Open Lung Biopsy in Nonresolving Acute Respiratory Distress Syndrome Commonly Identifies Corticosteroid-Sensitive Pathologies, Associated With Better Outcome*

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Objectives: Approximately half of the patients undergoing lung biopsy for nonresolving acute respiratory distress syndrome exhibit another histologic pattern than diffuse alveolar damage, with some of the pathologies characterized by a potential response to corticosteroids. This study aimed to assess whether open lung biopsy performed in the ICU for nonresolving acute respiratory distress syndrome was able to identify steroid-sensitive diseases and whether patients with a steroid-sensitive pathology experienced different clinical courses and outcomes.

Design: Retrospective analysis.

Setting: One 22-bed mixed ICU within a tertiary medical center.

Patients: Patients age greater than or equal to 16 years old who met the Berlin definition for acute respiratory distress syndrome and underwent open lung biopsy from January 2007 to January 2017.

Interventions: None.

Measurements and Main Results: During the study period, 695 patients diagnosed with acute respiratory distress syndrome were identified, 51 (7%) of whom underwent open lung biopsy. An alternative diagnosis to diffuse alveolar damage was found in 29 patients (57%), and a steroid-sensitive pathology was identified in 19 (37%). In-hospital and 180-day mortality rates were 55% and 61%, respectively. There was a significant difference in hospital mortality and 180-day mortality rates between patients with steroid-sensitive pathology and those with steroid-resistant pathology (37% vs 65%; $p < 0.045$ and 37% vs 75%; $p < 0.007$, respectively). We did not identify any variable that could reliably predict a steroid-sensitive histologic pattern before open lung biopsy.

Conclusions: Open lung biopsy was able to identify a steroid-sensitive pathology in a significant proportion of nonresolving acute respiratory distress syndrome patients. These patients had a better outcome, with lower hospital mortality and 180-day mortality. (*Crit Care Med* 2018; 46:907–914)

Key Words: acute respiratory distress syndrome; diagnosis; histology; open lung biopsy; outcome; steroid treatment

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Acute respiratory distress syndrome (ARDS) is common in critically ill patients, while associated with high mortality and morbidity (1). The Berlin definition of ARDS proposes clinical and radiologic criteria for ARDS diagnosis and classification (2). The Berlin criteria have been widely used in clinical practice and as inclusion criteria in numerous clinical trials. However, they do not take into account pathologic findings for diagnosing ARDS.

Although diffuse alveolar damage (DAD) is considered the pathologic hallmark of ARDS, it is known, since its original description (3), that many patients with ARDS diagnosis do not suffer from DAD. A recent autopsy study by Thille et al (4) showed that among 356 patients meeting the Berlin ARDS definition, only 45% had DAD at autopsy. Similar results were found in patients undergoing open lung biopsy (OLB) for non-resolving ARDS (5–8). Pathologic findings other than DAD comprise interstitial lung disease, pneumonia, cancer, organizing pneumonia, alveolar hemorrhage, or drug reactions (5–8).

These conditions unlikely share the same pathophysiology and the same response to pharmaceutical treatment. The heterogeneity of ARDS patients included in therapeutic trials remains a challenge when interpreting trial results. In particular, the use of steroids in ARDS has been a matter of debate for over 20 years, with some trials (9, 10) showing a decreased mortality, in contrast to others (11). However, since none of these trials used lung biopsy–based histologic diagnosis, the underlying pathology remains largely unknown.

Our study primarily sought to assess whether OLB in non-resolving ARDS would identify pathologies other than DAD, with a particular focus on corticosteroid-sensitive pathologies. In addition, we aimed to evaluate whether the clinical characteristics and outcomes differed in patients with steroid-sensitive pathologies, compared with patients with other pathologies.

MATERIAL AND METHODS

The appropriate ethics committee (Comité d'Ethique Hospitalo-Facultaire, Saint-Luc, UCL N° 2017/21AOU/408) approved the reporting of our study results. Informed consent from the patients or their next of kin was waived due to the retrospective nature of the analysis.

Patients

The hospital records of all ARDS patients who underwent OLB from January 2007 to January 2017 in a 22-bed tertiary care mixed ICU were reviewed. The medical files of all patients with a discharge diagnosis code of 518.82 (according to the *International Classification of Diseases*, 9th Revision [ICD-9], "clinical modification suggesting ARDS") and procedure code of 3,328 (OLB) or 3,402 (exploratory thoracotomy) were reviewed for possible inclusion in this study.

The inclusion criteria were as follows: 1) age greater than or equal to 16 years at the time of biopsy and 2) findings consistent with the Berlin ARDS definition (2). ARDS was characterized as mild/moderate/severe, as described in the Berlin definition, at the time of both diagnosis and biopsy (2).

OLB

OLB was conducted in the event of persistent respiratory failure, after ongoing lung infection was ruled out (via bronchoalveolar lavage [BAL] or via endotracheal aspirates) or when an alternative diagnosis was suspected, based on patient history, clinical and radiologic presentation. In most cases, OLB was performed at patient bedside in the ICU. In all cases, lung biopsy was performed using minithoracotomy. Two large lung samples were taken from two different lobes, with one chest tube inserted before suturing the chest.

Lung Pathology Grouping

All samples were examined by an experienced pathologist. In complex cases, a second pathologist was consulted, and discrepancies were resolved through consensus. The criteria for DAD diagnosis have been previously described (12). Other histologic patterns were defined in line with published guidelines (13–20). Patients were divided into a "corticosteroid-sensitive" and "corticosteroid-resistant" groups based on histologic findings, depending on published guidelines or commonly accepted expert opinions (13, 15, 17, 21–29). Importantly, the classification was based on histopathologic diagnosis and not on the presence or the absence of fibroproliferative response within the examined samples. Details regarding the exact methodology used for pathology classification are described in **Appendix 1** (Supplemental Digital Content 1, http://links.lww.com/CCM/D395).

Steroids Prescription Policy

When the risk is not deemed too high, empirical steroid therapy is systematically initiated right after OLB, while awaiting for definitive results of lung histology. Steroids are then usually discontinued if lung histology does not identify a steroid-sensitive pattern.

Data Collection

All hospital records were retrospectively reviewed. Study day 0 corresponded to the first day the patient met the diagnostic ARDS criteria. Demographic data and underlying conditions were recorded. Acute Physiology and Chronic Health Evaluation II score and Sequential Organ Failure Assessment (SOFA) score were calculated at ICU admission and lung biopsy days. In addition, laboratory data, ventilator settings, and respiratory variables were recorded for the first 7 days from ARDS diagnosis, on the day of lung biopsy, and for 7 days following corticosteroid introduction (if applicable) or lung biopsy (if no corticosteroids were given). Diagnostic procedures before lung biopsy (BAL and chest CT), adjuvant therapies, pathologic diagnosis, therapeutic alterations (new therapies or cessation of unnecessary therapy), as well as surgery-related complications were collected and recorded. Patients were followed up until hospital discharge, and it was recorded whether they were alive or dead at ICU discharge, at hospital discharge, and at 6-month follow-up.

Statistical Analyses

Statistical analyses were performed using the SPSS 21 software (SPSS software [IBM Corp. 2011. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp]), with graphs drawn using Graphpad Prism 7.5 (GraphPad Software, La Jolla, CA). Values were expressed as median (first–third quartiles) for continuous values and counts (per percent of group)

TABLE 1. Characteristics at ICU Admission and at Open Lung Biopsy for 51 Nonresolving Acute Respiratory Distress Syndrome Patients, With or Without a Pathologic Diagnosis Suggesting Beneficial Corticosteroid Effects

Variables	All Patients ($n = 51$)	Corticosteroid-Sensitive ($n = 19$) Pathology	Corticosteroid-Resistant Pathology ($n = 32$)	p
Age, median (IQR), yr	66.9 (52–76)	60.8 (49.1–76.3)	67.4 (54.8–75.8)	0.59
Male, n (%)	28 (55)	9 (47)	19 (59)	0.4
Immunocompromised, n (%)	27 (53)	8 (42)	19 (59)	0.23
Chronic respiratory disease, n (%)	5 (10)	1 (5)	4 (13)	0.64
SOFA at ICU admission, median (IQR)	6 (4–8)	5 (3–9)	6 (5–8)	0.42
Acute Physiology and Chronic Health Evaluation II at ICU admission, median (IQR)	17.5 (15–21.5)	16 (13.5–20)	18 (16–24)	0.06
Categories, ARDS diagnosis day, n (%)				0.48
Mild ARDS	24 (47)	10 (53)	14 (44)	
Moderate ARDS	21 (41)	8 (42)	13 (41)	
Severe ARDS	6 (12)	1 (5)	5 (16)	
Pao_2/Fio_2 (mm Hg), ARDS diagnosis day, median (IQR)	122 (93–157)	136 (88–159)	117 (93–157)	0.84
Bronchoalveolar lavage prior to biopsy, n (%)	40 (78)	18 (95)	22 (69)	**0.037**
Use of adjunctive therapies (from ARDS diagnosis to biopsy day), n (%)				
Prone positioning	8 (16)	3 (16)	5 (16)	1
Nitric oxide	6 (12)	2 (11)	4 (13)	1
Vasopressors	19 (38)	6 (32)	13 (42)	0.46
Renal replacement therapy	8 (16)	3 (17)	5 (16)	1
Duration from ARDS diagnosis to biopsy, median (IQR), d	7 (2–13)	5 (2–10)	8 (2–13)	0.16
SOFA, biopsy day, median (IQR)	7 (5–9)	6.5 (5.3–9)	7.5 (5–9)	0.92
Categories, biopsy day, n (%) ($n = 47$)				0.21
Mild ARDS	4 (9)	0 (0)	4 (13)	
Moderate ARDS	33 (70)	12 (71)	21 (70)	
Severe ARDS	10 (21)	5 (29)	5 (17)	
Pao_2/Fio_2 (mm Hg), biopsy day, median (IQR) ($n = 47$)	128 (101–155)	121 (97–144)	129 (103–158)	0.45
Positive end-expiratory pressure (cm H_2O), biopsy day, median (IQR) ($n = 47$)	9 (7–12)	8 (7–10)	10 (7–12)	0.47
Tidal volume (mL/kg), biopsy day, median (IQR) ($n = 47$)	6.8 (6.3–7.5)	7.2 (6.6–8.2)	6.7 (6.2–7.5)	0.09
Plateau pressure, biopsy day, median (IQR) ($n = 47$)	26 (23–31)	23 (20.5–26)	29 (24–32)	**0.013**
Dynamic respiratory system compliance (mL/cm H_2O), biopsy day, median (IQR) ($n = 47$)	26 (19–38)	32 (23–46)	24 (18–32)	**0.02**
Driving pressure, biopsy day, median (IQR) ($n = 47$)	17 (13–21)	13 (11–18)	18 (15.8–21.8)	**0.03**

ARDS = acute respiratory distress syndrome, IQR = interquartile range, SOFA = Sequential Organ Failure Assessment.
Boldface values indicate statistical significance ($p < 0.05$).

for qualitative variables. The data were subjected to Kolmogorov-Smirnov normality test and Bartlett's test for homogeneity of variance. We compared clinical and demographic variables between patients with and without a steroid-sensitive pathology, using the chi-square test (or Fisher exact test when appropriate) and unpaired t test (or the Wilcoxon rank-sum

test according to statistical distribution) for quantitative data, respectively. Besides, nonlinear regression was employed to adjust the variations of biological and ventilatory variables over time in each group (from day 0 to day 6). The extra sum-of-squares F test was applied for comparison between curves. Furthermore, survival curves were generated using the Kaplan-Meier method, compared by log-rank test. All tests were two sided, with significance level set at 0.05.

RESULTS

From January 2007 to January 2017, 695 patients admitted in the ICU with the diagnosis of ARDS were retrieved from ICD-9 coding. Among them, a surgical lung biopsy was performed in 51 patients (7%). Ventilatory data were partially missing in four patients. These patients were included in the review but excluded from the analysis of ventilatory variables.

The patient characteristics at baseline and at OLB have been summarized in **Table 1**. Twenty-seven patients had immuno-compromised status. The main immunocompromising conditions are listed in **Table S1** (Supplemental Digital Content 2, http://links.lww.com/CCM/D396).

When patients with and without corticosteroid-sensitive pathology were compared at baseline, we found no significant differences in terms of organ support, ARDS severity, or SOFA score. At OLB time, plateau pressure and driving pressure were significantly lower and dynamic respiratory system compliance significantly higher in the steroid-sensitive group.

When we compared between both groups, the progression of physiologic and respiratory variables, from day 0 (day of ARDS diagnosis) to day 6, no significant difference was, however, found, as shown in **Figure 1**. The progression of biological variables during the same period is summarized in **Figure S1** (Supplemental Digital Content 3, http://links.lww.com/CCM/D397; **legend**, Supplemental Digital Content 5, http://links.lww.com/CCM/D399).

The OLB results have been summarized in **Table 2**. OLB revealed a diagnosis other than DAD in 29 patients (57%), with a corticosteroid-sensitive pathology identified in 19 (37%).

Based on biopsy results, therapy modifications were carried out on 38 patients (75%) (**Table 3**), with significantly more therapeutic changes in the steroid-sensitive group (89% vs 66%; $p = 0.047$). Thus, systemic corticotherapy was initiated in more patients from the steroid-sensitive groups (89% vs 58%; $p < 0.001$), with a trend toward a longer duration of steroid therapy (25.5 vs 9 d; $p = 0.14$). Besides, the two patients in whom steroids were not initiated in the steroid-sensitive group were already under systemic steroids at the time of OLB. OLB complications occurred in six patients (12%), although no death was directly attributable to OLB. Two patients developed pneumothorax with subcutaneous emphysema requiring chest tube insertion, three patients had persistent air leaks, and another patient developed

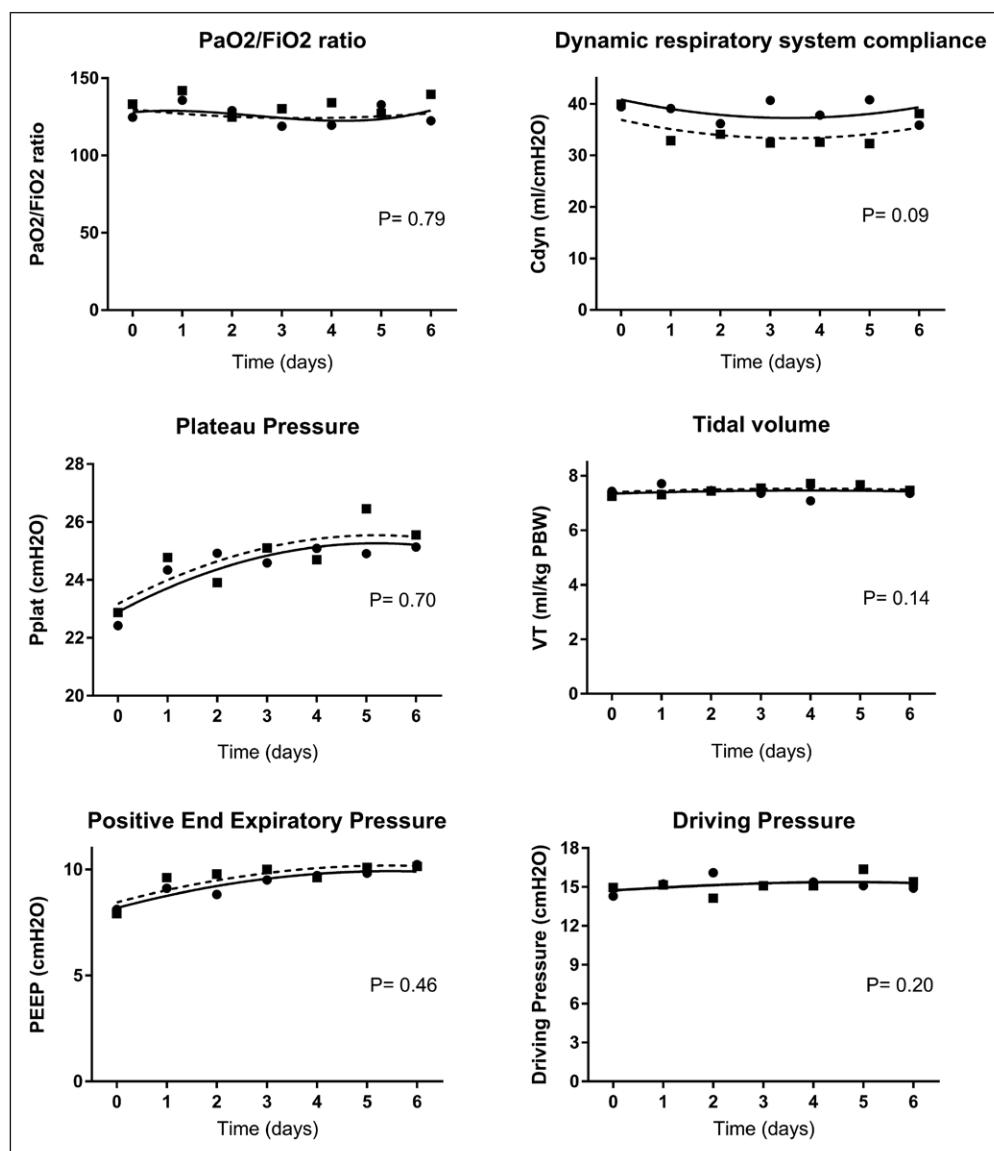**Figure 1.** Time course of respiratory variables of nonresolving acute respiratory distress syndrome (ARDS) patients with (*circles*, *continuous line*) or without (*squares*, *dashed line*) "corticosteroid-sensitive" pathology. Day 0 is the day of ARDS diagnosis. Cdyn = dynamic respiratory system compliance, Plat = plateau pressure, PEEP = positive end-expiratory pressure, VT = tidal volume.

TABLE 2. Pathologic Diagnosis of Patients With Nonresolving Acute Respiratory Distress Syndrome Undergoing Open Lung Biopsy (*n* = 51)

Results of Open Lung Biopsy	n (%)
Corticosteroid-resistant pathologies	**32 (62.7)**
Diffuse alveolar damage	22 (43.1)
Interstitial lung diseases	4 (7.8)
UIP (end-stage fibrosis)	4 (7.8)
Cancer	1 (2)
Drug reaction (bleomycin toxicity)	1 (2)
Infectious diseases	4 (7.8)
Invasive aspergillosis	1 (2)
Culture-negative bronchopneumonia	2 (3.9)
Cytomegalovirus pneumonia	1 (2)
Corticosteroid-sensitive pathologies	**19 (37.3)**
Cryptogenic organizing pneumonia/bronchitis obliterans with organizing pneumonia	11 (21.6)
Interstitial lung diseases	3 (5.9)
Acute interstitial pneumonia	2 (3.9)
Acute exacerbation of UIP	1 (2)
Acute eosinophilic pneumonia	1 (2)
Pneumocystis pneumonia	2 (3.9)
Alveolar hemorrhage	1 (2)
Amiodarone toxicity	1 (2)

UIP = usual interstitial pneumonia.
Classification according to the expected effect of corticosteroid therapy.
Boldface values indicate statistical significance ($p < 0.05$).

acute cor pulmonale with hypotension and low cardiac output in the post-OLB hours.

Overall in-hospital and 180-day mortality rates were 55 and 61%, with a significant difference between patients with and without steroid-sensitive pathology (37% vs 65%; $p < 0.045$ and 37% vs 75%; $p < 0.007$, respectively), which was confirmed by Kaplan-Meier analysis (**Fig. 2**) (log-rank $p < 0.015$). Conversely, there was no statistically significant between-group difference revealed in terms of mechanical ventilation duration or hospital length of stay.

The evolution of respiratory variables after lung biopsy is summarized in **Figure S2** (Supplemental Digital Content 4, http://links.lww.com/CCM/D398; legend, Supplemental Digital Content 5, http://links.lww.com/CCM/D399).

DISCUSSION

To our knowledge, this is the first study to address OLB's role in identifying corticosteroid-sensitive pathologies in patients with nonresolving ARDS. Based on our study findings, corticosteroid-sensitive pathologies were commonly observed in patients undergoing OLB for nonresolving ARDS and patients with steroid-sensitive pathology presented a better outcome, with lower hospital and 180-day mortality.

The relationship between histology and clinical outcomes in nonresolving ARDS has been previously studied, yet with conflicting results. In the only prospective study so far, Papazian et al [8] reported, in 2007, a contributive result of OLB associated with a better survival. Interestingly, there was an unexpectedly low rate of DAD and high rate of cytomegalovirus pneumonia found in their series. Furthermore, the major medication changes consisted of adding ganciclovir for cytomegalovirus infection or glucocorticoids for fibroproliferative ARDS, and thus therapies whose beneficial effects are still controversial. Recently, major studies were mainly focused on identifying DAD in patients with nonresolving ARDS, and they revealed conflicting results as to the relationship between a specific DAD pattern and mortality (5, 6, 30, 31). From a clinical point of view, however, DAD identification may not add any relevant information, given the lack of specific therapy targeting this condition. Conversely, identifying steroid-sensitive pathologies is associated with important therapeutic implications.

In our series, DAD was found in 59% of patients, being the only pathologic finding in 43% of all patients. This was in accordance with recent series, sharing comparable criteria in view of performing OLB (5, 6). We identified a corticosteroid-sensitive pathology in 37% of our patients. In our series, the main alternatives to DAD diagnosis were cryptogenic organizing pneumonia (COP), interstitial lung diseases, and infections, in line with previously reported studies (5–7, 30). However, we found an unexpectedly high frequency of bronchitis obliterans with organizing pneumonia (BOOP)/COP in our series (21% of patients vs 4–11% in previously reported studies) (5–7). One of the possible explanations could refer to the high proportion of immunocompromised patients in our series, (53% of patients vs 24–38% in other OLB series) (5–7), reflecting a possible selection bias. Since organizing pneumoniae are shown to be frequently associated with immunocompromising conditions (27), the characteristics of our population could likely explain the high COP/BOOP frequency.

Importantly, in some patients in our series, despite a comprehensive diagnostic workup including BAL, OLB showed pathologic processes that were theoretically amenable to a bronchoscopic diagnosis (such as Pneumocystis pneumonia, diffuse alveolar hemorrhage, acute eosinophilic pneumonia). In those cases, OLB was performed either because BAL was of poor quality and considered inconclusive or because there was a discrepancy between the conditions diagnosed by the BAL and the clinical evolution under an ongoing, well-conducted treatment. In our opinion, this underlines the limits of bronchoscopy performed in ARDS patients, in whom high F_{IO_2} and concerns about poor tolerance impose to limit the volume of the fluid used to perform BAL, potentially leading to decreased sensitivity or results interpretation issues. If BAL is commonly admitted as a powerful diagnosis tool in mechanically ventilated patients, to the best of our knowledge, its diagnostic yield has never been formally questioned in the context of ARDS.

TABLE 3. Outcomes After Open Lung Biopsy for 51 Acute Respiratory Distress Syndrome Patients, With or Without a Pathologic Diagnosis Suggesting a Beneficial Effect From Corticosteroids

Variables	All Patients (*n* = 51)	Corticosteroid-Sensitive Pathology (*n* = 19)	Corticosteroid-Resistant Pathology (*n* = 32)	*p*
Treatment alterations post OLB, *n* (%)	38 (75)	17 (89)	21 (66)	**0.047**
Introduction methylprednisolone (≥ 1 mg/kg/d, > 3 d), *n* (%)	35 (69)	17 (89)	18 (56)	**0.001**
Duration of corticosteroid therapy, d, median (IQR)	17 (7–40)	25.5 (7–85)	9 (6.5–28.5)	0.14
Duration from OLB to corticosteroids, d, median (IQR)	2 (0–3)	1.5 (0–3)	2 (0–3)	0.85
Complications after OLB, *n* (%)	6 (11.76)	1 (5.26)	5 (15.63)	0.39
Organ support (7 d following OLB), *n* (%)				
Vasopressors	18 (35)	5 (26)	13 (41)	0.3
Inotropes	3 (6)	1 (5.3)	2 (6.3)	0.9
Renal replacement therapy	14 (27)	5 (26)	9 (28)	0.9
Neuromuscular blockade	1 (2)	0	1 (3.1)	0.8
Extracorporeal life support	2 (3.9)	0	2 (6.3)	0.52
28-d mortality, *n* (%)	20 (39)	5 (26)	15 (46)	0.14
Hospital mortality, *n* (%)	28 (55)	7 (37)	21 (65)	**0.045**
180-d mortality, *n* (%)	31 (61)	7 (37)	24 (75)	**0.007**
Cause of death (*n* = 30), *n* (%)				
Shock/multiple organ failure	12 (40)	0 (0)	12 (50)	0.06
Refractory hypoxemia	5 (17)	2 (33)	3 (13)	0.24
Refractory respiratory acidosis	6 (20)	1 (17)	5 (20)	1
Withdrawal of life support	4 (13)	2 (33)	2 (8.5)	0.6
Other	3 (10)	1 (17)	2 (8.5)	0.4
Ventilatory-free days D14, median (IQR)	2 (0–6)	3 (1–7)	1 (0–6)	0.36
Ventilatory-free days D28, median (IQR)	5 (1–12)	7 (1–19)	4.5 (1–11)	0.23
LOS ICU, d, median (IQR)	22 (15–34)	23 (14–40)	21.5 (15–34)	0.92
LOS hospital, d, median (IQR)	32 (17–59)	33 (33–61)	30 (16–56)	0.28
ICU-free days D60, median (IQR)	10 (0–35)	20 (0–44)	0 (0–27.5)	0.08

IQR = interquartile range, LOS = length of stay, OLB = open lung biopsy.
Boldface values indicate statistical significance (*p* < 0.05).

One of our main study findings was that in-hospital and 180-day mortality rates were significantly lower in patients with a steroid-sensitive pathology (37% vs 65% and 37% vs 75%, respectively). Surprisingly, there was no statistically significant difference regarding ventilator-free days or regarding the evolution of the main respiratory variables (out of a statistically significant increase of dynamic compliance under steroid treatment, as shown in Fig S2, Supplemental Digital Content 4, http://links.lww.com/CCM/D398), possibly due to the limited number of patients in our series. We report an overall in-hospital mortality rate of 55% and 180-day mortality rate of 61%. Other studies involving patients with nonresolving ARDS found similarly high mortality rates (5–8, 30).

OLB safety in our study proved satisfactory with procedure-related complications in 12% of patients, without any death directly attributed to OLB. This is consistent with previous studies, yet lower than the overall surgical complication rate of 22% reported in a recent meta-analysis by Libby et al (32).

We were unable to identify any clinical, respiratory, or biological variable strongly related to a steroid-sensitive histologic pattern, out of a small difference in plateau pressure, driving pressure, and dynamic respiratory system compliance at the time of biopsy. However, there was a trend toward a shorter duration between ARDS diagnosis and OLB in the steroid-sensitive group (5 vs 8 d), possibly explaining the observed differences at the time of OLB.
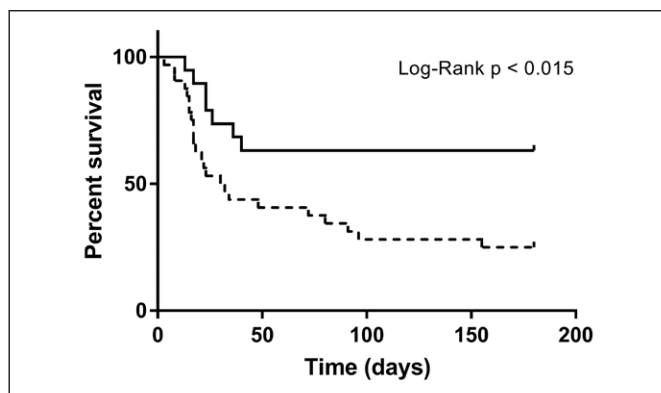
Figure 2. Kaplan-Meier survival analysis comparing nonresolving acute respiratory distress syndrome patients with (*continuous line*) or without (*dashed line*) "steroid-sensitive" pathology.

Our findings highlight how challenging the interpretation of previous trials with respect to corticosteroid benefits in ARDS may prove to be. In a small randomized controlled trial, Meduri et al (9) revealed a marked reduction in ICU mortality in patients treated with systemic corticosteroids for persistent ARDS. In addition, a recent patient-level meta-analysis conducted by Meduri et al (33) suggested a beneficial impact of corticosteroid adjunction, resulting in decreased in-hospital mortality. Conversely, a multicenter randomized controlled trial conducted by the ARDS Network failed to show any difference in ICU or hospital mortality rates, nor in ICU stay length, despite a shorter duration of mechanical ventilation in the steroid group (11). Furthermore, in the steroid group, mortality was increased in patients enrolled later in the course of ARDS, suggesting that unproper use of steroids could be harmful. It should, however, be noted that none of these trials required a histologic diagnosis using lung biopsy. Thereby, it is not possible for us to exclude that the beneficial effects on survival or ventilatory endpoints observed in these studies could, at least to some extent, be attributed to the favorable progression of steroid-sensitive pathologies, upon systemic corticosteroid exposure.

Evidently, lung biopsy is not a practical tool to prospectively improve patient selection for clinical trials. Therefore, there is a need for new strategies to better define ARDS patient subsets that might benefit from specific treatments, such as corticosteroids. Based on the data from large randomized ARDS trials, Calfee et al (34) recently identified two ARDS subphenotypes with distinct natural histories, clinical and biomarker profiles, and differential response to therapy consisting of positive end-expiratory pressure and fluid management (35). It is unclear whether both subphenotypes were related to distinct histopathologic patterns, such as corticosteroid-sensitive pathologies. Studies using OLB to compare underlying histology between both phenotypes could prove useful. Another approach might be to use specific biomarkers. Some of the latter, such as N-Terminal-Procollagen III, could help identify a specific patient subset with an expected good response to corticosteroids (36).

We recognize that there are limitations to our study. First, it is a retrospective analysis, involving a single referral center, with a relatively small sample size of OLB. Second, classifying pathologies according to their expected response to corticosteroids proves challenging, and our classification may be subject to criticism. Most of these diseases are rare, with scarce evidence as to their optimal treatment, particularly in ventilated, critically ill patients. Furthermore, even in pathologies allegedly steroid sensitive, the benefits from corticosteroids depend upon several factors such as daily dose and initiation timing. Third, as our classification did not take into account the presence of fibroproliferative response, we cannot rule out that some potentially beneficial effects of steroids might have been missed or that steroids could have contributed to improve outcomes in the steroid-sensitive group through the inhibition of fibroproliferation. Thus, the retrospective design of the study cannot rule out the confounding effect of a higher proportion of corticosteroid therapy introduced in the steroid-sensitive group. Fourth, the decision to perform OLB was highly selective, restricted to patients with nonresolving ARDS or a high suspicion of an alternative diagnosis. We calculated that only 7% of all ARDS patients underwent lung biopsy (based on an estimated 695 patients diagnosed with ARDS, retrieved from ICD-9 coding). Although this selection bias could likely increase the probability of an alternative diagnosis, other studies investigating OLB in ARDS report similar biopsy rates (5–8).

CONCLUSIONS

In this retrospective review of prospectively collected data in a single academic center, a significant proportion of patients who underwent OLB for nonresolving ARDS suffered from a pathologic process that could likely benefit from corticosteroids. Patients with steroid-sensitive pathology displayed a better outcome, with lower hospital and 180-day mortality rates. No demographic, clinical, biological, or respiratory variables could reliably predict a steroid-sensitive pattern on lung biopsy. Other less invasive strategies able to identify treatment-specific ARDS subsets are not yet available in clinical routine. Thus, as OLB was safe, well tolerated, and able to add clinically relevant information in a significant proportion of patients, it could be considered in patients with nonresolving ARDS.

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