

Open lung biopsy in patients with respiratory failure

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Abstract

Open lung biopsy (OLB) is known as the gold standard for the definitive diagnosis of parenchymal lung diseases, whether they are acute or chronic and/or localized or diffused. It has high diagnostic yield over bronchoalveolar lavage and transbronchial needle biopsy. The use of OLB in non-intensive care unit (non-ICU) patients is considered a relatively safe technique, but its use in critically ill patients and ICU patients is a subject of argument. Methods: This paper reviews the English literature to evaluate the role of OLB in critically ill patients to determine its safety and outcomes. Twenty-two, original, published articles were found in the literature. Analysis of each study was done regarding indication for OLB, post-OLB management, complications and outcome. In conclusion OLB is a potentially safe procedure that could help to establish a diagnosis in patients with diffuse lung disease and respiratory failure. It may lead to significant changes in therapy but also, it carries the risk of complications. A large randomized study should be performed to determine the benefits, value, and outcomes of the employment of OLB in critically ill patients with undiagnosed respiratory failure.

Keywords: Open lung biopsy; mechanical ventilation; diffuse lung disease; bronchoalveolar lavage; transbronchial needle biopsy

INTRODUCTION

Open lung biopsy (OLB) is considered the gold standard method for definitive diagnosis of parenchymal lung diseases, whether they are acute or chronic and/or localized or diffused [1-4]. Precise diagnosis helps to establish a specific therapy that may be lifesaving [5]. Although there are other different diagnostic methods that could be used, such as bronchoalveolar lavage (BAL) and transbronchial needle biopsy (TBB), the OLB is still considered the best tool to diagnose parenchymal lung disease [3, 6]. A complete history, physical examination, chest radiography, and cultures will provide a reliable diagnosis in approximately 30% of patients [7, 8]. The diagnostic yield of fiberoptic bronchoscopy investigations ranges from 38% to 85% according to the classification

of histological findings [7-9]. In contrast, the reported diagnostic yield of OLB ranges from 80% to 94% [8, 9].

Nevertheless, despite recent advances in surgical techniques with the use of thoracoscopy, OLB is still considered an invasive procedure requiring general anesthesia and is associated with substantial morbidity and mortality [10-16]. The use of OLB in non-intensive care unit (ICU) patients is considered a relatively safe technique, but its use in critically ill patients and ICU patients is not well-studied and unclearly defined. The use of OLB is considered the last choice for diagnosis in mechanically ventilated patients and in those for whom empiric therapy for respiratory failure has been unsuccessful [17-19]. There is considerable controversy regarding the use of OLB in patients with respiratory failure and those on mechanical ventilation because of the potential high morbidity and mortality associated with its use [20, 21]. While the role of OLB has become well-established in the diagnosis of interstitial lung disease [18], its utility and safety are more controversial in critically ill patients. Proponents of OLB argue that solid diagnosis of underlying etiology can be helpful in determination of the best course of treatment [22]. Moreover, the risk of

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Received: 24 February 2020 Accepted: 15 March 2020

Table 1. Summary of the original published studies.

No.	Authors	Journal	Year	Country	No. of Patients
1	Nelems <i>et al.</i> [5]	Ann Thorac Surg	1976	Canada	28
2	Warner <i>et al.</i> [40]	Am Rev Respir Dis	1988	USA	80
3	Wagner <i>et al.</i> [2]	Am J Surg	1992	USA	12
4	Canver <i>et al.</i> [46]	J Cardiovasc Surg	1994	USA	27
5	Lachapelle <i>et al.</i> [44]	Can J Surg	1995	Canada	31
6	Hughes <i>et al.</i> [47]	Can Respir J	1997	Canada	27
7	Papazian <i>et al.</i> [49]	Anesthesiology	1998	France	36
8	Kramer <i>et al.</i> [57]	Ann Thorac Surg	1998	Israel	103
9	Flabouris <i>et al.</i> [8]	Chest	1999	Australia	24
10	Chuang <i>et al.</i> [45]	J intensive care Med	2003	Taiwan	17
11	Patel <i>et al.</i> [23]	Chest	2004	USA	57
12	Soh <i>et al.</i> [50]	J Formos Med Assoc	2005	Taiwan	32
13	Monteiro <i>et al.</i> [52]	Rev Port Pneumol	2005	Brazil	24
14	Kao <i>et al.</i> [43]	Crit Care	2006	Taiwan	41
15	Barbas <i>et al.</i> [38]	J Bras Pneumol	2006	Brazil	12
16	Cho <i>et al.</i> [20]	Ann Thorac Surg	2006	USA	53
17	Arabi <i>et al.</i> [39]	Med Sci Monit	2007	KSA	14
18	Lim <i>et al.</i> [4]	Crit Care	2007	South Korea	36
19	Papazian <i>et al.</i> [59]	Crit care Med	2007	France	100
20	Baumann <i>et al.</i> [24]	Surgery	2008	Germany	27
21	Charbonney <i>et al.</i> [51]	J crit care	2009	Switzerland	19
22	Melo <i>et al.</i> [41]	Rev Port Pneumol	2009	Portugal	19

complications from biopsy is low if adequate precautions are undertaken [23]. In contrast, opponents of OLB believe that defining the underlying mechanism of injury is largely academic and will not affect the treatment of those patients because of the lack of specific therapies for underlying etiologies of Adult Respiratory Distress Syndrome (ARDS) and respiratory failure due to infiltrative lung diseases [17].

This paper reviews the literature to evaluate the role of OLB in critically ill patients to determine its safety and outcomes. Twenty-two large, original, published articles were found in the literature. Table 1 summarizes the essential data for each study.

DIAGNOSTIC INSTRUMENTS IN RESPIRATORY FAILURE

Different diagnostic instruments are available for diagnosing the causes of respiratory failure of unknown origin associated with pulmonary infiltrates. Clinical, laboratory, and serologic data can help to reduce the number of possible differential diagnoses. Chest x-rays and Computed Tomography of the Chest (CT- Chest) is useful for detecting complications of mechanical ventilation, such as atelectasis or pneumothorax [24]. Additionally, CT chest scans help to determine biopsy location, especially in nodular lesions or non-diffuse lesions [24]. However, regarding the underlying pathology, these tests have a limited informative role [25, 26].

BAL samples and the use of a bronchoscopic protected specimen brush are reliable for identifying both the quality and quantity of bacterial pneumonia microorganisms present in lung segments [27]. However, positive BAL results for infection may be difficult to interpret. Identification of *Candida* species in BAL represents a diagnostic difficulty because it is difficult to differentiate colonization from infection [28]. Moreover, identification of Cytomegalovirus in BAL fluid may indicate infection

Table 2. Percentage of specific diagnoses and alterations in therapy based on OLB

Authors	Diagnosis (%)	Change in Therapy (%)
Nelems <i>et al.</i> [5]	96.0	Undetermined
Warner <i>et al.</i> [40]	66.0	70.0
Wagner <i>et al.</i> [2]	56.0	78.0
Canver <i>et al.</i> [46]	100.0	67.0
Lachapelle <i>et al.</i> [44]	68.0	59.0
Hughes <i>et al.</i> [47]	63.0	85.0
Papazian <i>et al.</i> [49]	59.0	91.7
Kramer <i>et al.</i> [57]	85.0	46.0
Flabouris <i>et al.</i> [8]	46.0	39.0
Chuang <i>et al.</i> [45]	47.0	65.0
Patel <i>et al.</i> [23]	60.0	60.0
Soh <i>et al.</i> [50]	53.1	46.9
Kao <i>et al.</i> [43]	44.0	73.0
Barbas <i>et al.</i> [38]	100.0	Undetermined
Cho <i>et al.</i> [20]	Undetermined	Undetermined
Arabi <i>et al.</i> [39]	100.0	98.0
Lim <i>et al.</i> [4]	68.0	64.0
Papazian <i>et al.</i> [59]	71.0	78.0
Baumann <i>et al.</i> [24]	70.4	81.5
Charbonney <i>et al.</i> [51]	68.0	89.0
Melo <i>et al.</i> [41]	95.0	74.0

Table 3. Type of access and method of determination site for OLB

Authors	Type of Access	Method
Nelems <i>et al.</i> [5]	Limited thoracotomy	Bx determined by radiology findings
Warner <i>et al.</i> [40]	Limited thoracotomy	Bx from the most involved site
Wagner <i>et al.</i> [2]	Limited antero-lateral thoracotomy	Multiple wedges from involved area
Canver <i>et al.</i> [46]	Thoracotomy	N/A
Lachapelle <i>et al.</i> [44]	Limited anterior thoracotomy	Multiple Bx (two wedges from two lobes excluding lingual & including normal & abnormal lung)
Hughes <i>et al.</i> [47]	Thoracotomy	N/A
Papazian <i>et al.</i> [49]	Lateral thoracotomy	Bx from the most involved site
Kramer <i>et al.</i> [57]	Short anterior thoracotomy at the 3 rd intercostals space	Bx site determined upon radiology results from one or two lobes
Flabouris <i>et al.</i> [8]	Anterior mini-thoracotomy	Bx site based on radiology ± lingula
Chuang <i>et al.</i> [45]	Limited thoracotomy	Bx from site of infiltration
Patel <i>et al.</i> [23]	Thoracotomy/thoracoscopy	N/A
Soh <i>et al.</i> [50]	Limited anterior thoracotomy/VATS	N/A
Kao <i>et al.</i> [43]	N/A	Bx site new and progressive lesion identified by CT or CXR
Barbas <i>et al.</i> [38]	Limited thoracotomy	Two samples taken
Cho <i>et al.</i> [20]	Standard anterolateral/lateral muscle. sparing thoracotomy/thoracoscopy	Bx taken from two different areas
Arabi <i>et al.</i> [39]	N/A	N/A
Lim <i>et al.</i> [4]	VATS/Anterior mini-thoracotomy	Multiple wedge Bx based on radiology findings
Papazian <i>et al.</i> [59]	Lateral thoracotomy	Bx from most involved site
Baumann <i>et al.</i> [24]	Antero-lateral mini-thoracotomy	Bx site based on radiology & intraoperative findings
Charbonney <i>et al.</i> [51]	Axillary-anterior incision	Bx from tip of lingula
Melo <i>et al.</i> [41]	Thoracotomy	Bx site based on radiology findings

Bx = Biopsy, VATS = Video-assisted thoracoscopic surgery, N/A = Not applicable, CXR = Chest X-ray

or disease [29].

The value of Trans-bronchial Needel Biopsy (TBB) is well-established in the diagnosis of pulmonary infiltrates in spontaneously breathing patients [30]. TBB can be performed with acceptable risk in patients on a mechanical ventilator; the risk of pneumothorax can reach up to 19% in ARDS patients [31-35]. The main drawback of TBB is the small size of the specimens, which limits their use for further microbiologic studies. When BAL and TBB fail to provide diagnosis in patients with respiratory failure, the clinician must weigh the risk of empiric therapy against that of OLB [24].

OLB AND SPECIFIC DIAGNOSES

A complete history, thorough physical examination, radiologic studies, sputum cytologic analysis, and cultures can provide a reliable diagnosis in approximately 30% of patients [36]. However, OLB has been found to have a higher specific diagnostic yield, reaching up to 100% [37-39]. In reviewing the literature, it was found that many authors documented that OLB is useful and safe. Moreover, it can provide a diagnosis that was not previously suspected. This could be of utmost value in the instillation of a new therapy or changing a previously established therapy [23]. Table 2 shows the percentages of specific histological diagnoses obtained after OLB in different studies. In the majority of these studies, more than 50% of patients

received a specific diagnosis. Moreover, the specific diagnostic yield was 100% in the studies conducted by Arabi *et al.* [39] and Barbaras *et al.* [38]. Specific diagnosis could consequently alter the treatment plans and therapy in these patients and hence their outcome. These alterations can include changes in drugs, such as antibiotics and/or corticosteroids. Changes can also include heparinization and the initiation and/or discontinuation of antineoplastic drugs [40]. In a study by Baumann *et al.* [24], two patients were considered for lung transplantation based on the results of the OLB.

In the 22 studies reviewed, it was found that the specific diagnostic yield following OLB ranged from 44% to 100%. It is difficult to explain this variation in the specific diagnostic yield between different studies. However, it could be related to the size of the sample. Moreover, it could be explained by the variation in classification of the specific diagnosis among the studies. Melo *et al.* [41] stated that the ideal size of the specimen should measure at least 3 cm from the largest point and should be obtained from more than one lobe [41, 42]. Thoracotomy is preferred over video-assisted thoracoscopic biopsy as it is swifter and there is no need to replace the orotracheal tube with a double lumen tube or any need for selective lung ventilation [41]. Furthermore, OLB could be performed in either the operating room or bedside in the ICU by an experienced thoracic surgeon. Kao *et al.* [43] recommended bedside OLB

Table 4. List of complications that were encountered with OLB

Complication	Study & Percentages		
Hemothorax & Bleeding	-Baumann <i>et al.</i> [24]; 3.7%	-Charbonney <i>et al.</i> [51]; 10.5%	-Hughes <i>et al.</i> [47]; 3.7%
	-Flabouris <i>et al.</i> [8]; 4.2%	-Kramer <i>et al.</i> [57]; 1%	-Papazian <i>et al.</i> 1998 [49]; 2.7%
	-Nelmes <i>et al.</i> [5]; 3.6%	-Warner <i>et al.</i> [40]; 1.3%	-Patel <i>et al.</i> [23]; 3.5%
Infection	-Kramer <i>et al.</i> [57]; 7%		
Wound infection	-Baumann <i>et al.</i> [24]; 7%	-Soh <i>et al.</i> [50]; 3.1%	
Empyema	-Soh <i>et al.</i> [50]; 3.1%	-Wagner <i>et al.</i> [2]; 2%	-Lachapelle <i>et al.</i> [44]; 3.2%
Pneumothorax	-Baumann <i>et al.</i> [24]; 33%	-Canver <i>et al.</i> [46]; 18%	-Charbonney <i>et al.</i> [51]; 10.5%
	-Hughes <i>et al.</i> [47]; 3.7%	-Kramer <i>et al.</i> [57]; 7%	-Papazian <i>et al.</i> 2007[60]; 2%
	-Nelmes <i>et al.</i> [5]; 6.3%	-Papazian <i>et al.</i> 1998 [49]; 2.7%	-Wagner <i>et al.</i> [2]; 2%
	-Warner <i>et al.</i> [40]; 70%		-Patel <i>et al.</i> [23]; 8.8%
Persistent air leak	-Arabi <i>et al.</i> [39]; 33%	-Baumann <i>et al.</i> [24]; 11%	-Canver <i>et al.</i> [46]; 55%
	-Charbonney <i>et al.</i> [51]; 5.3%	-Cho <i>et al.</i> [20]; 30.2%	-Flabouris <i>et al.</i> [8]; 17%
	-Lim <i>et al.</i> [3]; 42%	-Melo <i>et al.</i> [41]; 21%	-Nelmes <i>et al.</i> [5]; 7.1%
	-Patel <i>et al.</i> [23]; 3.8%	-Soh <i>et al.</i> [50]; 28.1%	-Hughes <i>et al.</i> [47]; 18.5%
Subcutaneous emphysema	Lachapelle <i>et al.</i> [44]; 16.1%		
Tension pneumothorax	-Patel <i>et al.</i> [23]; 1.3%		
Pneumomediastinum	-Nelmes <i>et al.</i> [5]; 7.1%		
Bronchopleural fistula	-Kramer <i>et al.</i> [57]; 1%		
	-Baumann <i>et al.</i> [24]; 3.7%	-Soh <i>et al.</i> [50]; 6.3%	-Barbas <i>et al.</i> [38]; 16.7%
Atelectasis	-Wagner <i>et al.</i> [2]; 8%		
Pleural collection	-Kramer <i>et al.</i> [57]; 2%		
Postoperative progressive hypoxemia	-Warner <i>et al.</i> [40]; 1.3%		
Intraoperative hypotension	-Canver <i>et al.</i> [46]; 18%		
	-Canver <i>et al.</i> [46]; 9%	-Flabouris <i>et al.</i> [8]; 4.2%	-Hughes <i>et al.</i> [47]; 3.7%
Intraoperative desaturation	Lim <i>et al.</i> [3]; 13.9%		
Acute renal failure	-Flabouris <i>et al.</i> [8]; 17.7%	-Hughes <i>et al.</i> [47]; 3.7%	
New dialysis	-Patel <i>et al.</i> [23]; 10.5%		
Myocardial infarction	-Patel <i>et al.</i> [23]; 1.8%		
Multi-organ failure	-Kao <i>et al.</i> [43]; 2.4%	-Hughes <i>et al.</i> [47]; 3.7%	-Warner <i>et al.</i> [40]; 2.5%
	-Chuang <i>et al.</i> [45]; 24%	-Kao <i>et al.</i> [43]; 24.4%	
Septic Shock	-Kao <i>et al.</i> [43]; 21.9%		
Hypovolumic shock	-Kao <i>et al.</i> [43]; 2.4%		
Prolonged Mechanical Ventilation	-Kramer <i>et al.</i> [57]; 8%		
Ventricular tachycardia			
Cerebral haemorrhage	-Lachapelle <i>et al.</i> [44]; 3.2%		
Respiratory failure	-Lachapelle <i>et al.</i> [44]; 3.2%		
Sepsis	-Lachapelle <i>et al.</i> [44]; 9.7%		
	-Lachapelle <i>et al.</i> [44]; 16.1%		

if FiO₂ levels reach 1 with an applied positive end-expiratory pressure (PEEP) of at least 12 cm H₂O. Table 3 shows both the method of access and how the site of OLB was determined in each study.

COMPLICATIONS FOLLOWING OLB

OLB is an invasive surgical procedure, but it is believed to be safe in patients who are not critically ill. Many authors have studied the outcome of OLB in critically ill patients or those who are supported by mechanical ventilation [8,39,44]. However, this procedure can have considerable complications that may result in death [44]. The various complications that have been encountered with OLB are listed in Table 4, and their rates are shown in Table 5. In

the reviewed studies, complication rates ranged from 0% to 56%. Arabi *et al.* [39] reported complications in 0% of cases, which can be explained by the retrospective nature of this study. Also, minor complication may have been encountered but not mentioned, as this study only considered major complications. Melo *et al.* [41] experienced a high percentage of complications that can be explained by the fact that all patients in this study were under mechanical ventilator support with high PEEP, which predisposes patients to prolonged air leakage. In general, the difference in complication rates between studies could be attributed to differences in patient populations and in the various definitions of complications. The most common reported complication in ventilated patients who underwent OLB was persistent air leak [8,

Table 5. Incidence of complications in the studies

Authors	Complications (%)
Nelems <i>et al.</i> [5]	17.9
Warner <i>et al.</i> [40]	19.0
Wagner <i>et al.</i> [2]	14.0
Canver <i>et al.</i> [46]	40.0
Lachapelle <i>et al.</i> [44]	19.0
Hughes <i>et al.</i> [47]	37.0
Papazian <i>et al.</i> [49]	8.0
Kramer <i>et al.</i> [57]	25.0
Flabouris <i>et al.</i> [8]	17.0
Chuang <i>et al.</i> [45]	24.0
Patel <i>et al.</i> [23]	39.0
Soh <i>et al.</i> [50]	40.6
Kao <i>et al.</i> [43]	20.0
Barbas <i>et al.</i> [38]	16.7
Cho <i>et al.</i> [20]	30.2
Arabi <i>et al.</i> [39]	0.0
Lim <i>et al.</i> [4]	56.0
Papazian <i>et al.</i> [59]	10.0
Baumann <i>et al.</i> [24]	52.0
Charbonney <i>et al.</i> [51]	25.0
Melo <i>et al.</i> [41]	21.0

Table 6. Survival and mortality following OLB

Authors	Mortality (%)
Nelems <i>et al.</i> [5]	57.0
Warner <i>et al.</i> [40]	70.0
Wagner <i>et al.</i> [2]	14.0
Canver <i>et al.</i> [46]	51.9
Lachapelle <i>et al.</i> [44]	58.1
Hughes <i>et al.</i> [47]	63.0
Papazian <i>et al.</i> [49]	50.0
Kramer <i>et al.</i> [57]	20.0
Flabouris <i>et al.</i> [8]	67.0
Chuang <i>et al.</i> [45]	59.0
Patel <i>et al.</i> [23]	53.0
Soh <i>et al.</i> [50]	57.0
Kao <i>et al.</i> [43]	51.0
Barbas <i>et al.</i> [38]	50.0
Cho <i>et al.</i> [20]	11.3
Arabi <i>et al.</i> [39]	57.0
Lim <i>et al.</i> [4]	50.0
Papazian <i>et al.</i> [59]	59.5
Baumann <i>et al.</i> [24]	48.2
Charbonney <i>et al.</i> [51]	89.0
Melo <i>et al.</i> [41]	47.0

^{23, 45-49]}. The incidence of persistent air leak following OLB reached up to 42%. Peak airway pressure (Ppeak) was the only documented factor to predict persistent air leak after OLB. Persistent air leak was found to be reduced by 42% for each 5 cm H2O reduction in Ppeak ^[41]. Other reported complications included bleeding ^[8, 23, 46-48], pneumothorax ^[8, 46, 47, 49], myocardial infarction ^[47], intraoperative cardiac arrest ^[23], acute renal failure ^[23], hypotension ^[46, 47], bronchopleural fistula, empyema, wound infection ^[50], and respiratory deterioration ^[46-48].

MORTALITY AND SURVIVAL AFTER OLB

Mortality rates ranged between 11.3% and 89.0%. The high mortality rate of 89.0% was reported by Charbonney *et al.* ^[51], who did not attribute this to the OLB procedure but rather to the multiple associated organ disorders in those patients and the severity of their organ damage. Many of the studies had a low associated mortality rate, even in patients on mechanical ventilation ^[4, 8, 23, 38, 39, 43, 46, 52]. Causes of death related to OLB included cardiac arrest ^[23], hemorrhage, and tension pneumothorax ^[8].

Some of the studies attributed the deaths to the primary disease or multiple organ failure ^[39, 41, 51]. In fact, it is difficult to attribute the death of a critically ill patient who may be on mechanical ventilation or have multi-organ failure to a single cause. Death in this category of patients is always multi-factorial. While OLB can be ruled out as directly causing death in critically ill patients, it cannot be excluded as playing an indirect role in these

deaths. Table 6 provides the mortality and survival rates following OLB that were documented in the reviewed studies.

EFFECT OF OLB ON TREATMENT PLAN

OLB can potentially result in a specific diagnosis in up to 100% of patients ^[39]. Table 2 shows the rate of specific diagnosis and changes in therapy in the reviewed studies based on OLB results.

Therapy alteration following OLB ranged up to 75 % ^[8, 39]. The high percentage of therapeutic changes that were made based on the results of biopsy procedures suggests that lung biopsy provides information that is useful to clinicians in decision making and hence in improving patient outcome. Wagner *et al.* ^[2] stated uncertainty as to whether the information provided by OLB is sufficiently beneficial to justify its routine use. While some of the previous studies showed improved survival in patients for whom biopsy established a specific diagnosis ^[53, 54], another failed to demonstrate any difference in mortality ^[55]. Several studies that included immunocompromised patients showed only a modest impact of OLB on clinical course and no difference in long-term survival ^[10, 11, 56, 57]. Although Potter *et al.* ^[58] stated that OLB-directed therapy may offer no advantage over empiric therapy directed at the most likely pathogens, Charbonney *et al.* ^[51] and Papazian *et al.* ^[59] found that OLB helped doctors to avoid further futile care in patients with terminal illness. In summary, OLB is of value in establishing a solid diagnosis and hence a clear plan of treatment. While there

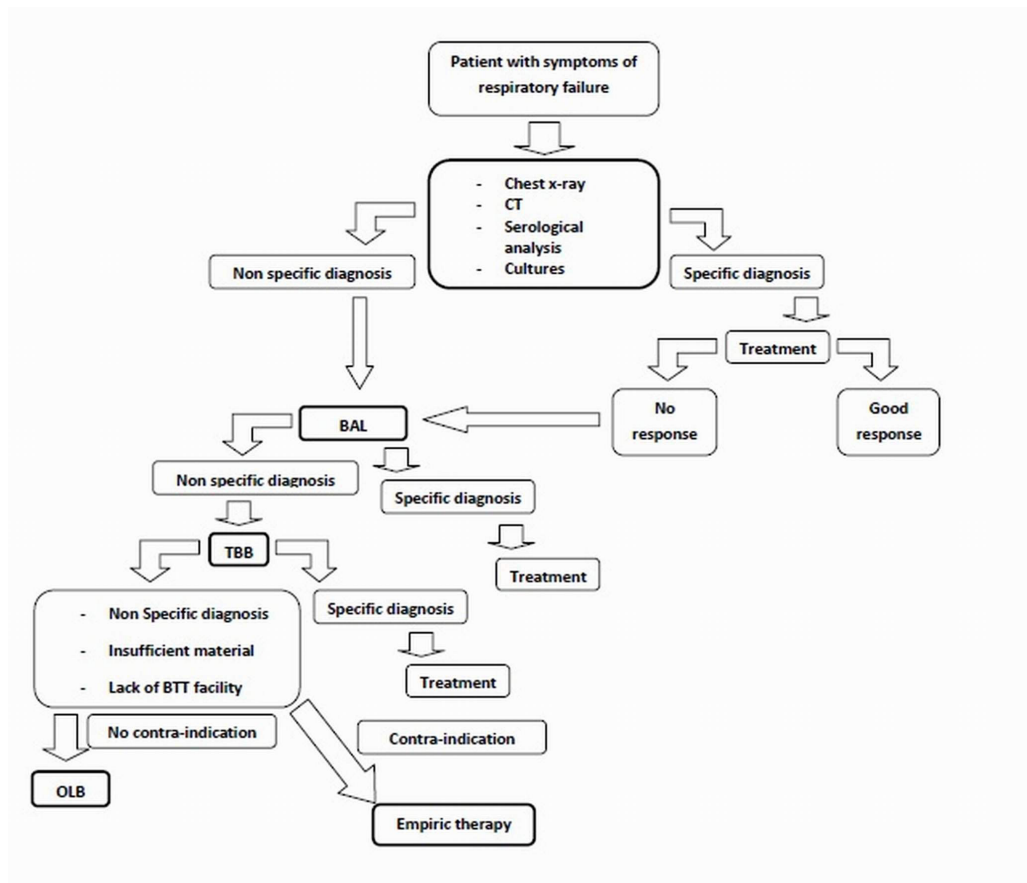


Figure 1. Algorithm for diagnosing patients with diffuse lung diseases and respiratory failure.

are some related complications, the most common complications have no or minor effects on outcome. Based on the literature review, we created a probable algorithm (Figure 1) that could be of value for determining if OLB should be used as a last choice to reach a diagnosis in critically ill patients after BAL and BTT trials. It should be noted that delay in diagnosis should be avoided, and these steps should be conducted in rapid sequence in order to reach a correct diagnosis and then to establish a proper treatment plan.

Conclusion

In conclusion, OLB is a potentially safe procedure that could help to establish a diagnosis in patients with diffuse lung disease and respiratory failure. It may lead to significant changes in therapy. Until now, the clinical or biomedical parameters that could predict those at high risk for complications following OLB were unknown. Further randomized clinical trials could be useful to clarify the benefits and drawbacks of OLB in critically ill patients.

DECLARATIONS

Authors' contributions

All authors have contributed equally in the manuscript.

Conflicts of interest

All authors declare that they are bound by confidentiality agreements that prevent them from disclosing their conflicts of interest in this work.

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