

Surgical lung biopsy in onco-hematological patients with diffuse pulmonary infiltrates and mechanical ventilation in the ICU

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Abstract. Among onco-hematological patients with acute respiratory failure (ARpF), surgical lung biopsy (SLB) could contribute to the medical management, by guiding initiation, maintenance or discontinuation of diagnostic and therapeutic interventions. The aim of the present study was to evaluate the results of SLB in these patients in an oncological center from a medium-income country, as well as analyze if this procedure is clinically useful in this context, and its impact on complications and mortality. This observational retrospective study analyzed onco-hematological patients with ARpF in the Intensive Care Unit (ICU) of a cancer center in southern Brazil between 2010-2016, who required mechanical ventilation and were submitted to open SLB. Among the studied population (n=17), the most commonly found etiology was infectious, present in ~50% of the biopsies, followed by unspecific inflammatory infiltrate acute respiratory distress syndrome and interstitial fibrosis, alveolar hemorrhage, neoplastic infiltrate and pulmonary embolism. Biopsy has led to a change of management in 63.3% of patients that were alive when results were available; however, 35% of patients succumbed prior to the pathological result. There was no requirement for re-operation or mortality attributable to the procedure. However, ICU mortality was elevated (88%). SLB in onco-hematological

patients mechanically ventilated in the ICU is a safe procedure with few severe complications and that contributes for diagnosis and management in the majority of cases. Due to the high mortality of this population, controlled trials may be required to establish its benefit in mortality and ICU outcomes.

Introduction

Associated to an increase in survival of cancer patients (1), in recent years it has been shown a reduction in mortality of oncological patients in the Intensive Care Unit (ICU) (2,3). Those patients, however, occupy 15% of all ICU beds, with significant costs (4,5). In the sub-population of onco-hematological patients, Acute Respiratory Failure (ARpF) is a common cause of ICU admission (6,7) and the strongest risk factor for mortality (8). The economic impact of ARpF, especially mechanical ventilation (MV), is enormous: Mean costs of hospitalization in patients with MV for more than 4 days exceeds US\$60,000 and, in prolonged VM (>21 days), \$200,000. Those expenses make up for 12% of hospital costs, in a total of \$27 billion dollars in the USA alone (9).

Common causes of ARpF in patients with hematological malignancy are infections (bacterial and opportunistic), acute pulmonary edema, alveolar hemorrhage, neoplastic infiltrate, chemotherapy adverse reactions, specific and unspecific inflammatory diseases, among other uncommon pathologies (10,11).

In these patients, surgical lung biopsy (SLB) can be performed when etiology has not been established by less invasive tests (cultures, serologies) and procedures [bronchoalveolar lavage (BAL), transbronchial biopsy] (12).

The aim of the present study was to evaluate open SLB as a diagnostic strategy in onco-hematological patients with ARpF without defined etiology, in MV, at the ICU. Specifically, we seek to understand what is the impact of the biopsy in medical management, what are the etiologies commonly found and what are the complications and outcomes of this group of patients submitted to this intervention.

Materials and methods

Study design and setting. Observational, retrospective study, based on analysis of databases, physical charts and electronic

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Abbreviations: APACHE, acute physiology and chronic health evaluation score; ARDS, acute respiratory distress syndrome; ARnF, acute renal failure; ARpF, acute respiratory failure; BMI, body mass index; BMT, bone marrow transplant; BOOP, bronchiolitis obliterans/organizing pneumonia; CHF, congestive heart failure; ICU, intensive care unit; MV, mechanical ventilation; PaO₂, pressure of arterial oxygen; PEEP, positive end-expiratory pressure; SLB, surgical lung biopsy; SD, standard deviation

Key words: hematology, neoplasms, biopsy, thoracic surgery, respiratory insufficiency, respiration, artificial, intensive care units

medical records of patients admitted to the ICU of a dedicated oncology hospital in southern Brazil. It is an 8 bed general ICU (medical and surgical) that assists almost exclusively oncological patients.

Patients admitted to the ICU between 2010 and 2016 were evaluated. Through databases, we selected all onco-hematological patients with ARpF and submitted to open SLB. We analyzed also physical charts to get further information regarding the realization of SLB, treatment plans before and after the biopsy, histopathology results, complications, and outcomes. The same pathologist (AGB) that performed the histological studies revised the microscope slides for this study.

Patients. Patients with onco-hematological disorders admitted to the general ICU from 2010 to 2016 with bilateral pulmonary infiltrates and ARpF, receiving MV, that underwent SLB during ICU stay. There were no exclusion criteria, except 2 patients whose data from physical charting and electronic medical records were scarce and insufficient. Based on these inclusion criteria, we analyze electronic medical records and paper (physical) charting of all 17 that met the criteria.

Definitions and variables. Onco-hematological disorders: Leukemias, lymphomas, multiple myeloma, bone marrow aplasia and chronic lymphoproliferative disorders.

ARpF: Was defined clinically by the assistant ICU team.

Acute Respiratory Distress Syndrome (ARDS): Was defined according to the Berlin Consensus Conference (13).

Acute Renal Failure (ARnF): Was defined according to the AKIN criteria (14).

Sepsis: Was defined according to Sepsis-3 criteria (15).

The diagnoses of comorbidities were made by the ICU and onco-hematology healthcare team, without pre-selected criteria for the study.

During ICU stay, the patients were treated according to the ICU's own protocols regarding mechanical ventilation and weaning, sedation, nutrition, as well as management of specific conditions such as infections, sepsis and choosing antibiotics.

SLB: Open technique was the only one performed at our study, using mini-thoracotomy access, done at the bedside or the operating room. It was performed by 2 thoracic surgeons and 1 oncological surgeon experienced in the procedure. The procedure, indications and their routines remained unchanged throughout the period relating to the collection of the study.

Statistical methods. A descriptive statistical analysis was performed and percentages expressed as frequency, mean and standard deviation. Data were compared using the Chi-square test and Statistica® 7.0 software (StatSoft, Inc., Tulsa, OK, USA). $P < 0.05$ was considered to indicate a statistically significant difference.

Ethical approval and Consent to participate. This study was conducted in accordance with the recommendations of Resolution 466/2012 of the Brazilian National Health Council. The project was approved by UNIOESTE (Western Paraná State University)'s Committee on Ethics in Research involving human beings. Due to the retrospective nature of this study the requirement for patient or the families' written informed consent was waived.

Results

The majority of the 17 patients submitted to SLB were young adults (mean: 33.8 years old-min=12; max=58) men (70.6%), without comorbidities (70.5%) and diagnosed with leukemia (53%) or lymphoma (41%). Most of them (88%) were submitted to chemotherapy recently. ICU admission cause was medical in all patients (no surgical cases), with mean MV time before biopsy of 2 days and total MV time of about 7 days. Immediately before the biopsy, these patients were being ventilated with high PEEP's (mean: 11 cmH₂O), frequently lightly thrombocytopenic (mean $99 \times 10^3/\text{mm}^3$), using vasoactive drugs and receiving several antibiotics (88% with 3 or more) with frequent covering of opportunistic infections-any antifungal in 70.5% of patients, antiviral in 41% or Trimethoprim-sulfamethoxazole in 41.2%. Most common comorbidities were Systemic Hypertension and Diabetes Mellitus (Table I).

The most commonly found etiology on histopathology was infectious (52.3%)-bacterial infections, Cytomegalovirus (CMV) pneumonitis, and *Pneumocystis jirovecii* pneumonia accounted for 17.6% of findings each. Unspecific inflammatory conditions were the second most common finding (ARDS and unspecific infiltrate), present in 29.5% of biopsies. Alveolar hemorrhage was shown in 3 biopsies (17.6%), neoplastic infiltrate in 2 (12%) and Pulmonary Embolism in 1 (6%) (Table II, and Figs. 1-5).

There were only minor complications related to the procedure, but no major or significative early complications (Table III).

Therapeutic modifications occurred in 41% of patients. However, it has to be considered that 35.3% patients died before the histology results were available. Thus, there were therapeutic modifications in 63.3% of patients whose biopsy's results were available before death. The most common therapeutic impact was changing in antibiotics-starting or stopping antibiotics (1 patient each), antivirals (2 patients) and antifungals (1 patient). In one patient it was started anticoagulation and in another chemotherapy was discontinued (Fig. 1).

The mean ICU length of stay was of 9.5 days, with high ICU and in-hospital mortality (88.2%). Approximately 1/3 (35.3%) of patients died before the availability of biopsy results.

Discussion

The indication for SLB in onco-hematological patients with ARpF is limited, according to the literature. Patients with ARpF of unknown etiology after less invasive tests, with clinical deterioration and BAL that is inconclusive, with low diagnostic yield or high risk of complications, are generally the circumstances in which this procedure is indicated by the literature (12,16-18).

In this present study, lung biopsy has evidenced a specific diagnosis in 70.5% of patients, similar to the 60-65% of previous studies (16-20). Infection was the most common finding (about 70% of biopsies), despite previous studies showing unspecific infiltrates (fibrosis, interstitial pneumonitis, ARDS) as the most prevalent biopsy finding, even though infections were still common (16-18). Among infections, the opportunistic ones were the most commonly found (52.8%) (16-20).

Table I. Characteristics and clinical course of patients submitted to SLB (n=17).

Characteristics	Value
Male sex, %	70.6%
Age, years, mean \pm SD	33.8 \pm 16.45
APACHE II admission, mean \pm SD	24.5 \pm 8.95
Type of neoplasm, %	
Solid	0
Onco-hematological	100
Multiple myeloma	0
Lymphoma	41
Leukemia	53
Others ^a	6
Other comorbidities ^a	29.5
CHF	6
DM	12
Other neoplasm (cured or not)	6
Others ^a	12
Previous oncological treatments, %	
Recent chemotherapy	88
Recent or previous radiotherapy	12
Recent or previous BMT	12
Cause of ICU admission, %	
Medical	100
Total MV, days, mean \pm SD	7.2 \pm 4.54
MV time before SLB, days \pm SD	2.1 \pm 2.8
Parameters immediately prior to SLB	
PEEP, cmH ₂ O, mean \pm SD	11.0 \pm 4.86
PaO ₂ /FiO ₂ , mean \pm SD	258.0 \pm 89.0
Norepinephrine dose, μ g/kg/min, mean \pm SD	0.4 \pm 0.57
Serum creatinine, mg/dl, mean \pm SD	1.3 \pm 0.60
Platelets, cells $\times 10^3$ /mm ³ , mean \pm SD	95.9 \pm 53.1
Use of antibiotics/antifungals/antivirals prior to SLB, %	
None	0
1-2 antibiotics/antifungals	12
≥ 3	88
Glycopeptides	88.2
Carbapenems	70.5
Amphotericin B or equinocandins	52.9
Trimethoprim-sulfamethoxazole	41.2
Gancyclovir	35.3
Polymyxin	17.6
Fluconazole	17.6
3rd - 4th generation cephalosporin	12
Aminoglycosides	12
Penicillin + penicillinase inhibitor	6
Acyclovir	6
Quinolones	0
Total ICU length of stay, days, mean \pm SD	9.5 \pm 5.68

Table I. Continued.

ICU mortality, %	88.2
Death prior to histopathology result	35.3
Hospital mortality, %	88.2

^aIncludes non-malignant hematological disorders, such as bone marrow aplasia (1 patient). APACHE, acute physiology and chronic health evaluation score; CHF, congestive heart failure; DM, diabetes mellitus; BMT, bone marrow transplant; MV, mechanical ventilation; PEEP, positive end-expiratory pressure; SLB, surgical lung biopsy.

Table II. Biopsy histopathological results (n=17).

No pathological findings	% ^a
CMV	17.6
ARDS	23.5
Bacterial pneumonia	17.6
Alveolar hemorrhage	17.6
<i>Pneumocystis jirovecii</i>	17.6
Neoplastic infiltrate	12
PE	6
Unspecific infiltrate	6
Others	0

^aThe total exceeds 100% as some patients had more than one biopsy diagnosis. CMV, cytomegalovirus; ARDS, acute respiratory distress syndrome; PE, pulmonary embolism.

Table III. Complications associated with the procedure (n=17).

Complications	Incidence, %
Hemoptysis, minor	0
Hemoptysis, major	0
Pneumothorax/broncho-pleural fistula	0
Minor bleeding from the thorax drain ^a	41
Major bleeding from the thorax drain ^b	9
Need to re-operation	0
Worsening of hypoxemia/need for increased ventilatory parameters	9

^aNo need for a blood transfusion; ^bRequired a blood transfusion, but there was no need to re-operate.

Previous studies have had inconsistent findings in terms of etiology prevalence. Infection was usually reported as the most common cause of ARpF in oncohematological patients. Among infections, bacterial and mixed are the most common previously reported etiologies. Opportunistic infections-such as fungal, viral and *P. jirovecii* are also frequently described (up to 30%). Non-infectious causes were less frequent, but very relevant management-wise-acute pulmonary edema (most incident non-infectious), alveolar hemorrhage, pulmonary

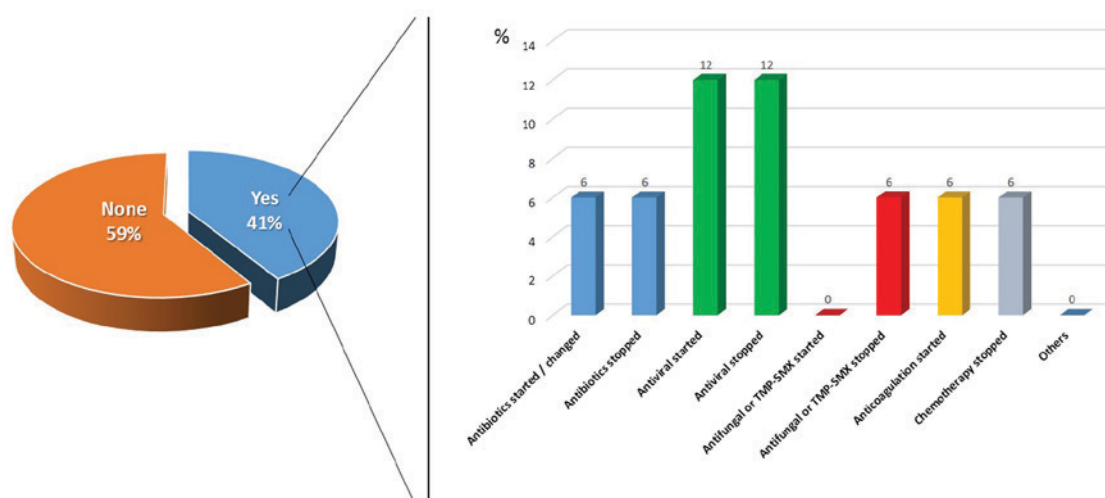


Figure 1. Therapeutic modifications following biopsy results (n=17). TMP-SMX, trimethoprim-sulfamethoxazole.

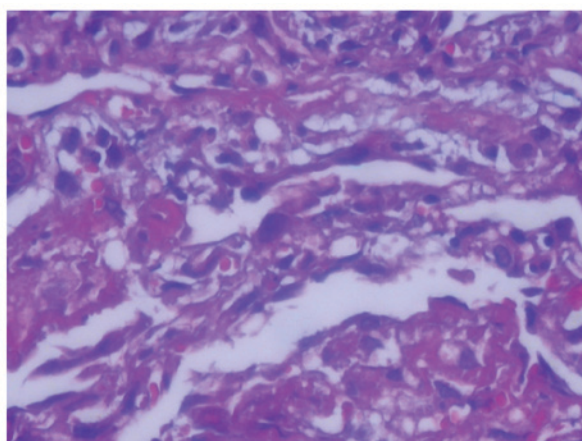


Figure 2. A 12 year-old female with lymphoma developing CMV pneumonitis. Biopsy slide OS-585554: Hematoxylin and eosin staining, magnification, x400. Pulmonary slide showing septa with lymphoid infiltrate, fibrinous material, with evidence in the center of the slide of a large endothelial cell with intense nuclear inclusion, rounded, condensed chromatin and poorly defined nuclear membrane, pressing the cytoplasm peripherally, characterizing a CMV infection. CMV, Cytomegalovirus.

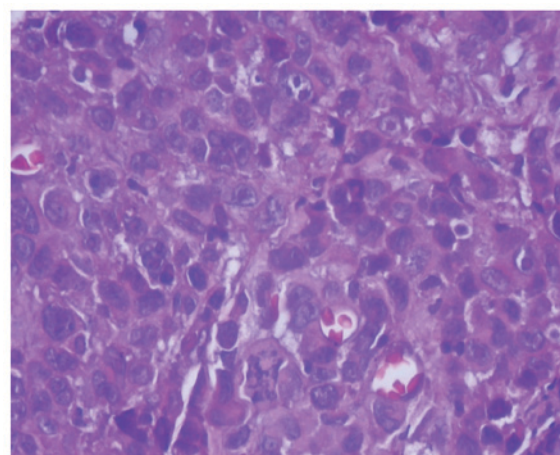


Figure 4. A 19 year-old male with Hodgkin's lymphoma, and lung infiltration by the disease. Biopsy slide OS-528700: Hematoxylin and eosin staining, magnification, x400. Pulmonary slide of an aggregate of atypical lymphoid cells, composed of large, bizarre, bi-nucleated nuclei that can be observed in the center of the figure. These cells also had central nucleoli and an evident, irregular, thickened nuclear membrane, with prominent and acidophilic cytoplasm, characteristic of Hodgkin's lymphoma, classical subtype.

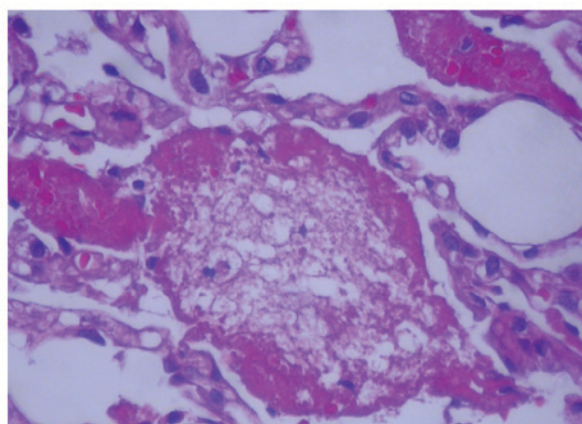


Figure 3. A 23 year-old male with acute leukemia developing *Pneumocystis jirovecii* Pneumonia. Biopsy slide OS-562073: Hematoxylin and eosin staining, magnification, x400. Pulmonary slide showing an alveolus partially hemorrhagic, filled by exudates of histiocytes with micro-vacuolated cytoplasm, cottonous and characteristics of *Pneumocystis jirovecii* infection.

embolism, TRALI, radiation pneumonitis, neoplastic infiltrate, Bronchiolitis obliterans/Organizing Pneumonia (BOOP) and chemotherapy-related adverse reactions (10,11).

In our study, fungal infections were uncommon (17.6%)-only 2 patients with *P. jirovecii* and none with Aspergillosis-, differently from other studies that have shown fungal infections as the most common and Aspergillosis as a frequent finding (17,18,20). A possible reason for no Aspergillosis findings is that we had few (two) patients that had underwent BMT, a population with a high incidence of that infection (21). Regardless of that, the high prevalence of antifungals and Trimethoprim-Sulfamethoxazole (70.5 and 41.2%, respectively) in our patients raised our attention as well. Other infectious causes, such as CMV and bacterial pneumonia, were found in our study and reported by previous literature with highly variable incidence. Unlike previous studies, we did not find any biopsy showing tuberculosis.

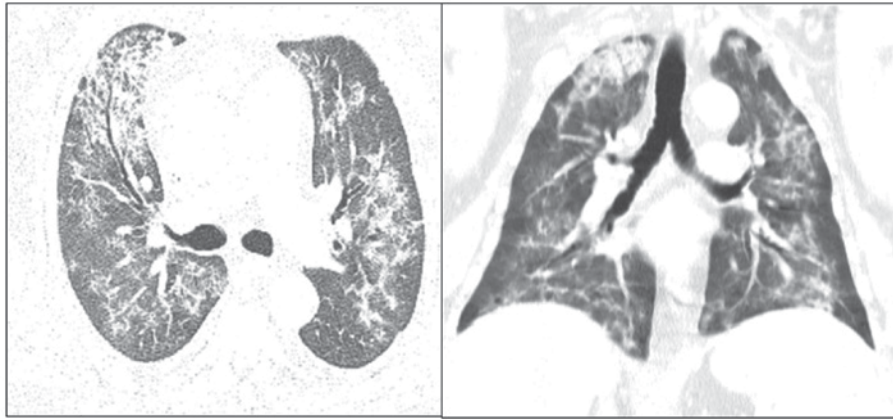


Figure 5. A 51 year-old male with multiple myeloma (post-autologous bone marrow transplant). Biopsy: Acute respiratory distress syndrome + alveolar hemorrhage. Chest computed tomography revealed heterogeneous bilateral pulmonary infiltrates, with a mosaic pattern.

Specific inflammatory findings, such as BOOP and granulomatous reactions were not found in our case series, even though they are reported as frequent in this patient group by the literature. Unspecific findings (ARDS and interstitial fibrosis) were found in 29.5% of biopsies, which is a similar prevalence to that of other studies (about 1/3). Alveolar hemorrhage was more prevalent (17.6%- 3 biopsies) in our study than reported previously. Neoplastic infiltrates, present in 2 biopsies (12%), was a frequent finding in the literature (16-20,22,23).

Therapeutic modifications can be defined as starting or stopping of therapeutic strategies or adoption of exclusive palliative care (therapeutic limitation). The rate of therapeutic modification due to the biopsy results was 41%, but, taking into account only the patients that were alive when the histopathological results were available, the rate was higher: 63.3%. This data corroborates previous findings, in which therapeutic modification was performed in 40-70% of patients, with specific diagnosis associated with lower mortality (16-20,22,23). Recently, studies on SLB in patients with pulmonary infiltrates and ARpF, in a population with 50% of immunocompromised patients (but not onco-hematological), has shown the importance of SLB in the diagnosis of potentially reversible diseases, particularly through the usage of high dose corticoids, and, consequentially, with the potential to lower mortality rate (22).

Gay *et al* (16) have studied necropsies of oncological patients with lung infiltrates, adding diagnostic accuracy. Unfortunately, due to cultural and organizational problems (especially due to low societal acceptance of necropsies), we do not have access in our institution to necropsies done for scientific purposes; thus, we could not compare our SLB findings with those of post-mortem histopathological study. Also in relation to the transbronchial biopsy it was not possible to make a comparison with the data of the patients submitted to SLB, since the majority of the patients had high levels of PEEP and several had coagulation disorders/thrombocytopenia, for which surgical procedure was considered the safest option, both to contain possible bleeding and to prevent arial fistulae.

However, it is necessary to outline that previous understanding of 'therapeutic modification' could underestimate the value of the SLB. Even in patients with unspecific findings, the information provided by the biopsy could have relevance in terms of avoiding further diagnostic and/or therapeutic

interventions that could have been pursued if there was no histopathological confirmation. Particularly, it could lead to the complete suspension of aggressive and 'heroic' efforts, allowing palliative and end-of-life care to provide dignity to the patients and family members. A relevant fact is that about one third of the patients died before the histopathological result. This denotes the high severity of the patients (since the histopathological result in our institution is available between 36-96 h on average), but also possibly a delay in indicating and performing the procedure. In any case, the authors intentionally kept these patients, not only by the number of patients, but also to demonstrate a 'real life' situation (even if with non-ideal results).

In relation to SLB complications, in our study, no death occurred during the biopsy or that had been directly attributed to the procedure—for example, due to hemorrhagic shock or pneumothorax. Several authors had not reported, as well, attributable deaths to SLB, however, there has been literature reports of need for reoperation and increased time of MV (16-19,22). There was no report in our study of pneumothorax and a very low incidence of major hemorrhages. No patient needed reoperation. Previous studies have shown 10-20% of complication in this population, and recently published study (in a non-oncological population) evidenced 12% of minor complications. Most commonly reported complications are bleeding and pneumothorax (including bronchopleural fistula), but there is also the chance of worsening respiratory failure and need to MV (in non-mechanically ventilated patients). In our study all patients were in MV already (16-19,22). It should be emphasized, however, that due to the high mortality and intrinsic severity of the patients, possibly early or late unrecognized complications (such as worsening respiratory function or secondary infections) could have occurred, even if not recognized as secondary to the procedure itself.

Another question that warrants further analyzes is the impact of SLB in mortality. In our study, we found a mortality rate of almost 90% (no deaths were directly attributable to the procedure or its complications), higher than previously reported (18-45%). Nevertheless, it is relevant to outline that in our study all the patients were in MV with high PEEP levels, which denotes higher severity and mortality (16-20,22,23).

Even though the authors could not correlate performing SLB and mortality, this was higher than previously reported (16-18). We believe that the high mortality we found could be secondary to several factors, such as: 1) Higher illness severity when compared to previous SLB population-which had a share of non-intubated patients. In our sample, all patients were intubated, most on high dose vasopressors and high PEEP levels. 2) The characteristics and eventual deficiencies in treatment and management. It has been shown, for example, that sepsis and ARDS patients in low to mid-income countries have worst outcomes than in high-income countries (24-26).

This study has several limitations that preclude the eventual generalization of its findings. It was a single center study, which makes the sample size (n) relatively small, but in line with the size of previous studies. This reduced size of the sample could justify the incidence of diseases (such as the lack of patients with tuberculosis) or even the low incidence of complications. Besides, for its local characteristics and possibly for a common limitation in developing countries, there was a paucity of less invasive procedures (such as BAL and serological tests in determined situations), and without performing necropsies in deceased patients (for eventual comparison), due to unavailability and/or high associated costs. However, this limitation puts it closer to the reality of developing countries. In addition to it, its design, a retrospective, observational, the reliability of data can be affected by the absence of previous uniformization of concepts to their registry, in addition to possibly time-related diagnosis and management changes (although the authors did not detect significant changes in the medical records evaluation). Also, it cannot establish the impact of the intervention (SLB) in morbidity and mortality, due to its design (observational, non-interventionist). Despite that, the goal of this study was to evaluate the 'real life' of an oncology ICU in a developing country, being appropriate for this objective.

Onco-hematological patients submitted to SLB in the ICU had an infectious process, mainly opportunistic, as the most common biopsy finding, followed by unspecific infiltrate. Therapeutic modification could be made in one third of the patients. However, hospital mortality in these patients was very high, possibly due to their illness severity. SLB helps the therapeutic management of these patients with few complications related to the intervention.

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Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Author's contributions

EMC and PADD designed the study, collected and analyzed the data, and wrote the manuscript. AGB, DAP, ADC and RCS

analyzed the data, wrote the manuscript and reviewed the manuscript. All the authors read and approved the final manuscript.

Ethical approval and consent to participate

This study was conducted in accordance with the recommendations of Resolution 466/2012 of the Brazilian National Health Council. The project was approved by Universidade Estadual do Oeste do Paraná Committee on Ethics in Research involving human beings (Cascavel, Brazil). Due to the retrospective nature of the study the requirement for patients' written informed consent was waived.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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