Surgical Lung Biopsy in Transplant Patients With Diffuse Lung Disease: How Much Worse When the Lung Is the Graft?

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Background. **There are no data that compare the clinical presentation and results of surgical lung biopsy (SLB) for diffuse lung disease (DLD) in lung transplant patients, in contrast to individuals with other type of solid organ grafts. Our objective was to compare the clinical picture, radiologic pattern, pathology results, and outcomes of SLB for DLD in these two subsets of patients.**

Methods. **We retrospectively reviewed the clinical records of transplant patients undergoing SLB for DLD at our institution between 2004 and 2011. Patients with lung transplants and those with other transplants were compared.**

Results. **During the study period, 1,232 solid organ transplants were done at our institution. Of these, 49 patients (4%) had DLD that needed SLB for diagnosis, and 24 of these patients had a lung transplant. Dyspnea and a radiologic reticular pattern were more frequent in lung transplant patients, 21 of 24 vs 11 of 25 ($p = 0.001$) and 14 of 24 vs 7 of 25 ($p = 0.03$), respectively. Although postoperative complications and in-hospital deaths were more common in lung transplant patients, the differences were not statistically significant. Having the SLB performed for diagnosis, as opposed to being conducted for DLD that did not improve on medical treatment, had a protective effect on multivariate analysis (hazard ratio, 0.39; 95% confidence interval, 0.16 to 0.96; $p = 0.042$). A prior lung transplant was the only independent predictor of survival (hazard ratio, 4.62; 95% confidence interval, 1.53 to 13.92, $p = 0.006$).**

Conclusions. **It is relatively uncommon for a solid organ transplant patient with DLD to require a SLB. Clinical and radiologic presentation differ in patients with lung transplants compared with other transplants. Postoperative outcomes are not significantly different between the groups. SLB performed early in the course of the disease might be beneficial. Having a lung transplant is a significant negative predictor of survival.**

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Diffuse lung disease (DLD) is a serious condition in transplant patients [1]. Surgical lung biopsy (SLB) is a useful diagnostic procedure to guide treatment in some individuals after other less invasive methods have been attempted and have not yielded a definite diagnostic result. Despite being a procedure with significant morbidity and mortality rates [2], SLB changes therapy in up to 80% of patients and is the best method to obtain a specific diagnosis [1, 3, 4]. Lung transplant patients with DLD might be in a n even more severe situation because the graft itself is the affected organ. However, there are no data comparing the clinical presentation, radiologic patterns, pathologic findings, and outcomes after SLB in lung transplant patients with DLD with those with DLD and other solid organ grafts. The objective of our study was to compare these two subsets of transplant patients.

Material and Methods

The study was approved by the Favaloro Foundation Institutional Review Board. The medical records of all transplant patients undergoing SLB for DLD between March 2004 and December 2011 were reviewed. Data collected included patient demographics, clinical presentation, radiologic findings, and operative, pathology, and microbiology reports.

Imaging Assessment

All patients had a computed tomography (CT) scan before SLB. The CT scans were reviewed by a radiologist, pulmonologist, and thoracic surgeon. The findings were classified in one or more of five different tomographic patterns: (1) reticular pattern, characterized by diffuse linear opacities with or without associated honeycombing; (2) nodular pattern, in which micronodules were seen in association with linear opacities along the

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bronchovascular bundles; (3) cystic changes, in cases in which cystic air-filled spaces predominated in the radiology; (4) ground glass opacities described as hazy opacities of the lung that still allow visualization of the pulmonary vessels; and (5) consolidation pattern that was defined as opacity obscuring the underlying vessels [5].

There were two different and mutually exclusive indications for the SLB in a transplant patient with DLD: (1) empirically treated DLD in a symptomatic transplant patient with no clinical or radiologic improvement of the medical condition and (2) need for diagnosis of DLD in a symptomatic transplant patient.

Surgical Procedures

All surgical procedures were performed by a certified thoracic surgeon in the operating room under general anesthesia. Surgical staplers were routinely used to obtain the specimens from at least two different lung zones. Patients were extubated in the operating room, except for those who were supported with mechanical ventilation before the procedure.

Biopsy specimens were fixed in formaldehyde solution, serially sectioned, and stained with hematoxylin and eosin. According to the findings on these sections, cytomegalovirus immunoperoxidase, acid-fast bacilli, Orcein-Giemsa stains for elastic tissue, and trichrome stains for collagen tissue were used. Lung tissue was also routinely sent for microbiologic analysis.

We defined change in therapy as a new treatment started based on the results of the SLB. Discontinuation of therapy was not considered a change in therapy, unless a highly toxic drug was discontinued.

Patients were observed from the time of SLB until death or until January 2012. Follow-up information was obtained during routine ambulatory visits and by telephone contact with patients.

We defined operative mortality as death occurring within 5 days after the SLB. In-hospital mortality was defined as deaths that occurred after postoperative day 5 and before hospital discharge. Survival was calculated using the time of death or last time seen on follow-up [1].

Statistical Analysis

Continuous variables are presented as mean ± standard deviations or median and interquartile (25th to 75th) range (IQR), and categoric variables as percentages of all patients. Differences between continuous variables were assessed with the Student *t* test or Mann-Whitney *U* test, when applicable. The χ^2 or Fisher exact tests were used to compare categoric variables.

Logistic regression was performed to identify predictors of complications and perioperative and in-hospital mortality. Univariate Cox proportional hazards regression analyses were used to calculate the hazard ratios with 95% confidence intervals for factors associated with survival.

Variables identified in the univariate analysis with a value of p of 0.05 or less were included in the multivariable model. The Kaplan-Meier survival method was used to estimate patient survival and the log-rank test to assess associations between potential risk factors and survival. We considered values of p of less than 0.05 to be statistically significant. SPSS 17.0 software (SPSS Inc, Chicago, IL) was used for all analyses.

Results

During the study period, 1,232 solid organ transplants were performed at our institution, comprising 435 kidney transplants, 432 liver transplants, 196 heart transplants, 137 lung transplants, 20 kidney-pancreas transplants and 12 heart-lung transplants; 49 transplant patients (4%) had SLB for DLD; 24 patients (49%) had a lung transplant (15 of 24 had bilateral lung transplants), and 25 patients (51%) had other transplants: 13 patients had a kidney transplant, 10 had a heart transplant, and 2 had a liver transplant.

Median elapsed time between the transplant date and the day of the SLB was 1,288 days (IQR, 15 to 6,204 days), and median follow-up after the lung biopsy time was 132 days (IQR, 1 to 2,476 days). Differences between the two groups are reported in Table 1.

The clinical presentation was different between the two groups. Dyspnea was the most common presenting symptom in the lung transplant patients (87.5% vs 44%; $p = 0.001$), and fever was the most frequent in patients with DLD and a transplant different than lung (72% vs 37.5%; $p = 0.015$). The CT reticular pattern was the most frequently observed (42.9%) and was significantly more common in patients with lung transplants (58.3% vs 28%; $p = 0.03$). Although the nodular and the ground glass opacities patterns were more common in patients with transplants different than lungs, the difference was not statistically significant. The consolidation pattern was equally distributed between both groups. Nine patients (18.4%) had two different CT scan patterns coexisting.

Organizing pneumonia was the most frequent pathologic finding (38.8%), followed by infectious pneumonia (28.6%). Among the infectious pneumonias, viral pneumonias were the most common (16.3%). Except for obliterans bronchiolitis (OB) and acute rejection, which were found almost exclusively in lung transplant patients, no other significant differences were observed between the two groups. Pathology findings are reported in Table 2. No statistically significant association was found between CT scan patterns and pathology findings. Figures 1 and 2 show four CT scan patterns paired with the pathology findings.

After the SLB, a new pharmacologic therapy was started in 16 patients (36.7%). No significant differences were observed between the two groups.

Although lung transplant recipients had more postoperative complications and a higher in-hospital mortality rate, the differences did not reach statistical significance. Patients supported with mechanical ventilation at the time of SLB also had a higher complication rate (53.8% vs 27.8%) and in-hospital mortality rate (41.7% vs 14.3%) than those who were not; however, neither these differences were statistically significant. Perioperative death occurred in

Table 1. Baseline Characteristics and Outcomes of Surgical Lung Biopsy in Transplant Patients

Characteristic[a]	All Patients (n = 49)	Transplant Type		p Value
		Lung (n = 24)	Other Solid Organ (n = 25)	
Demographic variables				
Age, y	49 ± 16.7	42.6 ± 15.98	55.12 ± 15.3	0.007
Female sex	18 (36.7)	7 (29.2)	11 (44)	0.28
In-hospital at the time of SLB	44 (89.8)	20 (83.3)	24 (96)	0.18
CT scan findings				
Reticular pattern	21 (42.9)	14 (58.3)	7 (28)	0.03
Nodular pattern	11 (22.4)	3 (12.5)	8 (32)	0.06
Ground glass opacities	13 (26.5)	5 (20.8)	8 (32)	0.37
Consolidation	12 (24.5)	5 (20.8)	7 (28)	0.56
Symptoms				
Fever	27 (55.1)	9 (37.5)	18 (72)	0.015
Dyspnea	32 (65.3)	21 (87.5)	11 (44)	0.001
Cough	11 (22.4)	4 (16.7)	7 (28)	0.34
Bronchorrhea	7 (14.3)	4 (16.7)	3 (12)	0.7
Onset of symptoms to SLB, days	15 (10–30)	15 (10–25)	15 (10–30)	0.1
Indication for SLB				
Need for diagnosis	30 (61.2)	13 (54.2)	17 (68)	0.32
No improvement on implemented treatment	19 (38.8)	11 (45.8)	8 (32)	0.32
Mechanical ventilation at the time of SLB	13 (26.5)	6 (25)	7 (28)	>0.99
Preoperative bronchoscopy	44 (89.8)	24 (100)	20 (80)	0.05
TBLB performed	22 (44.9)	16 (66.7)	6 (24)	0.003
BAL performed without TBLB	44 (89.8)	24 (100)	20 (80)	0.05
VATS SLB	27 (57.5)	9 (37.5)	18 (72)	0.015
Change in treatment after SLB	18 (36.7)	9 (37.5)	9 (36)	0.9
Operative death (≤5 days of SLB)	2 (4.1)	1 (4.2)	1 (4)	>0.99
Post-op complications	17 (34.7)	10 (41.7)	7 (28)	0.31
Respiratory failure	6 (12.2)	3 (12.5)	3 (12)	>0.99
Sepsis	4 (8.2)	2 (8.3)	2 (8)	>0.99
Prolonged air leak	4 (8.2)	4 (16.7)	0 (0)	0.05
Pneumothorax	5 (10.2)	5 (20.8)	0 (0)	0.022
In hospital death	10 (21.3)	7 (30.4)	3 (12.5)	0.16
Length of stay, days	14 (6.5–35.5)	15 (10.5–43.5)	11.5 (5.5–29.5)	0.21
Survival time (95% CI)	1,380 (1,002–1,759)	765.39 (298–1,233)	1,768.9 (1,475–2,062)	0.002

[a] Categoric variables are shown as number (%) and continuous variables as mean ± standard deviation, median (interquartile range), or as indicated.

BAL = bronchoalveolar lavage; CI = confidence interval; CT = computed tomography; SLB = surgical lung biopsy; TBLB = transbronchial lung biopsy; VATS = video-assisted thoracoscopic surgical.

2 patients (4.1%), and 10 more patients (21.3%) died during the same of hospitalization from other causes different than SLB related complications. OB accounted for 4 of 15 deaths (26%) in lung transplant patients during follow-up.

Univariate analysis identified the following as factors negatively associated with survival: a lung transplant, dyspnea as presenting symptom, reticular pattern on CT, mechanical ventilation at the time of the SLB, and the indication of the SLB being not improvement on the initial treatment. Clinical presentation with fever and the indication of the lung biopsy being the need for diagnosis behaved as protective variables on univariate analysis (Table 3). However, on multivariate analysis, only having a lung transplant was negatively associated with survival (hazard ratio, 4.62; 95% confidence interval, 1.53 to 3.92, $p = 0.006$). Patients with lung transplants had a significantly lower 3-year survival rate than patients with other solid organ transplants (Figure 3).

Comment

Solid organ transplant patients receive pharmacologic immunosuppressive therapy to avoid rejection. As a consequence, they are individuals at increased risk of having DLD from infrequent causes such as unusual viruses, fungus, atypical mycobacterium, opportunistic microorganisms, rejection, bronchiolitis obliterans, and neoplastic diseases [6–11]. All these diagnostic possibilities should be considered when treating a transplant patient with DLD. In our practice, among 1,232 transplant patients, only 4% had DLD that required SLB.

Table 2. Pathologic Results of Lung Biopsy Specimens

Pathologic Results	All Patients (n = 49) No. (%)	Transplant Type		*p* Value
		Lung (n = 24) No. (%)	Other Solid Organ (n = 25) No. (%)	
Pneumonia				
Infectious	14 (28.6)	8 (33.3)	6 (24)	0.47
Viral	8 (16.3)	6 (25)	2 (8)	0.13
Bacterial	4 (8.2)	3 (12.5)	1 (4)	0.34
Fungal	3 (6.1)	0 (0)	3 (12)	0.23
Mycobacterium	1 (2)	0 (0)	1 (4)	>0.99
Organizing	19 (38.8)	10 (41.7)	9 (36)	0.68
Unspecific inflammation	7 (14.3)	1 (4.2)	6 (24)	0.09
Granulomatous	2 (4.1)	0 (0)	2 (8)	0.49
Tuberculosis	1 (2)	0 (0)	1 (4)	>0.99
Histoplasmosis	1 (2)	0 (0)	1 (4)	>0.99
Idiopathic interstitial pneumonias				
Interstitial fibrosis	3 (6.1)	1 (4.2)	2 (8)	>0.99
Cancer	2 (4.1)	1 (4.2)	1 (4)	>0.99
Lung transplant pathology				
Acute rejection	10 (20.4)	10 (41.7)	0 (0)	<0.001
Obliterans bronchiolitis	9 (18.4)	8 (33.3)	1 (4)	0.011

DLD is a life-threatening condition in any transplant patient. The severity of the disease will depend on the offending agent and the type of transplant the patient has [12]. Patients with a lung transplant have a worse survival than those with other solid organ transplants [12–14]. Like no other graft, transplanted lungs are exposed through the airway to environmental bacteria, virus, and fungi. Also, inflammatory conditions as OB and acute rejection

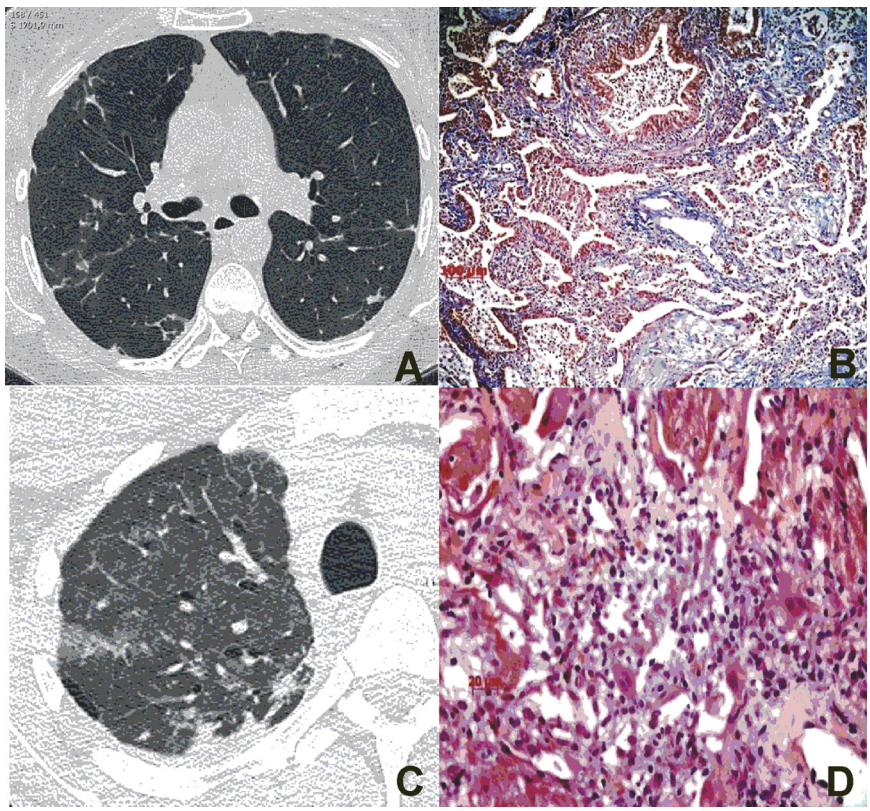

Fig 1. (A) Reticular computed tomography pattern is seen in a bilateral lung transplant patient. Bilateral subpleural linear opacities are seen in both upper lobes. (B) Pathologic findings of panel A show obliterans bronchiolitis, with bronchioli showing active inflammatory changes and scar tissue (Masson trichrome stain; original magnification ×100). (C) Ground glass opacities are seen in a computed tomography pattern in a lung transplant patient. Diffuse ground glass opacities in the right upper lobe are more evident in a subpleural lateral situation. There is also some consolidation in a posterior localization. (D) Pathologic findings of panel C show interstitial viral pneumonia with diffuse alveolar damage signs. Lung tissue shows acute and chronic interstitial inflammatory infiltrate, hyaline membranes, and intraalveolar exudate (hematoxylin and eosin stain; original magnification ×200).

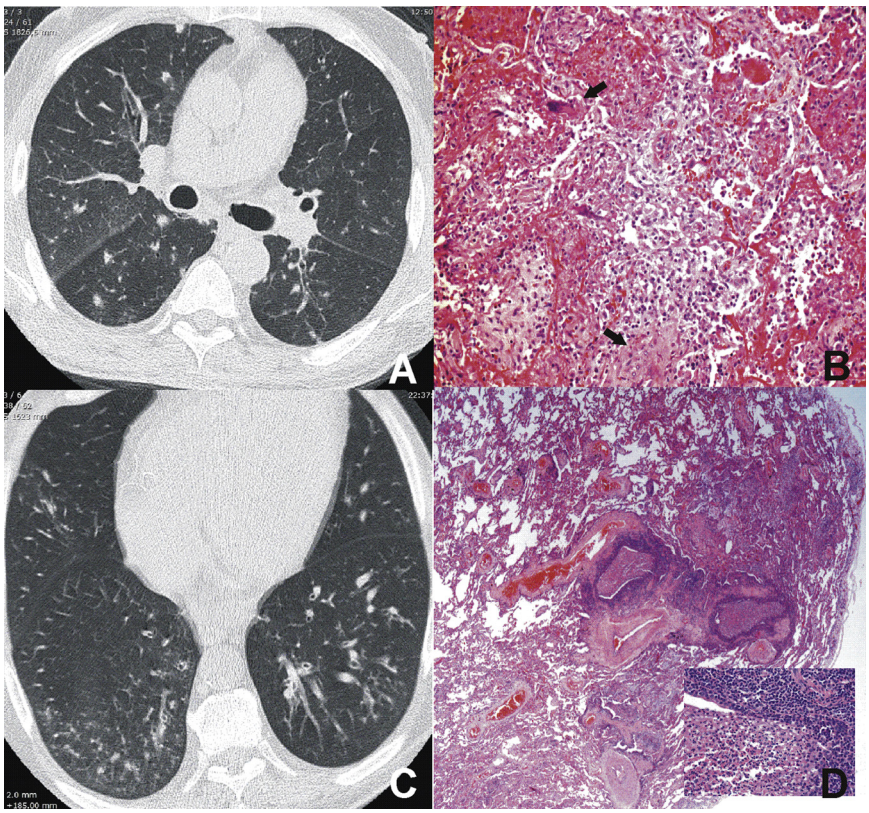

Fig 2. (A) Nodular computed tomography pattern in a heart transplant patient. Nodular pattern is involving both lungs, especially the apical segment of the right inferior lobe. The contours are ill defined and some of the nodules have ground glass surrounding. (B) Pathology findings of panel A show tuberculosis, granulomas with caseous necrosis and Langhans giant cells (arrows; hematoxylin and eosin stain; original magnification ×25). (C) Reticular computed tomography pattern in a kidney transplant patient. Both lungs show interlobular septal thickening, particularly in the subpleural location. Peribronchovascular interstitium is spared, and no honeycomb is seen. (D) Pathologic findings of panel C show acute unspecific bronchiolitis as evidenced by the acute inflammatory infiltrate into the walls of bronchioles and intraluminal collections of neutrophils and mucus (magnification ×25). A magnified view of the acute inflammation is seen in the inset (magnification ×400).

are almost exclusive to lung transplant patients. Although the etiologic causes of DLD in lung transplant patients and patients with other solid organs might not be that different, we hypothesized that lung transplant patients with DLD represent a different subset of patients among the entire cohort of transplant individuals. The graft itself is the affected organ in lung transplants with DLD, and this condition is unique to such patients.

This was the rationale to look for differences in the clinical presentation, radiologic, patterns and outcomes of DLD that needed SLB for diagnosis in these two distinctive groups of patients. To our knowledge there are no other published data that explicitly compare both groups [15, 16].

Not every transplant patient with DLD needs a SLB [17]. After a complete medical history, physical examination, and CT scan, an accurate diagnosis can be made by flexible bronchoscopy with bronchoalveolar lavage and transbronchial lung biopsy [6]. When these tests are not diagnostic, further work-up needs to be done and SLB comes into consideration.

Our findings show that the main presenting symptoms are different between both groups. The major symptom in lung transplant patients was dyspnea, whereas it was fever in patients with other transplants. The CT pattern was also different: lung transplant patients presented more frequently with reticular infiltrates.

Reticular infiltrates are the expression of interstitial pulmonary edema or pneumonia [18]. Idiopathic pulmonary fibrosis is a common cause of reticular infiltrates in the immunocompetent patient but is not a usual cause of reticular infiltrates in the transplant patient population [1, 18]. Any form of interstitial pneumonia or inflammation can cause reticular infiltrates in transplant patients, and although it is an unspecific pattern, we found it was more common in patients with lung grafts.

A video-assisted thoracoscopic surgical (VATS) approach was more frequently used in patients with solid organ transplants other than lungs. VATS in a lung transplant patient means a repeat operation, which sometimes is not possible. Adhesions in the pleural space can become quite firm after a lung transplant. SLB is most often started by VATS at our institution, but a thoracotomy is performed if adhesions can not be taken down safely. Miller and colleagues [19] reported similar outcomes after VATS vs thoracotomy for lung biopsy in patients with DLD. Although both approaches might lead to the same results, the reason to do a thoracotomy in lung transplant patients is adhesions from the prior surgery and not just a surgeon's preference.

SLB is a diagnostic procedure that can reach substantial morbidity and mortality rates [2]. Complications occurred in one-third of the patients. Although complications were more frequent in lung transplant patients, the difference was not statistically significant. In particular, lung transplant patients presented complications related to the reoperation, such as prolonged air leaks and pneumothorax. These complications were not observed in any patient with another solid organ transplant.

Table 3. Univariate Cox Analysis

	Univariate Analysis	
Variable	HR (95% CI)	*p* Value
Clinical characteristics		
Age	0.98 (0.95–1.01)	0.27
Male sex	1.12 (0.44–2.84)	0.79
Lung transplant	4.72 (1.57–14.19)	0.006
In-hospital at the time of SLB	1.43 (0.33–6.18)	0.62
Type of SLB		
Thoracotomy	1.43 (0.59–3.46)	0.42
Video-assisted thoracoscopic	0.69 (0.28–1.68)	0.42
Symptoms		
Fever	0.35 (0.14–0.91)	0.031
Dyspnea	13.01 (1.74–98.05)	0.012
Cough	0.39 (0.09–1.71)	0.21
Bronchorrhea	1.53 (0.44–5.29)	0.5
Computed tomography findings		
Reticular pattern	3.82 (1.45–10.04)	0.006
Nodular pattern	0.028 (0.001–1.73)	0.08
Ground glass opacities	1.01 (0.36–2.79)	0.97
Consolidation pattern	0.68 (0.22–2.05)	0.49
Mechanical ventilation at the time of SLB	2.71 (1.1–6.75)	0.03
Indication no improvement on treatment	2.5 (1.03–6.06)	0.04
Indication need for diagnosis	0.35 (0.16–0.96)	0.04

CI = confidence interval; HR = hazard risk; SLB = surgical lung biopsy.

We defined perioperative mortality as deaths that occurred within 5 days of the SLB. Given the short interval elapsed between the SLB and death, we assume that the lung biopsy was a key determinant of death. Two patients died within 5 days of SLB. Ten other patients were never discharged from the hospital and died later as a consequence of the progression of the underlying disease.

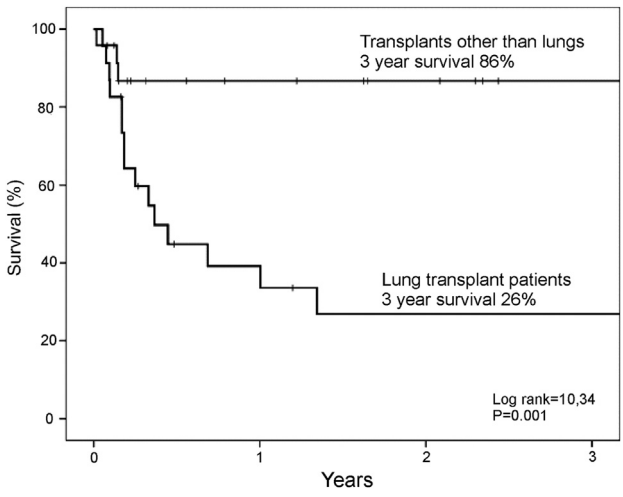

Fig 3. Survival curve comparing lung transplant patients vs patients with other solid organ grafts.

Survival rate was significantly lower in lung transplant patients. The reasons for this finding admit at least two possible explanations: the lung symptom that led to the SLB and the lower survival rates observed in lung transplants.

The rate of treatment change after the SLB was not significantly different in both groups. We have previously reported that SLB alters the treatment of DLD in transplant patients around 30% of the times and found similar rates in this current report [1]. As previously stated, the causes of DLD in transplant patients can be numerous. Some of these conditions have substantially different therapies, which makes it necessary to have a definite diagnosis to guide treatment.

Many variables were found to affect death on univariate analysis. Given the low number of events observed in our study and to avoid overfitting, only three of these variables were included in a multivariate analysis. The selection criteria for choosing those variables were to include those that were more objective or the most clinically significant. Instead of dyspnea as presenting symptom and reticular CT pattern (the two that were negatively associated with survival), having a lung transplant was included in the multivariate analysis because both former variables were more common in lung transplant patients. The other two variables included in the multivariate analysis were no improvement with the implemented treatment as indication for the SLB and a patient supported with mechanical ventilation at the time of the SLB. Having a lung transplant was the only variable associated with survival on multivariate analysis. However, given the few number of patients and events, any recommendation based on the multivariate analysis should be interpreted with caution.

When the indication of the SLB was the need of diagnosis in a symptomatic transplant patient, it carried a protective effect on survival on univariate analysis. We believe this indication leads to an earlier diagnosis and hence adequate treatment. A high number of patients with OB diagnosis might weaken this recommendation, because an earlier diagnosis will not yield to a better outcome. However, only one-third of lung transplant patients were diagnosed with OB, as reported in Table 2. The most frequent pathologic findings have specific treatments and could lead to a better survival when initiated on time.

Median length of stay was 14 days, which is quite a long interval for an SLB. Many of these postoperative days are spent in the intensive care unit. Length of stay can be a surrogate marker of complications, and we believe complications at least partly explain the prolonged hospitalization of our patients [20]. It will be very valuable to further study the economic effect that SLB in transplant patients might have in health care.

The limitations of our study include its retrospective nature, the small number of patients, and our bias on how we treat and proceed with our patients.

In conclusion, DLD requiring SLB for diagnosis in transplant patients is a relatively uncommon situation. Clinical

presentation and radiologic patterns are different in lung transplant patients compared with patients with other solid organ transplants. Lung transplant patients are more likely to require thoracotomy for lung biopsy. There are no significant differences in postoperative complications and in hospital death rates between the groups. A protective effect might be conferred by performing the SLB early in the course of the disease. Having a lung transplant is the most relevant factor associated with poor survival.

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INVITED COMMENTARY

In the present article, Dr Bertolotti and associates [1] seek to address the very interesting but seldom-debated questions of surgical lung biopsy (SLB) in transplant patients. Indeed, very little is known to date about the clinical presentation and results of SLB for diffuse lung disease (DLD) in lung transplant patients, in contrast to individuals with other type of solid organ grafts.

This study follows a previous work in the same era, published in *The Annals* in 2010 [2]. It contributes to a better understanding of the impact of SLB in patients after transplantation. Indeed, in this retrospective single-center cohort of 1,232 solid organ transplants, the authors individualized 49 DLD patients having undergone SLB for diagnosis. Among them, 24 had a previous lung transplant and 25 a transplant for other types of solid organs. The authors' conclusions were the following: (1) the clinical and radiologic presentation of DLD requiring SLB differs in patients with lung transplants as opposed to other transplants, although the postoperative outcomes were not significantly different between groups; (2) SLB performed early in the course of the disease might be beneficial; and (3) having a lung transplant is a significant negative predictor of survival.

This stimulating article makes it very clear that the development of a significant lung disease in solid organ transplant recipients represents a short-term illness, albeit with a significant mortality risk. On the other hand, the requirement for a surgical lung biopsy in a lung transplant recipient is associated with a much more accelerated rate of patient mortality over the next few years. Clearly, this is not surprising, and it likely reflects the different diagnosis obtained, from infectious to inflammatory conditions such as obliterans bronchiolitis, acute rejection, and late-onset diffuse alveolar damage [3].

Although this article suffers from a real lack of statistical power, it carries and emphasizes the important, if sobering, intuitive message that the onset of DLD in a lung transplant patient had a negative impact on survival. Indeed, the graft itself is the affected organ in lung transplant patients with DLD, and that makes this condition unique to such patients. Obviously, further research is needed to confirm the results of this single-center investigation. For this purpose, the use of the United Network for Organ Sharing database, promoting organ procurement and transplantation network, would be useful.

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