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► **To cite this version:**

Yaël Levy, Lauren Bitton, Chiara Sileo, Jérôme Rambaud, Yohan Soreze, et al.. Lung biopsies in infants and children in critical care situation. *Pediatric Pulmonology*, 2024, Online ahead of print. 10.1002/ppul.26845 . inserm-04412829

HAL Id: inserm-04412829




<https://inserm.hal.science/inserm-04412829>

Submitted on 23 Jan 2024

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Lung biopsies in infants and children in critical care situation

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Funding information

Chancellerie des Universités de Paris

Abstract

Introduction: Lung biopsy is considered as the last step investigation for diagnosing lung diseases; however, its indication must be carefully balanced with its invasiveness. The present study aims to evaluate the diagnostic yield of lung biopsy in critically ill patients hospitalized in the pediatric intensive care unit (ICU).

Material and Methods: Children who underwent a lung biopsy in the ICU between 1995 and 2022 were included. Biopsies performed in the operating room and post-mortem biopsies were excluded.

Results: Thirty-one patients were included, with a median age of 18 days (2 days to 10.8 years); 21 (67.7%) were newborns. All patients required invasive mechanical ventilation, 26 (89.7%) had a pulmonary hypertension, and 22 (70.9%) were placed under extracorporeal membrane oxygenation (ECMO). The lung biopsy led to a diagnosis in 81% of the patients. The diagnostic reliability seemed to decrease with age (95% in newborns, 71% in 1 month to 2 years and 0/3 patients aged over 2 years old). Diffuse developmental disorders of the lung accounted for 15 (49%) patients, primarily alveolar capillary dysplasia, followed by surfactant disorders in 5 (16%) patients. Complications occurred in 9/31 (29%) patients including eight under ECMO, with massive hemorrhages in seven cases.

Discussion and Conclusion: In critical situations, lung biopsy should be performed. Lung biopsy is a reliable diagnostic procedure for neonates in critical situation when a diffuse developmental disorder of the lung is suspected. The majority of lung biopsy complication was associated with the use of ECMO. The prospective evaluation of the complications of such procedure under ECMO, and particularly over 10 days of ECMO and in children over 2-year-old remains to be ascertained.

KEYWORDS

childhood interstitial lung disease, children, diffuse parenchymal lung disease, extra-corporeal membrane oxygenation, intensive care unit, interstitial lung disease, lung biopsy

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1 | INTRODUCTION

Lung biopsy is an invasive procedure that serves as the final diagnostic step for undefined chronic or subacute lung lesions. It is considered as the last step investigation for diagnosing diffuse parenchymal lung diseases.¹⁻³

In cases where a precise diagnosis is lacking, lung biopsy is considered in the following situations: (i) childhood interstitial lung diseases (chILD), which constitute the majority of cases; (ii) acute or sub-acute respiratory distress syndrome of unknown origin; and (iii) distal nodules or tumors. Lung biopsy allows for the assessment of the distal lung parenchyma and can be performed using various techniques, such as transbronchial (cryo)-biopsy during a bronchoscopy, percutaneous biopsy under CT-control or surgical lung biopsy by thoracoscopy or thoracotomy.⁴⁻⁶ After lung biopsy, the histological examination of the lung sample relies on the expertise of the pathologist, who will analyze the lung parenchyma's appearance, taking into account the patient's age, lung development stage and standardized procedures.

In stable patients, lung biopsy is often performed as the final step in the diagnostic workup.⁷ However, in ICU patients, where a rapid diagnosis and optimal management are crucial, evaluating the benefit/risk balance is of utmost importance. The diagnostic yield of a lung biopsy depends on several factors, including accurate indication, proper sample collection, and expert pathology analysis. The expected benefits include a precise etiological diagnosis, an evaluation of disease severity and prognosis, and/or guidance for therapeutic management. However, it is essential to consider that the procedure may yield non-contributive results. The primary risk is its invasiveness, which can lead to various complications such as hemorrhage, pneumothorax, and infections, especially in critically ill patients in the intensive care unit (ICU) receiving invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO).^{8,9} Currently, the value and safety of this procedure in neonatal and pediatric patients hospitalized in the ICU have not yet been thoroughly analyzed. Therefore, this study aims to evaluate the diagnostic yield and to discuss the safety of lung biopsy in critically ill patients.

2 | MATERIAL AND METHODS

The study was conducted between 1995 and 2022 in the Pediatric and Neonatal (PN-ICU) of Armand Trousseau Hospital, AP-HP, Sorbonne University, Paris, which is a Reference Center for rare lung diseases RespiRare. Due to the hospital's expertise in rare lung diseases, patients were recruited not only locally but also from other centers in France.

The PN-ICU department admits pediatric patients of all ages and has 18 beds, with up to five patients under ECMO simultaneously. Since 2007, a total of 482 patients have received ECMO support. The study included all patients under noninvasive (NIV) or invasive ventilation support who underwent a lung biopsy between 1995 and

2022. Postmortem biopsies and autopsies were excluded, as well as patients who required ICU management following a planned lung biopsy in the operating room.

All the lung biopsies were evaluated by a pediatric pathologist, with an expertise in rare lung diseases (ACL). In this study the lung biopsy was considered reliable when it provided a definite etiologic classification.

Complications were defined as unexpected events occurring during or within hours after the lung biopsy (hemorrhage, thromboembolism, pneumothorax, infection, death). Patients and/or parents were informed about the study and gave their consent for retrospective data collection for research purposes, as required by the local ethical authorities. Data were extracted from the patients' medical records, and the data collection process was declared to the legal authorities under the number 2226380 (Commission Nationale de l'Informatique et des Libertés, CNIL).

Categorical variables are presented as number and percentage, while continuous variables are presented as mean and standard deviation or median and interquartile ranges (IQR). Fisher's exact test was used to compare proportions and was performed using R Project version 4.2.2. A p value of ≤ 0.05 was considered significant.

3 | RESULTS

Between 1995 and 2022, a total of 60 patients underwent lung biopsy. After excluding non-PN-ICU biopsies and post-mortem samples, 31 patients with diffuse parenchymal lung disease met the inclusion criteria, while no patients with localized lung lesion were included (Figure 1). The distribution of the biopsies over time showed

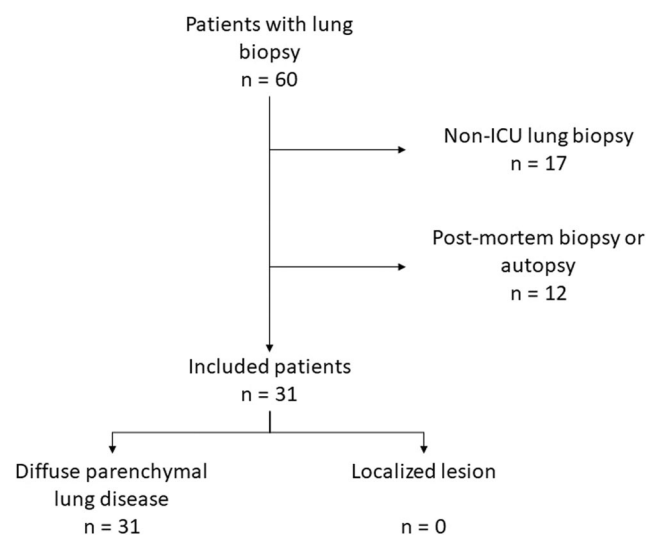


FIGURE 1 Flow chart of the study. Among 60 patients whose lung tissue was analyzed, 31 patients were included. A total of 29 patients were excluded because the lung biopsy performed outside of the NP-ICU (operating room; stable patients). We also excluded postmortem biopsies and autopsies.

that only one biopsy was performed before 2000, four were performed between 2000 and 2009 and 26 were performed since 2010.

The median age of the patients at the time of the biopsy was 18 days (extreme 2 days to 10.8 years). Among the patients, 21 (67.7%) were newborns. Only three patients (9.7%) were aged 2 years and older. The sex ratio was 1.8 boys per girl.

The main clinical characteristics of the patients are summarized in Table 1. Notably, neonatal respiratory distress was reported in 23 patients (85.2%) and pulmonary hypertension (PHT) was present in 26 (89.7%). At the time of the lung biopsy, the patients had been in the ICU for an average duration of 19.3 (\pm 24.9) days. All patients were under invasive mechanical ventilation, and 22 of them (70.9%) were receiving ECMO support, with 15 of those (55.6%) on veno-arterial ECMO. During the diagnostic work-up, the patients underwent various investigations. Half of the patients (13/26, 50%) had a thoracic CT-scan, which mostly revealed alveolar condensations (7/13), ground glass opacities (6/13), thickened interlobular septa (2/13), pneumothorax or pneumomediastinum (2/13), and enlarged pulmonary artery (2/13). A next generation sequencing (NGS) analysis of surfactant and alveolar proteinosis-related genes (Supporting Information: Data) was performed in 23/31 (74.2%) and PHT-related genes were tested in 8/23 (34.8%). This analysis revealed 9 patients with one or two disease-causing mutation in *ABCA3* (3/9), *SFTPB* (2/9), *NKX2-1* (1/9), *FOXF1* (2/9) and *TBX4* (1/9) (Table 2).

All lung biopsied were surgically performed in the PN-ICU under general anesthesia performed by the anesthesiologists. Out of the included patients, 2 (7%) underwent thorascopies, and 26 (93%) underwent thoracotomies, while the data for 3 patients were not available. In all the included patients, histopathological examination of the lung biopsies revealed the pattern of diffuse parenchymal lung diseases. Furthermore, an etiologic diagnosis could be proposed in 25 out of 31 (80%) patients. Among the 31 patients, the most frequent diagnosis was a diffuse developmental disorder of the lung, which was found in 15 patients (48%) (Figure 2). Out of these, 9 (29%) patients were diagnosed with alveolar capillary dysplasia (ACD), with or without misalignment of pulmonary veins, three (10%) had congenital alveolar dysplasia and one (3.3%) patient had acinar dysplasia (AcDys), while two patients had an unclassified diffuse developmental disorder of the lung. Other identified diagnoses were surfactant disorder pattern in 5 (16%) patients, pulmonary interstitial glycogenosis pattern in 3 (10%) patients, meconium aspiration in one patient (3.3%) and alveolar growth abnormalities related to bronchopulmonary dysplasia in one patient (3.3%). In 6 (19%) patients, the lung biopsy excluded previously mentioned diagnoses, confirming a diffuse ILD pattern but without a specific chILD etiology. Altogether, 4 (13%) patients had lung fibrosis on their biopsy, including one patient with a surfactant disorder related to a *SFTPB* homozygous mutation and three patients with undefined ILD. The diagnosis value of the lung biopsy was higher in newborns with 20 out of 21 patients (95%) receiving a diagnosis, compared to patients aged 1 month to 2 years, where 5 out of 7 patients (71%) received a diagnosis. In the

TABLE 1 Clinical characteristics and diagnosis work-up of the 31 patients at the time of the lung biopsy.

Main clinical characteristics	N	%, SD, [Q1–Q3]
Sex ratio boys/girls	20/11	1.82
Premature birth (<35 WG) ^a	5	18.5%
Post-term birth (>39 WG) ^a	7	25.9%
Neonatal respiratory distress ^a	23	85.2%
Median age at lung biopsy	18	[11.5–62.5]
<i>Medical condition at the time of the biopsy</i>		
Mean duration of ICU hospitalization	19.3	24.9
Patients under noninvasive ventilation	0	0%
Patients under invasive ventilation	31	100%
Mean duration of invasive ventilation	16.2	22.9
Patients under ECMO	22	70.9%
Mean duration of ECMO	10.5	6.6
Veno-arterial ECMO	15	48%
Pulmonary hypertension ^b	26	89.7%
Coagulation impairment ^c	8	42.1%
<i>Diagnosis work-up</i>		
Chest radiography ^d	25	100%
CT-scan ^e	13	50%
Median age at CT-scan	43	[22.25–50.25]
Bronchoalveolar lavage	5	-
Median age at BAL	25	[17–1233]
chILD NGS panel	23	74.2%
PHT NGS panel	8	34.8%

Note: Age and durations are expressed in days. Coagulation impairment were defined as: disseminated intravascular coagulation (thrombopenia, elevated D-dimer concentration, decreased fibrinogen concentration, and prolongation of clotting times such as prothrombin time) or isolated thrombopenia.

Abbreviations: BAL, bronchoalveolar lavage; chILD, childhood interstitial lung disease; ECMO, Extracorporeal Membrane Oxygenation; ICU, intensive care unit; n, number of cases; N, number of patients with available data; NGS, next generation sequencing; PHT, pulmonary hypertension; Q1–Q3, 1st and 3rd interquartile range; SD, standard deviation.

^aout of 27 patients with available data.

^bout of 29 patients with available data.

^cout of 19 patients with available data.

^dout of 25 patients with available data.

^eout of 26 patients with available data.

three patients aged over 2 years, the lung biopsy revealed an undefined pattern of ILD but did not provide a definite etiologic classification (diagnostic yield 89% in <2 years-old patients vs. none of the three patients over 2 years-old patients) (Figure 3). In infants below 1 year of age, the most frequent diagnosis was a diffuse

developmental disorder of the lung (median age 12 days at the time of the lung biopsy; range 2–86 days) and a surfactant disorder (median age 18 days at the time of the lung biopsy; range 12–137 days).

Following the lung biopsy, a change in therapeutic management occurred in 12/21 (57.1%) patients for whom information was available. Among these patients, corticosteroid treatment was initiated in four individuals. For the remaining eight patients (38.1%) with either a diffuse developmental disorder or a critically severe form of surfactant disorder, where no therapeutic options were available and no improvement was observed over time, an ethical multidisciplinary discussion led to provide palliative care.

Genetic analyses allowed the identification of pathogenic variants in 9/31 (29%) patients. Out of these, eight patients had a histologic diagnosis of either diffuse developmental disorder of the lung or a surfactant disorder. The genes involved in these cases are provided in Table 2. During follow-up, 21 (67.7%) patients died at a median age of 28 days [15–92] and after a mean duration of 23.5

(±51.1) days after the lung biopsy was performed. Their final etiological diagnosis revealed that 11 patients had a diffuse developmental disorder of the lung (*FOXF1*, $n = 2$; *TBX4*, $n = 1$, *NKX2-1*, $n = 1$), four patients had a surfactant disorder (*SFTPB*, $n = 2$; *ABCA3*, $n = 2$), one patient had bronchopulmonary dysplasia, one patient had a working diagnosis of pulmonary interstitial glycogenosis, and four patients had another unclassified ILD. It is worth noting that the results of the genetic analysis were available 3–11 days before the lung biopsy in only 5/31 patients, including two patients with identified mutations (*ABCA3*, *NKX2.2*). For all the other patients, the genetic results were available within an average of 55 days after the lung biopsy.

Nine (39.1%) patients suffered from complications directly related to lung biopsy (Table 3). The mean age at the time of the lung biopsy for patients with complications was 1.6 years, whereas it was 3 months for patients without complications. Notably, despite not reaching significance, the complications rate under ECMO was 8/22 (36%) while it was only 1/9 (11%) without ECMO support ($p = .22$). The majority of the complications (8/9, 88.9%) occurred in patients who were under ECMO support, with 7/8 (87.5%) experiencing a massive hemorrhage shock. Among the 22 patients under ECMO, the risk of hemorrhage was 32%, compared to 0% in patients under invasive ventilation only ($p = 0.08$). A longer duration of ECMO at the time of the biopsy (≥ 10 days) did not significantly increase the risk of complications ($n = 5$, 42% vs. $n = 3$, 30%, $p = 0.67$). Despite the small number of patients, there appeared to be a trend suggesting that a young age at the time of the lung biopsy (<2 year-old) was associated with a lower rate of hemorrhagic complications during the lung biopsy under ECMO (6/20, 30%). However, it is important to note that this finding is based on a limited number of cases. The type of surgery, whether thoracoscopy or thoracotomy, did not significantly affect the risk of complications during the lung biopsy procedure.

TABLE 2 Histologic diagnosis and correlation with the molecular defect.

Histologic diagnosis	Number of patients	Gene (number of patients)
Diffuse developmental disorder	4	<i>SFTPB</i> (bi-allelic) (1)
		<i>NKX2-1</i> (heterozygous) (1)
		<i>FOXF1</i> (heterozygous) (2)
Surfactant disorder	4	<i>ABCA3</i> (bi-allelic) (3)
		<i>TBX4</i> (bi-allelic) (1)
Unclassified ILD	1	<i>SFTPB</i> (bi-allelic) (1)

Abbreviation: ILD, interstitial lung disease.

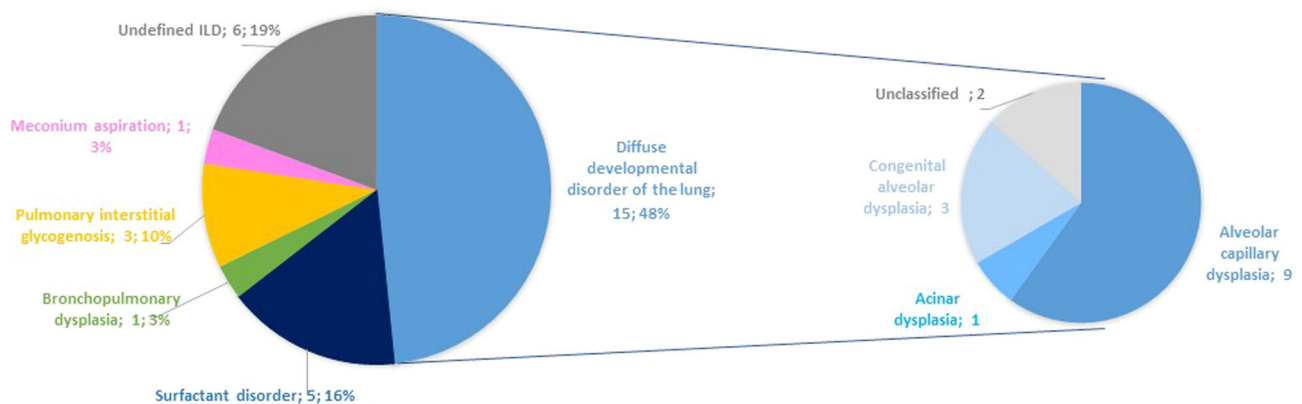


FIGURE 2 Diagnoses proposed after analysis of the lung biopsy samples. Half of the patients had a diagnosis of diffuse developmental disorder of the lung, most of them being alveolar capillary dysplasia. Surfactant disorder was the second most frequent suggested diagnosis followed by a pattern of pulmonary interstitial glycogenosis, meconium aspiration and alveolar growth abnormalities related to the bronchopulmonary dysplasia. Finally, in 6 (20%) patients, the lung biopsy could not ascertain a diagnosis. [Color figure can be viewed at wileyonlinelibrary.com]

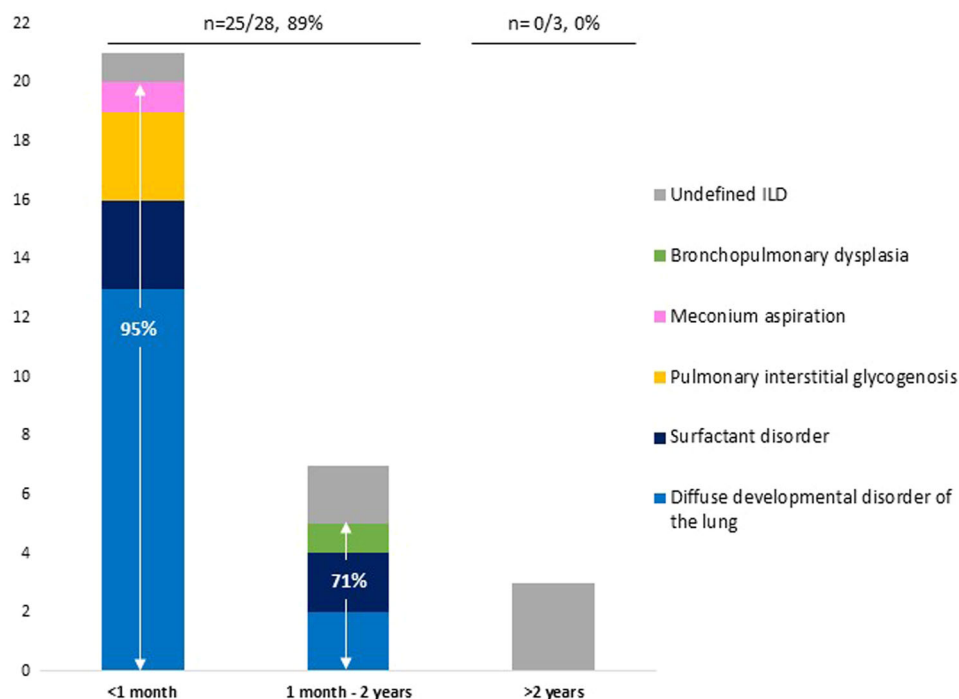


FIGURE 3 Reliability and repartition of the diagnoses by age at the lung biopsy. The age at lung biopsy seemed to be predictive of the diagnosis: in neonates (<1 month), 13 (65%) patients had a diffuse developmental disorder of the lung and 3 (15%) patients had a surfactant disorder. In this age group, the lung biopsy allowed to ascertain a diagnosis in 20/21 (95%) cases compared to 5/7 (71%) in the 1 month to 2 years group and 0/3 patients in the >2 years group. [Color figure can be viewed at [wileyonlinelibrary.com](https://onlinelibrary.wiley.com)]

4 | DISCUSSION

This study presents the outcomes of 31 lung biopsies performed under invasive ventilation in a single tertiary center PN-ICU. The results demonstrate that lung biopsy is highly valuable in terms of diagnostic yield, particularly in neonates, with a diagnostic rate of 95%. In line with previous studies, the main diagnoses identified were chILD, particularly diffuse developmental disorders of the lung and surfactant disorders.^{1,10} It is noteworthy that lung biopsy related complications occurred in only one patient who were not on ECMO, and the majority of patients who experienced complications were on ECMO, suggesting a superimposed adverse effect of ECMO on lung biopsy safety in patients in the ICU. Despite this, the study highlights that the lung biopsy was crucial in ascertaining fatal forms of congenital diseases in critically ill newborns.

In the past decades, lung biopsy was considered the last step of chILD diagnostic workup. However, it may not provide a definite diagnosis in a number of cases and needs to be correlated with clinical, imaging and genetic studies, leading to a final multi-disciplinary diagnosis.⁷

Recent advances in molecular genetics have prompted expert chILD groups like the American Thoracic Society (ATS) in the US and the Clinical Research Collaboration for Childhood interstitial lung diseases (CRC ChILD-EU) of the European Respiratory Society (ERS) in Europe to reevaluate the indication for lung biopsy. While they agree that both genetic test and lung biopsy may be conducted during chILD diagnostic

work-up, the timing between these explorations remains a topic of debate. It is now suggested that genetic analyses should precede the lung biopsy during chILD work-up.^{2,3,7} However, this approach faces challenges, particularly in critically ill patients in the ICU where the time required to obtain genetic results may not align with the patients' medical condition. Lung biopsy can offer a rapid diagnosis within a few days (usually 2–7 days in our center) whereas genetic tests often take longer (10 days for targeted Sanger sequencing to 3 months for NGS panel in our center) and their availability is highly variable in different country. In the present study, genetic analysis provided a defined diagnosis before the lung biopsy in only two patients with a surfactant disorder. Furthermore, genetic tests only provide answers in a portion of cases (9/21, 43% in this study) and do not eliminate the need for lung biopsy in all cases. Moreover, when a genetic variation is identified, its interpretation in terms of pathogenicity and prognosis may be challenging and the value of an investigation takes into account not only its ability to assess a definite diagnosis but also its impact in terms of management.

For example, *ABCA3* bi-allelic mutations' pathogenicity can range from fatal (null/null mutations) to less severe forms of the disease (null/hypo; hypo/hypo) with variations in individual expression of the diseases within a single family.^{11,12} For other than null/null mutations, early therapeutic intervention with corticosteroids, azithromycin and hydroxychloroquine may hold the potential to improve the prognosis. However, patients with null/null mutations may not respond to these treatments at all.^{13–15} Additionally, even for the same mutation, *NKX2-1*

TABLE 3 Complications after lung biopsy.

Complications	Total (n = 31)	Invasive ventilation only (n = 9)	ECMO (n = 22)	p	ECMO <10 days (n = 10)	ECMO ≥10 days (n = 12)	p	ECMO in <2 year-old patients (n = 20)	ECMO in ≥2 year-old patients (n = 2)	Thoracotomy (n = 26)	Thoracoscopy (n = 2)	p
Total	9 (29%)	1 (11%)	8 (36%)	0.22	3 (30%)	5 (42%)	0.67	6 (30%)	2	8 (31%)	1 (50%)	1
Hemorrhage	7 (23%)	0 (0%)	7 (32%)	0.88	2 (20%)	5 (42%)	0.38	4 (20%)	2	6 (23%)	1 (50%)	0.44
Thromboembolism	2 (6%)	0 (0%)	2 (9%)	1	0 (0%)	2 (17%)	0.48	1 (5%)	1	1 (4%)	1 (50%)	0.14
Pneumothorax	4 (13%)	1 (11%)	3 (14%)	1	2 (20%)	3 (25%)	1	4 (20%)	1	0 (0%)	1 (50%)	0.07
Infection	1 (3%)	0 (0%)	1 (5%)	1	0 (0%)	1 (8%)	1	1 (5%)	0	1 (4%)	0 (0%)	1
Death	2 (6%)	0 (0%)	2 (9%)	1	0 (0%)	2 (17%)	0.48	0 (0%)	2	1 (4%)	1 (50%)	0.14

Abbreviation: ECMO, Extracorporeal Membrane Oxygenation

and *TBX4* mutations are associated with extreme variations in phenotypes.^{16–20} *FOXF1*, mostly associated with fatal forms of ACD, has also been reported in patients with prolonged survival (with or without lung transplantation).^{21–24} Conversely, some mutations lead to a more homogeneous and unfavorable prognosis such as *SFTPB* mutations that are associated with fatal forms of chILD in newborns.^{25–27} In case where these genes are involved in newborns with severe initial respiratory distress requiring invasive ventilation, a poor outcome can be predicted with a high degree of confidence.

In critically ill newborns with refractory hypoxemia, particularly those with or without PHT under ECMO support, time is of essence and a diffuse developmental disorder of the lung has to be suspected.^{28,29} In this specific group of patients, genetic tests alone may not provide a prognosis in all cases and may offer less immediate value than the lung biopsy. Our study demonstrates that lung biopsy is a valuable tool in identifying fatal lung diseases, especially ACD, in a timely manner for most of these patients. While some reports have shown prolonged survival in less severe forms of the disease, there are currently no effective treatments for critically severe presentation in newborns. Some centers have used ECMO as a bridge to neonatal lung transplantation in cases of ACD and *SFTPB* surfactant disorders.^{30–32} However, not all institutions offer this procedure to newborns and when potentially fatal forms of neonatal lung disease are swiftly identified, multidisciplinary discussions may assess the potential for survival, with or without lung transplantation and determine if futile aggressive life-sustaining treatments should be withdrawn.⁸ Altogether, in neonates with critical conditions, both lung biopsy and genetic tests have their intrinsic advantages and limitations. It seems crucial to carry out both investigations within the first days of ECMO support to achieve two primary objectives: 1/obtain a prompt histological diagnosis of fatal/nonfatal lung disease and 2/specify the diagnosis to offer appropriate genetic counseling to the parents.

In patients beyond the neonatal period, the indication for lung biopsy need to be carefully considered in light of its potential diagnostic yield over different age groups. Consistent with findings from other studies such as one reporting 22 patients who underwent a lung biopsy under ECMO support, our study also confirms that the specific etiologic diagnostic reliability of the lung biopsy decreases with age.^{33,34} This could be attributed to the diversity and rarity of diseases observed in older children, but also to progressive fibrosing evolution of lung diseases with age that may contribute to less typical histological findings in older compared to conditions that are more commonly seen in neonates.^{1,10,35–37} Furthermore, a certain vagueness persists regarding the significance of certain patterns, such as pulmonary interstitial glycogenosis: while current chILD classifications include it as a separate entity, other authors consider pulmonary interstitial glycogenosis a marker of impaired lung maturity.³⁸ When discussing a lung biopsy, it is crucial to consider its expected value: not reaching an etiologic diagnosis can still have a significant therapeutic impact. For example, excluding certain fatal diagnoses or understanding the degree of inflammation or lung fibrosis is of major importance particularly in the context of promising results from novel anti-fibrosing therapies in children.³⁹

Complications of the lung biopsy were observed in 29% of the cases and an interesting finding was the link between the age at biopsy and the risk of complications. Patients with complications were older than patients without complications with a median age at lung biopsy of 1.6 years versus 3 months. Notably, the two oldest patients in the cohort (10.8 and 3.5 years old, respectively) experienced major hemorrhage complications following their lung biopsies. These results emphasize the importance of carefully evaluating the therapeutic impact of obtaining an etiological diagnosis in older children, balanced with the patient's clinical status, particularly with regard to vital functions and the risk of hemorrhage. Most of the complications were hemorrhage occurring under ECMO support. Pneumothorax was also a frequent complication, sometimes occurring simultaneously with hemothorax. In a limited series including 9 patients (11%), a study reported only one nonsevere bleeding complication.⁹ Similarly, two other studies including 9 and 25 patients under ECMO did not report severe hemorrhage. However, the interpretation of these results needs to consider the completeness of reporting such complications and the differences between the studied populations.^{6,8} ECMO is associated with coagulopathy and disseminated intravascular coagulation, which become more prevalent with the duration of ECMO support.^{40,41} The higher complication rate of lung biopsies performed after 10 days of ECMO likely reflects these coagulation disorders, which could be an argument for conducting the procedure earlier in the management of critically ill patients. Assessing the therapeutic impact of lung biopsies in this study proved to be challenging. It was moreover difficult to evaluate the individual benefit on the patient's management in this retrospective study. Although a management change was noted in 12 (57%) of the children following the lung biopsy, only a minority of cases (4/12 patients) aged 12–50 days resulted in a therapeutic change, with corticosteroid treatment being initiated. When the clinical and biopsy findings strongly suggest a surfactant disorder, immediate treatments with intravenous methylprednisolone pulses, azithromycin and possibly hydroxychloroquine should be initiated.³ However, in the few older children, the biopsy's impact on therapeutic management did not seem to be significant, and the benefit-risk balance might lean toward starting empirically corticosteroids without performing the biopsy.

The study has several additional limitations, mainly due to its retrospective design with biases in collecting data spanned a wide period from 1995 to 2022, and the low number of patients in the >2 years-old age group. Exclusion of patients due to a lack of data from older medical files and those who underwent lung biopsy at other centers for second opinions may have affected the generalizability of the results. Furthermore, attributing the reported deaths solely to the complications of the lung biopsy was difficult in most cases, as other factors such as the underlying disease, ECMO course, or other comorbidities might have contributed to the outcomes. Despite these limitations, the study gathered a valuable number of cases and constitutes one of the largest cohort series reported in this field.

In conclusion, lung biopsy proves to be a valuable diagnostic tool in critically ill neonates suspected of having a diffuse developmental disorder of the lung. However, in older children, the decision to perform a lung biopsy should be carefully considered, weighting the

potential benefits against the associated risks. The prospective evaluation of the complications of such procedure under ECMO, and particularly bleeding complications over 10 days of ECMO and in children over 2 year old remains to be ascertained. In conjunction with lung biopsy, genetic analyses can play a crucial role in confirming the diagnosis and providing valuable genetic counseling for families. A multidisciplinary approach is essential to guide the decision-making process, particularly in critically ill pediatric patients, to ensure accurate diagnosis and guide appropriate therapeutic management.

AUTHOR CONTRIBUTIONS

Yaël Levy, Lauren Bitton, and Nadia Nathan wrote the manuscript. Jérôme Rambaud, Yohan Soreze, Harriet Corvol, Pierre-Louis Leger, Chiara Sileo, Sabine Irtan, Hubert Ducou le Pointe, and Erik Hervieux contributed to the data analysis. Camille Louvrier contributed to the molecular diagnosis. Aurore Coulomb L'Herminé performed the histological analyses. Blandine Prévost performed the statistics. All authors reviewed the manuscript.

ACKNOWLEDGMENTS

We thank the French national networks for rare lung diseases: Centre de référence des maladies respiratoires rares (RespiRare), Centre de référence des maladies pulmonaires rares (OphaLung) and Filière de soins pour les maladies respiratoires rares (RespiFIL). The ILD cohort has been developed in collaboration with the Rare Disease Cohort (RaDiCo)-ILD project (ANR-10-COHO-0003), the Clinical research collaboration for chILD-EU and the COST Innovative Grant OpenILD CIG16125. Our work is supported by the Legs Poix from the Chancellerie des Universités (grant 2022 n° 2022000594).

CONFLICT OF INTEREST STATEMENT

The author declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Levy Y, Bitton L, Sileo C, et al. Lung biopsies in infants and children in critical care situation. *Pediatr Pulmonol*. 2024;1-8. doi:10.1002/ppul.26845