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ORIGINAL ARTICLE

Autopsy findings in patients with acute myeloid leukemia and non-Hodgkin lymphoma in the modern era: a focus on lung pathology and acute respiratory failure

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Abstract

We aimed to report autopsy findings in patients with acute myeloid leukemia (AML) and non-Hodgkin lymphoma (NHL) in the modern era, and also to focus on lung pathology in the subgroup of patients with acute respiratory failure (ARF) of unknown etiology, which is associated with especially high mortality rates. Charts and autopsy reports of 107 patients (59 AML and 48 NHL) autopsied between 2003 and 2018 were reviewed. More than 50% of patients had missed major diagnoses found at autopsy with 95% of lungs displaying abnormal findings. Malignant infiltration in at least one organ was observed in about 70% of patients with either no complete remission or relapse at the time of death ($n = 92$) versus 20% in patients without signs of active malignancy ($n = 15$) ($p = 0.001$). In patients with ARF of unknown etiology ($n = 59$), the proportion of malignant lung infiltration was 27% and equilibrated with bacterial pneumonias (29%), fungal pneumonias represented 8%, and isolated alveolar damage or pulmonary edema were the only findings in 32% of patients. Overall, 85% of patients with ARF of unknown etiology had either relapsed or not achieved remission at time of death and 80% of patients with malignant lung infiltration had ARF of unknown etiology. Ninety percent of malignant infiltration and fungal infections were observed in patients with no complete remission or relapse. Autopsy remains valuable in AML and NHL patients; besides infections, malignant infiltration is a significant contributor to ARF of unknown etiology and is rarely diagnosed ante mortem.

Keywords Acute myeloid leukemia · Non-Hodgkin lymphoma · Autopsy · Acute respiratory failure · Lung pathology

Introduction

In immunocompromised patients with hematological malignancies, acute respiratory failure (ARF) is a leading cause for ICU admission [1] and is associated with mortality rates as high as 60% [2]. The most frequent etiologies of acute respiratory failure are bacterial infections, viral or opportunistic infections, followed by disease-related infiltrates and cardiogenic pulmonary edema [3]. Documenting an ARF etiology is challenging and requires thorough, comprehensive testing, either invasive (bronchoscopy and bronchoalveolar lavage) or non-invasive, using a checklist of tests as proposed by Azoulay et al. [4]. The non-invasive approach has proven to be non-inferior to invasive testing [4]; however, what several studies have shown is that the lack of etiological diagnosis is associated with increased mortality [2, 3], emphasizing the importance of efforts aimed at finding a cause for ARF. Whether patients with ARF of unknown etiology die from non-documented infections, malignant lung infiltration, or other process (thrombo-embolic, cardiogenic pulmonary edema) remains unknown, but is crucial to understand in order to potentially improve survival.

This question is particularly relevant in patients with hematological malignancies with a high potential for organ invasion, like acute myeloid leukemia (AML) and non-Hodgkin lymphoma (NHL), who are also often profoundly immunocompromised and prone to infectious complications.

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Regarding AML, autopsy studies have documented extramedullary leukemic involvement in about 40% of cases in the 1980s [5, 6], down from 90% in the 1960s [6]. Lung was frequently involved in these studies, but no information linking lung pathology to premortem respiratory status was provided. Regarding lymphoma, despite numerous autopsy case reports in the literature, there is no large series of patients reporting lung pathology. Moreover, most published studies were performed before major therapeutic and diagnostic advances in AML and NHL, for instance prior to the wide implementation of "7 + 3" chemotherapy for AML [7]. Whether extramedullary malignant infiltration, and especially lung involvement, still accounts for acute respiratory failure and death in AML and NHL patients as opposed to infectious complications or other processes remains unknown.

Therefore, the objective of this study was to provide a description of autopsy findings in the modern era for AML and NHL patients, focusing on cause of death and lung pathology in patients with acute respiratory failure.

Methods

This retrospective study was approved by the Pennsylvania State University Institutional Review Board (numbers 374 and 5590) and informed consent was waived due to the retrospective design of data collection. All patients with a diagnosis of AML or NHL who had an autopsy performed between 2003 (2005 for NHL patients) and April 2018 were included. All charts were reviewed by a pulmonary and critical care physician with experience in the management of critically ill immunocompromised patients (AV), and the following data were collected: age, gender, chronic tobacco or alcohol abuse, main comorbidities (chronic obstructive pulmonary disease (COPD), congestive heart failure (CHF), coronary artery disease (CAD), hypertension, diabetes, chronic kidney, liver or neurological disease, previous thromboembolic event or solid tumor), types of AML (French American British (FAB) classification) or NHL (with stage according to Ann Arbor classification), chemotherapy or hematopoietic stem cell transplant (HSCT) received, achievement of remission, relapse diagnosis. For the hospital admission leading to death, length of stay, main clinical findings (including acute hypoxic respiratory failure and encephalopathy), administration of steroids, chemotherapy, antibiotics, antivirals or antifungals, intensive care unit (ICU) admission, and length of stay were collected. Acute hypoxic respiratory failure was defined by the presence of clinical signs of respiratory distress (dyspnea, tachypnea, labored breathing) associated with documented hypoxemia (SpO2 < 90% or PaO2 < 60 mmHg on room air) or oxygen requirement > 4 l/min. Diagnostic work-up including chest X-rays and computed tomography, echocardiogram, fiberoptic bronchoscopy with bronchoalveolar lavage (BAL), and results of infectious tests were reviewed. Vital organ support with vasopressors, mechanical ventilation, and renal replacement therapy was recorded along with the presence of neutropenia (defined by an absolute neutrophil count < 500/mm^3), coagulopathy and graft versus host disease (GVHD). Presumed cause of death and whether it was formally documented was recorded.

Consent for autopsies was obtained from the legal next-of-kin of deceased patients and autopsies included gross and histopathologic examination of all internal organs and the brain, except in cases of restrictions requested by the family. Discrepancies between ante mortem and autopsy diagnoses were classified according to the Goldman criteria [8]: class I and II are missed major diagnoses with and without potential impact on survival and ante mortem management respectively, class III are missed minor diagnoses related to terminal disease but not to the cause of death, class IV are other missed minor diagnoses.

Statistical analysis

Data were analyzed using r statistical package (https://www.R-project.org/) and are presented as median (inter-quartile range) for quantitative variables and number (percentage) for categorical variables respectively. Continuous and categorical variables were compared between groups with the Wilcoxon rank sum test and Fisher's exact test respectively. All tests were two-sided with $p < 0.05$ being considered for statistical significance.

Results

During the study period, the average autopsy rate at our institution was 9% (range 7–13% annually). We included 107 patients (59 AML and 48 NHL), their main characteristics are detailed in Table 1. Overall, about a third of the patients had HSCT and 85% had either not achieved complete remission or had clinical suspicion for relapse at the time of admission, 85% had acute respiratory failure and required ICU admission. About 60% of patients had a documented infection during their admission, but the cause of ARF was formally documented for only a third of patients.

Missed clinical diagnoses

Figure 1 displays the autopsy results according to Goldman classification: about 60% of AML and 50% of NHL patients had major diagnoses missed before autopsy, and perfect diagnoses concordance was observed in only 3% and 17% of AML and NHL patients respectively. Class I missed major diagnoses were acute myocardial infarction ($n = 3$), severe congestive heart failure ($n = 2$), acute pulmonary embolism

Table 1 Main characteristics of the 59 AML and 48 NHL patients who had autopsy performed

	AML ($n = 59$)	NHL ($n = 48$)
Age (years)	56 (45–64)	58 (44–68)
Gender (M/F)	31/28	28/20
Smoking, *n* (%)	25 (46)	13 (31)
Alcohol abuse, *n* (%)	9 (17)	5 (12)
COPD, *n* (%)	4 (7)	4 (8)
CAD, *n* (%)	5 (9)	3 (6)
CHF, *n* (%)	5 (9)	2 (4)
Hypertension, *n* (%)	19 (32)	19 (40)
Chronic liver disease, *n* (%)	0 (0)	3 (6)
Chronic kidney disease, *n* (%)	1 (2)	4 (8)
Diabetes, *n* (%)	9 (16)	9 (19)
Thromboembolic disease, *n* (%)	6 (10)	6 (13)
Neurological disease, *n* (%)	2 (3)	3 (6)
Cancer, *n* (%)	9 (16)	7 (15)
FAB 3, *n* (%)	7 (12)	–
FAB 4/5, *n* (%)	11 (19)	
Stage 1/2/3/4 (%)	–	10/7/0/83
Type (%):		
- DLBCL	–	44
- T cell	–	8
- Follicular	–	6
- Mantle cell	–	6
- Mediastinal	–	4
- Other	–	32
CR achieved, *n* (%)	22 (38)	19 (40)
HSCT, *n* (%)	19 (33)	15 (31)
Relapse, *n* (%)	17 (29)	12 (25)
ICU admission, *n* (%)	53 (90)	39 (81)
Acute respiratory failure, *n* (%)	50 (85)	42 (88)
Chest computed tomography, *n* (%)	36 (61)	30 (63)
Echocardiogram, *n* (%)	39 (66)	28 (58)
Bronchoscopy with BAL, *n* (%)	12 (20)	9 (19)
Infection documented, *n* (%)	36 (62)	27 (60)
ARF cause identified, *n* (%)	18 (31)	13 (27)
Mechanical ventilation, *n* (%)	49 (83)	37 (77)
Vasopressors, *n* (%)	41 (70)	34 (74)
Coma, *n* (%)	23 (39)	25 (52)
Renal replacement therapy, *n* (%)	7 (12)	18 (38)
Antibiotics administered, *n* (%)	55 (97)	45 (96)
Antifungals administered, *n* (%)	42 (79)	31 (78)
Antivirals administered, *n* (%)	29 (56)	20 (49)
Neutropenia, *n* (%)	32 (54)	18 (38)
Steroids administered, *n* (%)	32 (62)	31 (72)
Chemotherapy administered, *n* (%)	21 (36)	11 (23)
DIC/coagulopathy, *n* (%)	27 (46)	24 (52)
GVHD, *n* (%)	10 (17)	9 (19)
Code status (full/DNR-DNI/comfort) (%)	51/7/42	23/2/75

COPD chronic obstructive pulmonary disease, *CAD* coronary artery disease, *CHF* congestive heart failure, *FAB* French-American-British classification, *DLBCL* diffuse large B cell lymphoma, *CR* complete remission, *HSCT* hematopoietic stem cell transplant, *ICU* intensive care unit, *BAL* bronchoalveolar lavage, *DIC* disseminated intravascular coagulation, *GVHD* graft versus host disease, *DNR-DNI* do not resuscitate-do not intubate

($n = 2$), recurrence of lymphoma ($n = 5$), bacterial infections ($n = 7$, 6 pneumonias and 1 endocarditis), fungal infections ($n = 4$, 2 invasive pulmonary aspergillosis, 1 invasive fungal infection, 1 cerebral mucormycosis), hematophagocytic lymphohistiocytosis ($n = 1$), severe brain edema ($n = 1$), adrenal insufficiency due to massive adrenal lymphomatous involvement ($n = 1$), diffuse alveolar hemorrhage ($n = 1$), and systemic ANCA negative vasculitis ($n = 1$).

Pathology results by organ

Figure 2 displays the rate of abnormal autopsy findings by organ: except for the skin, more than 50% of organs had abnormal lesions on pathology, the rate reaching almost 100% for the lungs.

The central nervous system (CNS) lesions observed were hemorrhage ($n = 18$), leukemic ($n = 11$) or lymphomatous ($n = 10$) infiltration, hypoxic-ischemic injury ($n = 19$), arteriosclerosis ($n = 4$), cerebral edema ($n = 3$), ischemic stroke ($n = 2$), fungal abscesses ($n = 1$), aspergillosis ($n = 2$), mucormycosis ($n = 1$), necrotizing multifocal leukoencephalopathy ($n = 1$), and cavernous hemangioma ($n = 1$).

Main cardiovascular lesions were pericardial effusion ($n = 45$), coronary artery disease ($n = 43$), cardiac hypertrophy ($n = 31$), dilated cardiomyopathy ($n = 12$), acute myocardial infarction ($n = 5$), leukemic ($n = 11$) or lymphomatous ($n = 5$) infiltration, fungal abscesses ($n = 2$), endocarditis ($n = 1$), intracardiac thrombus ($n = 4$), and aortic dissection ($n = 1$).

Pathological lung lesions observed were bacterial pneumonia (about 30%), followed by malignant infiltration (20–25%), fungal pneumonia (10–15%) and thromboembolic events (10–15%). Isolated diffuse alveolar damage and pulmonary edema were observed in about 15% of patients each. Some degree of lung fibrosis was observed in 8 patients (7 of whom with ARF), either focal ($n = 2$) or diffuse ($n = 6$), but none of these cases was associated with malignant lung infiltration; the presumed causes of fibrosis were previous radiation therapy ($n = 3$) or chronic lung disease ($n = 2$), busulfan toxicity ($n = 2$), and idiopathic pneumonia syndrome post HSCT ($n = 1$). In one case of presumed busulfan toxicity, lung fibrosis was considered as the direct cause of ARF. Figure 3 displays a few examples of pathological lung lesions observed in patients with AML or NHL.

Liver lesions were hepatomegaly ($n = 26$), leukemic ($n = 16$) or lymphomatous ($n = 18$) infiltration, focal or diffuse centrilobular necrosis ($n = 18$), steatosis ($n = 10$), GVHD ($n = 2$), candida ($n = 2$) or aspergillus ($n = 2$) infections, hemosiderosis ($n = 4$), and veno-occlusive disease ($n = 2$).

Gastrointestinal findings were mostly ascites ($n = 35$), followed by gastrointestinal tract petechiae/hemorrhage ($n = 16$), ulcerations ($n = 12$), colitis ($n = 13$), candida ($n = 4$), aspergillus ($n = 1$) and mucormycetes ($n = 1$) infection, leukemic ($n = 8$) or lymphomatous ($n = 7$) infiltration, esophagitis/gastritis ($n = 6$), and acute pancreatitis ($n = 9$).

Pathological findings of the hematopoietic system are not detailed as they were almost exclusively infiltration of the bone marrow, lymph node or spleen by underlying

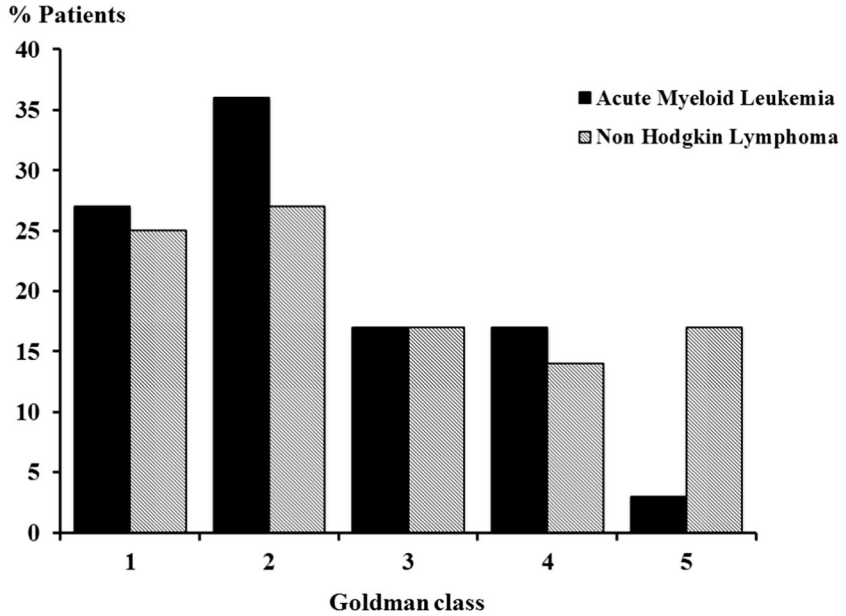

Fig. 1 Concordance between clinical and autopsy diagnoses according to the Goldman classification in 107 AML and NHL patients. Percentage of patients in each Goldman class is represented for AML and NHL. Goldman criteria: class 1, missed major diagnosis with potential adverse impact on survival and that would have changed management; class 2, missed major diagnosis with no potential impact on survival and that would not have changed therapy; class 3, missed minor diagnosis related to terminal disease but not related to the cause of death; class 4, other missed minor diagnosis; class 5, perfect concordance between premortem clinical diagnoses and autopsy diagnoses

malignancy, except for 3 patients with spleen fungal abscesses and 1 with spleen aspergillosis.

Finally, the most frequent genitourinary findings were acute tubular necrosis ($n = 17$), leukemic ($n = 9$) or lymphomatous ($n = 14$) infiltration, renal cell carcinoma ($n = 4$), bacterial abscesses ($n = 3$), fungal abscesses ($n = 4$), aspergillosis ($n = 2$), mucormycosis ($n = 1$), renal infarcts/ischemia ($n = 3$), acute pyelonephritis ($n = 1$), signs of microangiopathic hemolytic anemia ($n = 1$), and pheochromocytoma ($n = 1$).

Figure 4 displays the distribution of malignant infiltration by organ according to the hematological malignancy (AML/NHL). The distribution was relatively similar between AML and NHL and almost every organ could be involved, the most frequent being the hematopoietic system (70%), followed by

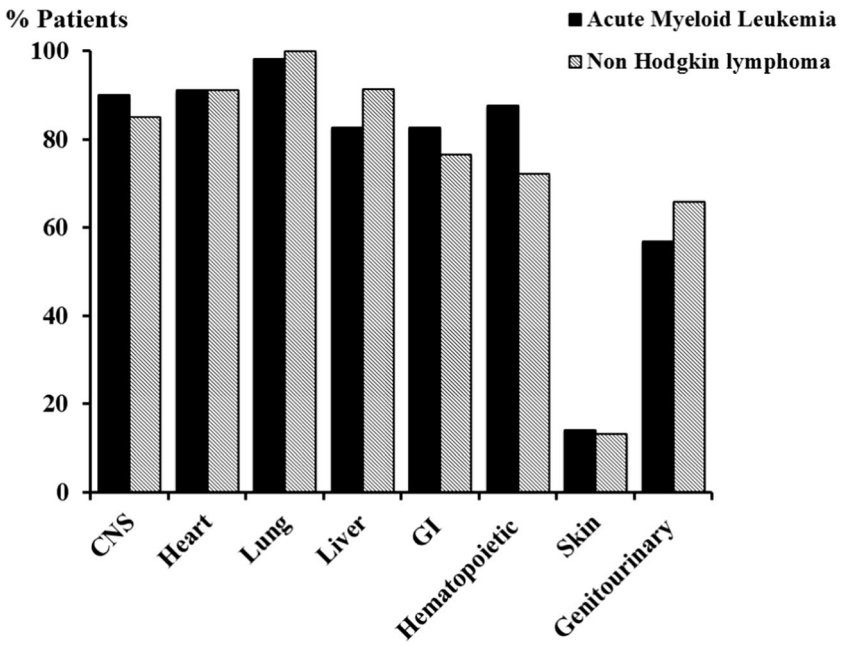

Fig. 2 Distribution of abnormal pathology findings at autopsy by organ for the 59 AML and 48 NHL patients (y-axis represents the percentage of patients with abnormal findings)

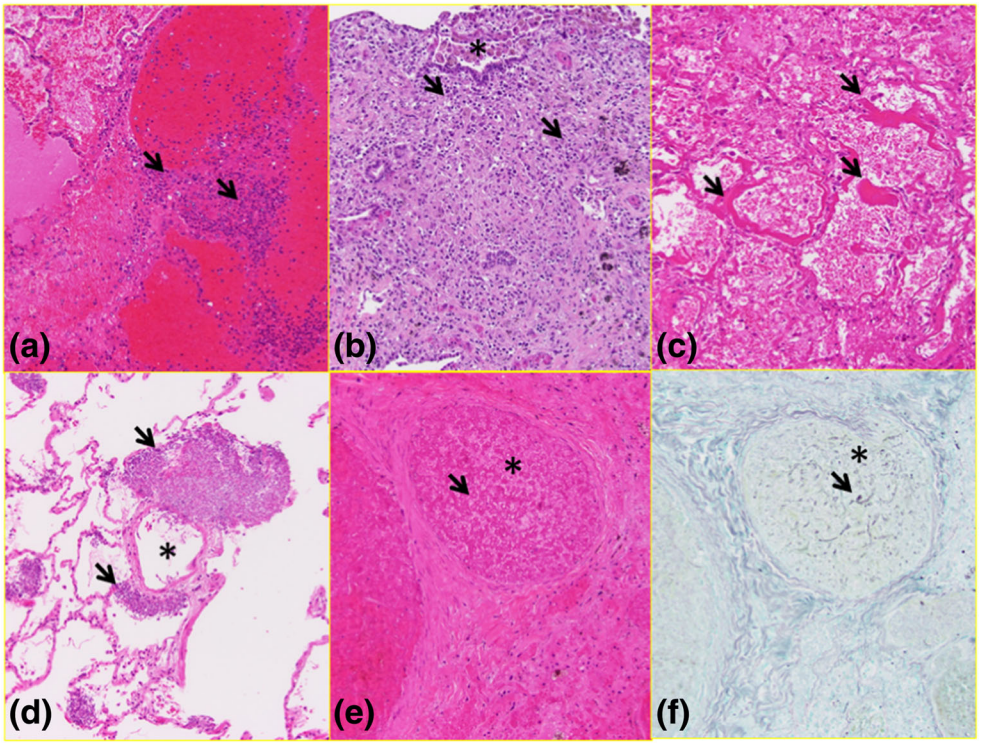

Fig. 3 Examples of lung pathology in patients with AML or NHL. **a** Leukemic infiltration (arrow) with alveolar hemorrhage in a patient with AML. **b** interstitial infiltration and expansion by lymphoma cells (arrow) in a patient with angioimmunoblastic T cell lymphoma status post chemotherapy. *, residual partial bronchiole. **c** Diffuse alveolar damage and hemorrhage in a patient with diffuse large B cell lymphoma status post chemotherapy. Arrow, hyaline membrane. **d** Disseminated candidiasis in a patient with AML status post chemotherapy. Arrow, clusters of fungal organisms with yeast and pseudohyphae. There is also invasion into a blood vessel (*). **e**, **f** Angioinvasion by mucor species accompanied by hemorrhage in a patient with diffuse large B cell lymphoma status post bone marrow transplant. Arrow, mucor fungal hyphae filling the blood vessel (*). **a**–**e** H&E stain, **F** GMS stain, original magnification × 200

liver, genitourinary system and CNS (about 35% each), heart and lung (about 20% each), and gastrointestinal system (15%). Figure 5 displays pathological findings in a patient with AML who had leukemic infiltration in multiple organs. Malignant infiltration in at least one organ was observed in about 70% of patients who had not achieved complete

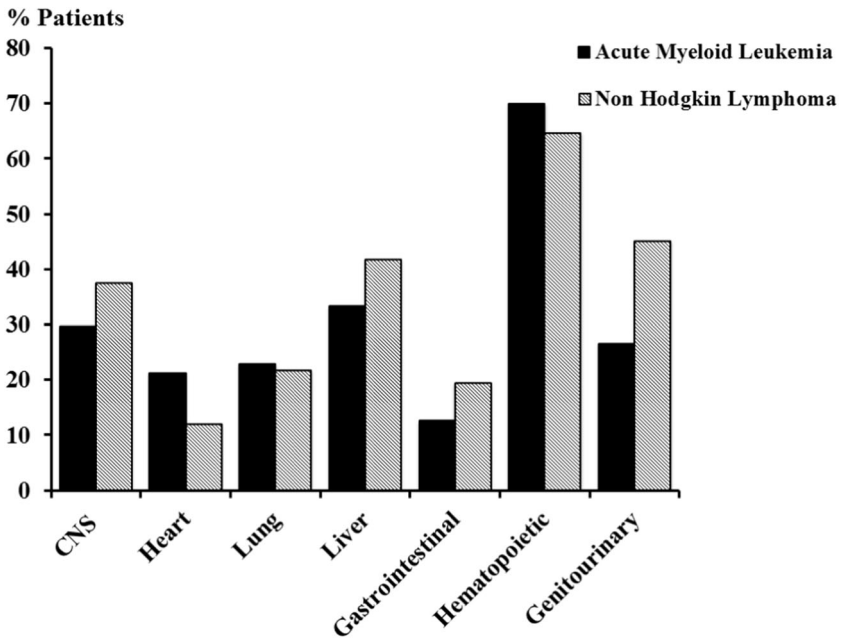

Fig. 4 Distribution of malignant infiltration found at autopsy by organ for the 59 AML and 48 NHL patients (*y*-axis represents the percentage of patients with lymphomatous or leukemic infiltration)

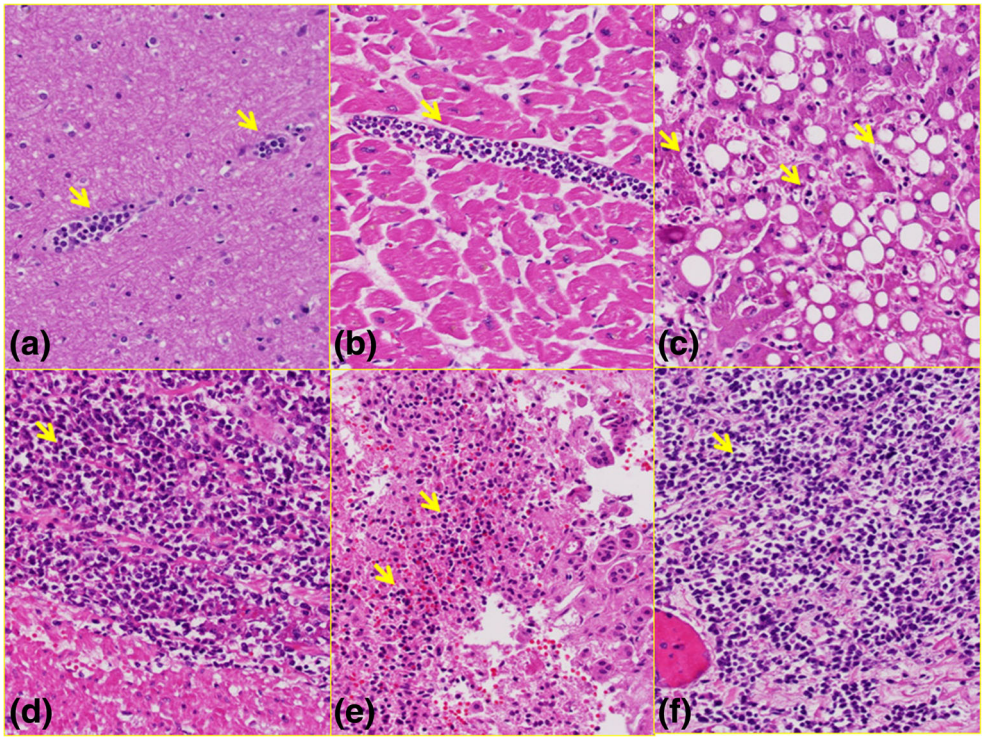

Fig. 5 Multi-organ involvement in a patient with AML. **a** Intravascular leukemic involvement in the cerebellum. **b** Intravascular leukemic involvement in the left ventricle of the heart. **c** Sinusoidal leukemic involvement in the liver. This liver also showed macrovesicular steatosis. **d** Leukemic involvement of the muscularis propria of the colon. **e** Leukemic involvement of the adrenal cortex. F: Leukemic nodule (myeloid sarcoma) in the lamina propria of the bladder. Arrow, acute leukemic cells. H&E stain, original magnification × 400

remission or had clinical suspicion of relapse at the time of death ($n = 92$) versus 20% in patients without signs of active malignancy ($n = 15$) ($p = 0.001$).

Autopsy findings in patients with acute respiratory failure

Figure 6 summarizes in a tree diagram the main lung disorders diagnosed in the whole population (diagnosis missed antemortem and established by autopsy, diagnosis performed antemortem, non-specific autopsy lung findings), according to the type of malignancy (AML or NHL) and the presence of ARF.

Figure 7 describes the lung pathology findings for the subgroup of patients with acute respiratory failure ($n = 90$): bacterial pneumonia was the most frequent autopsy diagnosis (about a third of patients) followed by malignant infiltration (about 20%), isolated diffuse alveolar damage (DAD) (18%) and pulmonary edema (15%), fungal pneumonias and thromboembolic events representing about 10% of patients each. When we included only patients with acute respiratory failure of unknown etiology ($n = 59$), the proportion of malignant infiltration increased to 27% and tended to equilibrate with bacterial pneumonias (29%) (Fig. 8), whereas fungal pneumonias represented 8% and isolated DAD or pulmonary edema were the only findings in 32% of patients. Finally, for patients with acute respiratory failure of unknown etiology and a completely negative infectious work-up during admission ($n = 27$), the main cause for respiratory failure was malignant infiltration ($n = 10$) followed by isolated DAD ($n = 7$) or pulmonary edema ($n = 4$); bacterial pneumonias were observed for 7 patients and fungal pneumonias and thromboembolic events were much less frequent (1 and 2 patients respectively).

Main characteristics of patients with acute respiratory failure and autopsy findings of either fungal pneumonia or malignant lung infiltration are reported in Table 2. We observed a significantly higher proportion of HSCT (5/11 versus 2/20, $p = 0.02$), documented infections during admission (10/11 versus 9/20, $p = 0.01$) and a higher rate of ante mortem ARF cause identification (6/11 versus 4/20, $p = 0.048$) in patients with fungal pneumonias as compared to patients with malignant lung infiltration. Table 3 reports the lung pathology findings according to the presence of active malignancy (no complete remission achieved or clinical suspicion of relapse): interestingly, 19 out of 20 malignant infiltrations and 10 out of 11 fungal infections were observed in patients with active malignancy. Figure 9 displays the number of patients with malignant lung infiltration at autopsy, based on the presence of acute respiratory failure (none, known etiology, unknown etiology) and the presence of active malignancy (no complete remission achieved or suspicion for relapse): overall, 85% of patients with ARF of unknown etiology had active malignancy at time of death and 80% of patients with malignant lung infiltration at autopsy had ARF of unknown etiology.

Discussion

The main findings of this study were that in a population of AML and NHL patients dying at an academic medical center,

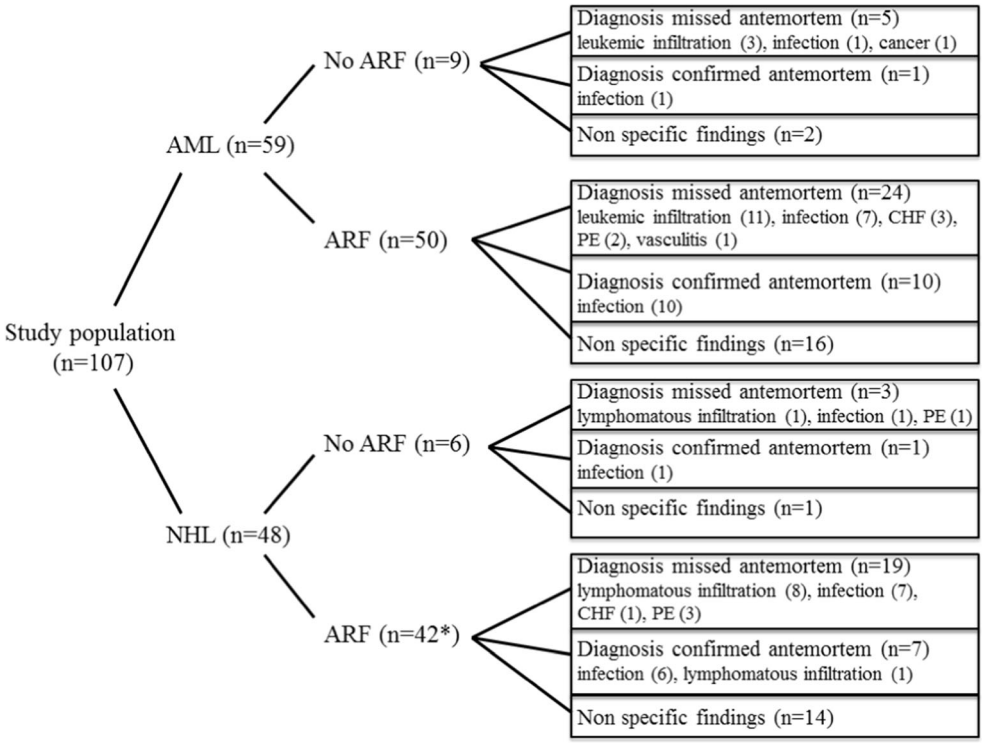

Fig. 6 Tree diagram representing the main lung disorders diagnosed in the whole population (diagnosis missed antemortem and established by autopsy, diagnosis performed antemortem, non-specific autopsy lung findings), according to the type of malignancy (AML or NHL) and the presence of ARF. * Lung findings were not available for 2 patients (autopsy restricted to abdomen). CHF, congestive heart failure; PE, acute pulmonary embolism

autopsy reported missed major diagnoses in more than 50% of patients with 60–100% of organs displaying pathological lesions overall. Lung pathology revealed malignant infiltration and fungal infections in 20% and 10% of patients respectively; these proportions were slightly higher in patients with ARF of unknown etiology, for whom isolated DAD/edema were the only findings in a third of cases.

The first objective of this study was to provide a description of autopsy findings in AML and NHL patients in the modern era, as most autopsy studies in this specific population were published decades ago and considerable progress has been made since in treatments and diagnostic tests. The autopsy rate at our institution was about 9% for in-hospital deaths during the study period, much lower than the rate of 38%

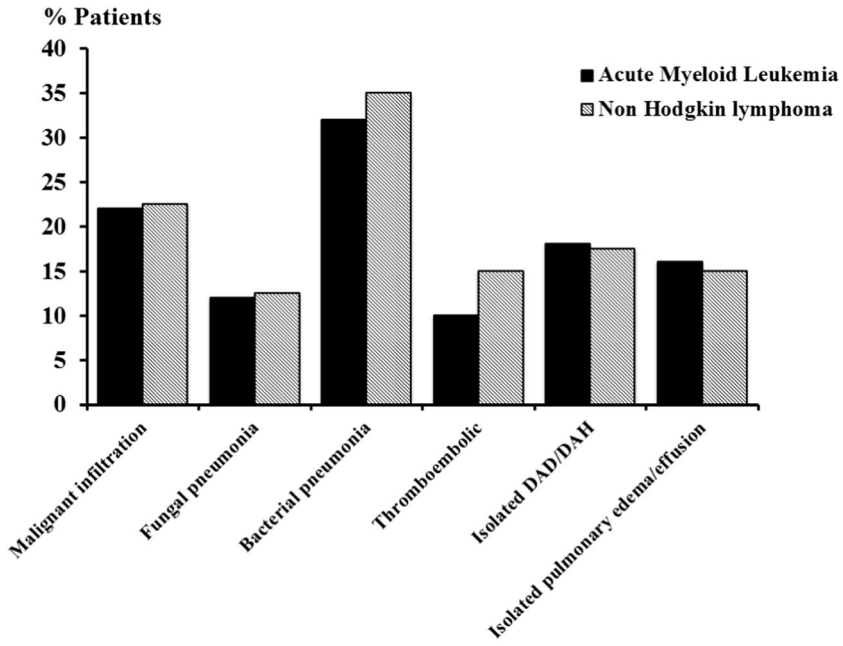

Fig. 7 Lung pathology findings at autopsy for the subgroup of patients with acute respiratory failure ($n = 90$, 50 AML and 40 NHL patients)

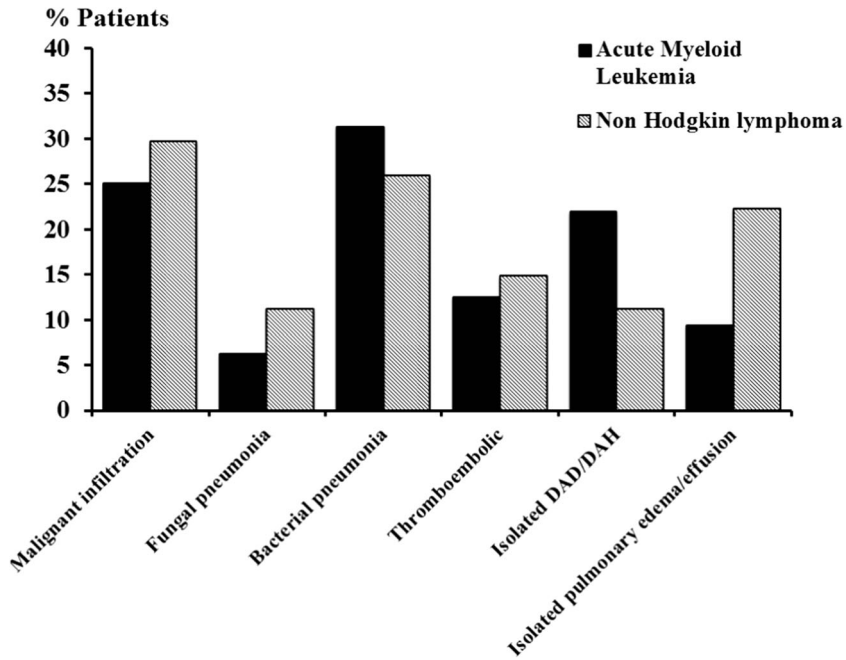

Fig. 8 Lung pathology findings at autopsy for the subgroup of patients with acute respiratory failure of unknown etiology (n = 59, 32 AML and 27 NHL patients)

reported in 1980 by Goldman et al. [8], but close to the 13% rate more recently reported in critically ill cancer patients [9] and consistent with the reported overall decline in autopsy rate over the last decades [10]. We observed that autopsies reported major missed clinical diagnoses (Goldman class I and II) in 60% of AML and 50% of NHL patients respectively. These results are difficult to compare with previous studies which, for those focused on leukemia and lymphoma patients, did not report Goldman classification [5, 6, 11]; however, in a series of 167 critically ill autopsied patients (including 20% immunocompromised subjects), Combes et al. reported major diagnostic errors (Goldman class I and II) in 32% of patients, noticing a high proportion of immunocompromised patients in this group [12]. Another study reported missed major diagnoses in 26% of critically ill patients in a heterogeneous population of medical and surgical patients with various hematological malignancies and solid organ tumors [9]. The higher proportion of missed major diagnoses in our study highlights the difficulty in reaching a diagnosis in AML and NHL patients developing complications: cardiovascular complications (acute myocardial infarction or pulmonary embolism) and fungal infections should be especially considered in patients with unclear diagnoses are they are the most accessible to treatments. Assessing whether malignant infiltration diagnosed ante mortem would have changed patients` management is more difficult, but lymphomatous or leukemic organ infiltration certainly accounted for a significant part of missed diagnoses, as overall 60% of our patients had malignant organ infiltration at autopsy; this is very similar to the 63% of residual leukemia detected in 138 AML patients autopsied between 1977 and 1982 [6], whereas no similar data is available for NHL patients to allow comparison. This rate has significantly decreased from 95% of residual leukemia detected at autopsy in the 1960s [6] but may have reached a plateau now. It is worth noticing that our population included a high proportion of patients with signs of active malignancy at the time of death, so that a high rate of residual disease detected at autopsy is not unexpected; this probably applies to previously published studies but most did not provide detailed ante mortem information. However, even among patients with no suspicion of active malignancy at the time of death, 20% had malignant organ infiltration in our series.

Regarding the organs involved by malignant infiltration, there is scarce data in the literature related to lymphomas and mostly two studies in AML patients with somewhat different results: McKee et al. reported that lungs, brain and cardiovascular system were the organs mostly involved by leukemic thrombi and aggregates in autopsies performed between 1956 and 1971, with respective frequencies of 35%, 25%, and 20%, whereas other organs were rarely affected [5]. Barcos et al. in their series of more recent autopsies (1977–1982) reported that, besides the hematopoietic system, liver, lungs, and kidneys were involved in 28%, 18%, and 20% of patients with residual leukemia respectively [6] whereas brain was affected in only 5% of patients. In our series, almost every organ could be affected without a clear predominance besides the hematopoietic system. The distribution was relatively similar between AML and NHL patients and involved by order of frequency CNS, liver and genitourinary system, followed by lungs, heart, and gastrointestinal system.

The second objective of our study was to focus on lung pathology findings in patients with acute respiratory failure of unclear etiology. Indeed, even though the mortality associated

Table 2 Characteristics of patients with acute respiratory failure and autopsy findings of fungal pneumonia versus malignant lung infiltration

	Fungal pneumonias ($n = 11$)	Malignant lung infiltration ($n = 20$)	p
Gender (M/F)	3/8	11/9	0.26
Age (years)	62 (44–68)	59 (45–68)	0.89
AML/NHL (n)	6/5	11/9	0.98
HSCT (n)	5	2	0.02
Relapse (n)	4	4	0.47
Chest CT (n)	7	13	1
Echocardiogram (n)	7	12	1
Bronchoscopy + BAL (n)	3	2	0.32
Documented infection (n)	10	9	0.01
ARF cause identified (n)	6	4	0.048
Neutropenia (n)	7	6	0.13
Steroids (n)	7	11	0.42
Chemotherapy (n)	2	6	0.68
Antifungals (n)	9	–	0.20
Mechanical ventilation (n)	10	18	0.93
Vasopressors (n)	8	13	0.68
Encephalopathy/coma (n)	5	8	1
Renal replacement therapy (n)	2	6	0.68
Micro-organism (n)	Aspergillosis = 6 Candida = 4 Mucormycosis = 1	–	

Table 3 Lung pathology findings in 90 patients with acute respiratory failure according to the presence of active malignancy (no complete remission achieved or clinical suspicion of relapse)

	No active malignancy ($n = 12$)	Active malignancy ($n = 78$)	p
Bacterial pneumonia, n (%)	4 (33)	26 (33)	1
Fungal pneumonia, n (%)	1 (8)	10 (13)	0.66
Malignant infiltration, n (%)	1 (8)	19 (24)	0.21
Isolated pulmonary edema, n (%)	1 (8)	13 (17)	0.46
Isolated DAD/DAH, n (%)	2 (17)	14 (18)	0.91
Thromboembolic, n (%)	3 (25)	8 (10)	0.15

DAD diffuse alveolar damage, *DAH* diffuse alveolar hemorrhage

with ARF in immunocompromised patients is known to be high [2], it is even higher for ARF of unknown etiology [3], hence the importance of lung pathology findings in these patients. Among the 107 patients included, 92 had ARF and among them, 59 (64%) had no clear etiology documented. Our proportion of ARF of unknown etiology was much higher than the 20% rate generally reported in series of critically ill immunocompromised patients with ARF [3], probably because patients with ARF of unknown etiology were more likely to have autopsy requested by the medical team and granted by families. In agreement with our results, another autopsy study in HSCT recipients reported that only 28% of pulmonary complications were diagnosed ante mortem [13]. Among patients with ARF of unknown etiology, we observed that about 30% had malignant lung infiltration, as compared to 13% of patients with known etiology of ARF ($p = 0.18$). Lung malignant infiltration, almost never documented ante mortem and rarely suspected, was mostly found in patients with no remission achieved or suspicion for relapse at the time of death. Our results overall suggest a possible link between active malignancy at the time of death, ARF of unknown etiology and malignant lung infiltration. Indeed, studies showing an association between the lack of ARF etiology and mortality all included a proportion of patients with disease progression [3, 14] without autopsy results; a high proportion of lung malignant infiltration, as observed in our patients without ARF etiology, may have contributed to the increased mortality reported in these studies [3, 14]. For most of our patients, the diagnosis would probably not have been made without autopsy as none had a lung biopsy performed. The impact of other lung pathology findings, like bacterial pneumonias, on mortality is more difficult to assess as most patients were receiving adequate antibiotics before death. Fungal infections were less frequent but not uncommon in our population and 2 out of 11 patients with ARF and fungal pneumonia reported at autopsy were not receiving antifungals at the time of death. In their series of HSCT recipients, Sharma et al. also reported that 5 of the 11 patients with autopsy-proven pulmonary aspergillosis had not been treated for that condition [13]. Invasive fungal infections are not only common in patients with hematological malignancies (identified in 31% of 1017 autopsies in a study by Chamilos et al. [15]) but also difficult to diagnose with up to 75% being missed ante mortem [15]. This highlights the need to develop performant diagnostic tools (molecular diagnostic in blood and BAL for instance) and to consider empiric antifungal treatment in selected patients. Lung biopsy has proven to be useful for the diagnosis of invasive fungal infections, otherwise difficult to confirm [16]; in a series of 63 patients with hematological malignancies, a specific diagnosis was found in 62% of lung biopsies with a change in management in 57% of patients, and again the mortality was higher in

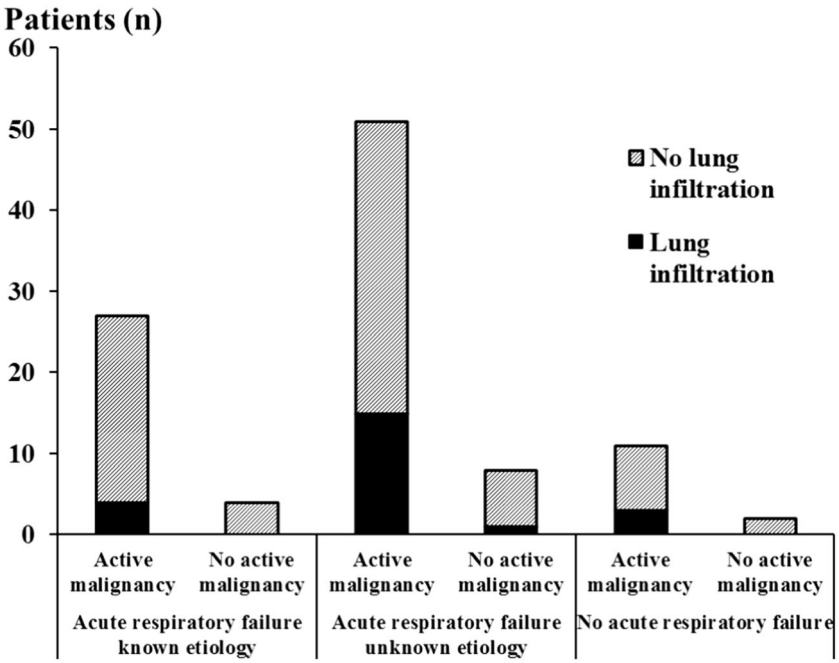

Fig. 9 Bar plots representing the number of patients with malignant lung infiltration at autopsy, based on the presence of acute respiratory failure (none, known etiology, unknown etiology) and the presence of active malignancy (no complete remission achieved or suspicion for relapse)

patients without specific diagnosis [17]. Lung biopsy may also be useful in diagnosing pulmonary fibrosis, which was not uncommon in our series (7 out of 92 patients with ARF); however in 4 cases lung fibrosis was likely chronic (due to previous radiation therapy or chronic lung disease) and not the cause of ARF; the impact that a biopsy would have had on outcome in 3 other cases (two busulfan toxicities and one idiopathic pneumonia syndrome) remains uncertain, as administration of corticosteroids has been suggested in both conditions [18, 19] but without proven benefit. In patients with hematological malignancies and undiagnosed pulmonary lesions, the relatively high diagnostic yield of lung biopsies (transbronchial, CT-guided or surgical), which can lead to therapeutic changes in up to 80% cases [20] has to be balanced with a complication rate of about 20–30% (mostly pneumothorax and bleeding) [21]; some authors recommend to consider lung biopsy only when no diagnosis can be obtained after a comprehensive diagnostic work-up, including microbiological analyses, echocardiogram, high-resolution chest computed tomography (HRCT), and fiberoptic bronchoscopy with BAL [22]. In this setting, HRCT has significantly higher sensitivity and negative predictive value than chest X-ray, may help differentiate fungal and non-fungal infiltrates and should be widely used in evaluating ARF [23]. Patients with no specific diagnosis even after lung biopsy may correspond to the patients with isolated pulmonary edema or alveolar damages in our series; the cause of these findings (unidentified pathogens, drug toxicity, atypical organ involvement by the disease?) remains to be elucidated.

A limitation of our study is the selection bias due to its retrospective design: as patients who had autopsies performed were likely the most complicated ones or those with a high suspicion for a specific diagnosis (malignant infiltration, fungal infection), our results may not be generalizable to all AML and NHL patients. Another limitation for patients with ARF of unknown etiology is that bronchoscopy and BAL were not consistently performed and could have documented a diagnosis ante mortem in some patients. However, our results are consistent with a recent large prospective cohort study reporting that only 60% of immunocompromised patients with ARF had bronchoscopy and BAL performed [3]; moreover, even BAL has a limited sensitivity for detecting malignant cells (about 65% in a series of 145 patients with lung malignancies [24]).

In conclusion, in a selected population of 59 AML and 48 NHL patients who had autopsy performed between 2003 and 2018, we found that more than 50% of patients had missed major clinical diagnoses (Goldman class I and II). In patients with ARF of unknown etiology, lung malignant infiltration was frequently found and accounted for most of deaths in the subgroup of patients with no complete remission or suspected relapse at the time of death. Bacterial pneumonias and less often fungal pneumonias were also observed, however in about a third of cases of ARF without identified cause, pulmonary edema or alveolar damage were the only findings.

Data availability All data generated or analyzed during this study are included in this published article.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. For this type of study, formal consent is not required.

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