were significantly more frequent in transplant recipients than in other patients with a previous diagnosis of COPD and higher cumulative tobacco consumption but with a better respiratory functional status. However, no risk factors have yet been identified that enable the identification of these patients to modify pretransplantation handling and optimize their respiratory function.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1160/rc

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1160/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). 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 2021.395. Individual consent for this retrospective analysis was waived, in accordance with ethics committee approval.

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