Annals of Hematology (2019) 98:195–203
https://doi.org/10.1007/s00277-018-3496-1

ORIGINAL ARTICLE

Intensive care unit admission in patients with T cell lymphomas: clinical features and outcome

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Received: 14 May 2018 / Accepted: 6 September 2018 / Published online: 14 September 2018

Abstract

T cell non-Hodgkin lymphomas (T-NHLs) are aggressive malignancies which have a high risk of life-threatening complications. However, their prognosis in the intensive care unit (ICU) setting has not yet been assessed. We conducted a study including 87 ICU patients either with newly diagnosed T-NHLs or those undergoing first-line therapy admitted between January 1, 2000, and December 31, 2014. The primary subtypes were peripheral T cell lymphoma (PTCL) ($n = 41$, 47%), anaplastic large-cell lymphoma (ALCL) ($n = 13$, 15%), and adult T-leukaemia/lymphoma (ATLL) ($n = 11$, 13%). Six in every ten patients had malignancy-related complications (haemophagocytic syndrome 37%, tumour lysis syndrome 18% and hypercalcaemia 9%), while infections accounted for one quarter of ICU admissions. Nine fungal infections were documented, including six invasive aspergillosis. Urgent chemotherapy was started in the ICU in 59% of the patients, and urgent surgery was required in 13%. ICU and day-90 mortality were 22% and 41%, respectively. Multivariate analysis showed that SOFA score at day 1, age, sepsis and haemophagocytic syndrome were independent predictors of day-90 mortality. Compared to 66 ICU-matched controls with non-Hodgkin B cell lymphomas, patients with T-NHLs had a similar ICU survival. Overall survival rates of patients with T cell NHLs and B cell NHLs were 20% and 46%, respectively (hazard ratio for death associated with T cell NHLs 2.00 [1.12–3.58]). Patients with T cell NHLs had a very poor long-term outcome. Although the high rate of short-term survival suggests that an ICU trial is a reasonable option for patients newly diagnosed for the malignancy, extended stay in the ICU or further readmission should be considered only for highly selected patients who respond to the haematological treatment.

Keywords Fungal infection · Haemophagocytic syndrome · Intensive care unit · T cell lymphoma · Tumour lysis syndrome

Introduction

Non-Hodgkin's lymphomas (NHLs) are among the most common haematological malignancies (HMs), and their incidence is increasing in most regions of the world [1]. Survival has significantly improved over time and more than half of patients can expect to be alive 10 years after the diagnosis [2]. However, treatment toxicities or the malignancy itself may lead to life-threatening complications which require intensive care unit (ICU) management [3, 4]. Substantial therapeutic advances have improved the outcome of critically ill patients with HMs [5]. Nonetheless, most of the studies conducted in the ICU environment have included all types and stages of HMs, which have major difference in treatment options and outcomes. Thus, accurate data on the prognosis of critically ill patients with homogeneous HMs are limited [6].

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00277-018-3496-1) contains supplementary material, which is available to authorized users.

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In the Western world, T cell NHLs represent approximately 10 to 15% of all NHLs [7]. At the time of diagnosis, most cases of T-NHLs are readily advanced with marked symptoms and altered status [7, 8]. Consequently, these patients are very likely to experience various life-threatening complications requiring a close collaboration between haematologists and intensivists and complex management in the ICU. However, no data are available to guide clinical practice of patients with T-NHLs in the ICU environment.

Accordingly, we conducted a study to investigate the clinical features and outcomes of critically ill patients with newly diagnosed T-NHLs. We sought to identify predictors of survival 90 days after ICU admission. In addition, we assessed the influence of T cell phenotype (versus B cell phenotype) on the outcome of critically ill patients with NHLs.

Methods

This study was approved by our institutional review board (CECIC Clermont Ferrand – IRB no.5891; Ref. 2007-16). According to French law, informed consent was not required in this retrospective observational study in which the collected data were anonymised.

Inclusion criteria

We retrospectively included all adult patients (≥ 18 years old) admitted to the medical ICU of Saint-Louis University Hospital between January 1, 2000, and December 31, 2014 who had a mature T or NK lymphoid neoplasm according to the World Health Organization (WHO) classification [9]. Only patients newly diagnosed with malignancy or those undergoing a first line of chemotherapy were included. For patients admitted more than once to the ICU, only the first episode was considered. Patients were identified from the ICU databases using codes C84, C85 and C86 from the International Classification of Diseases system (ICD-10). All patients' medical records were reviewed by the two investigators (GD and EC) to confirm the diagnosis of mature T or NK lymphoid neoplasm.

Design and setting

The Saint-Louis University Hospital is a 650-bed public hospital, with 330 beds dedicated to patients with various conditions associated with immunodeficiency (haematological malignancies, solid cancers and solid organ transplantation). There are seven haematology wards (adolescent and young adult haematology, acute leukaemia, senior haematology, clinical immunology, myeloma, lymphoma and allogeneic stem cell transplantation) and four oncology wards (general oncology, lung cancer, gastrointestinal oncology, and radiation therapy).

The medical ICU of Saint-Louis University Hospital is a 12-bed unit which admits 750–850 patients per year, of whom over one third have malignancies. Information on the organisation of the ICU and criteria for ICU admission have been published elsewhere [10]. Mandatory ICU admission reasons are defined by at least one organ failure and the need for at least one of the following therapies: supplemental nasal oxygen ≥ 3 L/min, use of vasoactive drugs, sustained fluid administration, invasive or non-invasive mechanical ventilation, or renal replacement therapy. At our institution, intensivists and haematologists are available 24 h a day, 7 days a week and work together to manage all high-risk patients with haematological malignancies.

Data collection

The data reported in the tables were abstracted from medical charts. Baseline patient characteristics were collected, including demographics, comorbidities, and best performance status (PS) within 3 months before ICU admission. Data regarding the malignancy phenotype and anticancer treatments were also taken from the medical charts. Variables recorded regarding ICU admission and treatments were data related to clinical presentation, reason for ICU admission, time of admission and discharge from the ICU, diagnostic procedures, therapies implemented and outcome data. Disease severity at ICU admission was assessed using the sequential organ failure assessment (SOFA) score at day 1 [11]. For each patient, two investigators (EC and GD) analysed the medical charts blinded from the diagnosis established by clinicians in charge. Cases of disagreement were then discussed among the investigators until a consensus could be reached. Established criteria were used to define haemophagocytic syndrome [12] together with histological evidence of activated macrophages engulfing erythrocytes, leukocytes, platelets and their precursor cells in bone marrow smears or biopsies and/or in liver or spleen biopsies. Sepsis was retained in patients with clinically and/or microbiologically documented infection within ICU admission without alternative diagnosis. Sepsis and septic shock were defined according to the Third international Consensus Definitions for Sepsis and Septic Shock [13].

The primary objective of the study was to report the clinical features of critically ill patients with a recently diagnosed mature T or NK lymphoid neoplasm, and to identify factors associated with mortality 90 days after ICU admission. The secondary objective was to assess the influence of a T cell phenotype (versus B cell phenotype) on the outcome of critically ill patients with NHLs.

Statistical analysis

Quantitative variables are described as median and interquartile range (IQR) and compared using Wilcoxon's rank sum

test; qualitative variables are shown as counts (percent) and compared using Fisher's exact test. Day-90 mortality was analysed as a binary variable. Factors associated with day-90 mortality were assessed using multivariate analysis by logistic regression. Variables achieving $P < 0.20$ in univariate analyses were entered into the multivariate logistic regression model. A multiple backward-stepwise selection procedure eliminated those variables with an exit threshold set at $P = 0.05$, after testing for collinearity between variables and checking the assumption of log-linearity. Goodness of fit was evaluated using Le Cessie-van Houwelingen's method and discrimination with AUC statistic.

To assess the prognostic effect of a T cell phenotype (versus B cell phenotype) in the context of an observational cohort, a matched comparison of patients with T cell NHLs and B cell NHLs was performed. Patients with T cell NHLs were individually matched in a 1:1 ratio to a control group of patients with B cell NHLs. The five matching criteria were age (matched within 0.4 SD, corresponding to 6.6 years), gender (exact match), year of ICU admission (matched within 1 SD, corresponding to 3.4 years), IPI score (exact match) and date of malignancy diagnosis (classified as newly diagnosed or undergoing a first-line chemotherapy; exact match). First, we used Cox regression models with a random effect on matching clusters to understand association between NHL phenotype, patient's characteristics and overall survival by univariate analysis. Second, all factors with P values smaller than 0.10 by univariate analysis were included in the multivariate analysis. The final multivariate model was selected by a stepwise backward selection based on the P values.

The measures of associations are presented with odds ratios or hazards ratio and confidence intervals at 95%. All tests were two-sided, and P values lower than 5% were considered to indicate significant associations. Analyses were performed using R statistical platform, version 3.0.2 (https://cran.r-project.org/).

Results

Study population

Eighty-seven patients (58 men; median age 50 years [IQR 38–60.5]) were included in the present study. Patients' characteristics are listed in Table 1. Most patients were admitted from their referred doctors ($n = 70$, 80%). Almost two-thirds of the patients had an altered performance status (i.e. bedridden/disabled). The most common T cell neoplasms were peripheral T cell lymphoma-not otherwise specified (PTCL-NOS) ($n = 41$, 47%), and anaplastic large-cell lymphoma ($n = 13$, 15%). Median time from neoplasm diagnosis to ICU admission was 4 [0–26] days, including 34 (39%) patients newly diagnosed during the ICU stay. The median aa-IPI score was 3 [2, 3]. Extensive disease (Ann Arbor stages III–IV) was noted in 80 (94%) patients, and 74 (85%) had at least one extra-nodal involvement. Thirty-seven (43%) patients had proven bone marrow involvement. Thirty-six (41%) patients had received chemotherapy and 50 (58%) steroids before ICU admission. Neutropenia was present at ICU admission in 21 patients

Table 1 Baseline characteristics of patients with newly diagnosed T cell lymphoma ($n = 87$)

Variable	*N* (%) or median [IQR]	*N* missing[a]
Age (years)	50 [38–60.5]	
Female gender	29 (33)	
Body mass index (kg/m^2)	22.7 [19.6–25.4]	
PS 3 or 4	56 (64)	
Time from hospital admission to ICU admission (days)	7 [1–20]	
Direct ICU admission	17 (20)	
Comorbidities		
HIV infection	8 (9)	
Chronic cardiovascular disease	7 (8)	
Cirrhosis	2 (2)	
Chronic kidney disease	2 (2)	
COPD	1 (1)	
Histology of T cell NHLs		
PTCL-NOS	41 (47)	
ALCL	13 (15)	
ATLL	11 (13)	
HSTCL	8 (9)	
NK/TCL	8 (9)	
AITL	6 (7)	
Extra-nodal involvement		
Hepatosplenomegaly	50 (57)	
Skin	22 (25)	
Lung	20 (23)	
Gastrointestinal tract	15 (17)	
Central nervous system	9 (10)	
Time from malignancy diagnosis to ICU admission (days)	4 [0–26]	
Malignancy diagnosed during ICU stay	34 (39)	
Time from first course of chemotherapy to ICU admission (days)	10 [3–15]	
B symptoms	49 (57)	
Ann Arbor stage III-IV	80 (94)	2
IPI score ≥ 2	58 (85)	19
Laboratory data at diagnosis		
Albumin < 30 g/L	46 (71)	22
Elevated LDH level	70 (84)	
Haemoglobin (g/dL)	9.5 [7.8–11]	
Platelets (G/L)	72 [30.5–171]	
Neutropenia at ICU admission (≤ 1.0 G/L)	21 (24)	

PTCL-NOS peripheral T cell lymphoma-not otherwise specified, *ALCL* anaplastic large-cell lymphoma ALK+, *ATLL* adult T cell leukaemia/lymphoma, *HSTCL* hepatosplenic T cell lymphoma, *NK/TCL* NK/T cell lymphoma, *AITL* angioimmunoblastic T cell lymphoma, *ICU* intensive care unit, *HIV* human immunodeficiency virus, *COPD* chronic obstructive pulmonary disease, *PS* performance status, *IPI* international pronostic index, *LDH* lactate dehydrogenase

(24%) and developed during ICU stay in another 39 (45%) patients. As shown in Table 2, two-thirds of the patients were admitted for tumour-related complications (haemophagocytosis, tumour lysis syndrome, hypercalcaemia, cardiac tamponade, airway compression), while 25 (29%) had sepsis. Regarding patients with haemophagocytic syndrome, all had an acute presentation with organ dysfunction requiring ICU monitoring or organ support (SOFA score at day 1: 7 [5–12]) and the median serum ferritin level was 24,000 [4984–107,500] μg/L.

ICU management and outcomes

The median SOFA score at day 1 was 7 [4–9]. Invasive mechanical ventilation was needed in 39 patients (45%), vasoactive drugs in 33 (38%) and renal replacement therapy in 34 (39%). Urgent chemotherapy was required in 51 (59%) patients, and 11 (13%) patients underwent an urgent surgical procedure. Nine patients (10%) were diagnosed for invasive fungal infections (IFIs): six invasive aspergillosis, two invasive candidiases and one *Geotrichum* fungemia. All the patients who had fungal infections died within their hospital stay.

Table 2 ICU management and outcomes

Variable	*N* (%) or median [IQR]
SOFA score at day 1	7 [4–9]
Reason(s) for ICU admission[a]	
Acute kidney injury	39 (45)
Acute respiratory failure	28 (32)
Shock	26 (30)
Coagulation disorders	20 (23)
Neurological failure	19 (22)
Main diagnosis[a]	
Tumour-related complications	57 (65)
Haemophagocytosis	32 (37)
Tumour lysis syndrome	16 (18)
Hypercalcaemia	8 (9)
Airway compression	5 (6)
Cardiac tamponade	3 (3)
Sepsis	25 (29)
Others[b]	5 (6)
Life-sustaining therapies	
Invasive mechanical ventilation	39 (45)
Renal replacement therapy	34 (39)
Vasoactive drugs	33 (38)
Chemotherapy during ICU stay	51 (59)
Urgent surgery	11 (13)
Antibiotic therapy during ICU stay	70 (80)
Antifungal treatment during ICU stay	25 (29)
Outcome	
ICU-acquired infection	35 (40)
Decision to withhold/withdraw treatments	18 (21)
ICU Length of stay (days)	12 [14–17]
ICU crude mortality	19 (22)
Day 90 mortality	36 (41)

ICU intensive care unit, *SOFA* sequential organ failure assessment

[a] Some patients had more than one cause

[b] Others: major bleeding $n = 2$, cardiogenic pulmonary oedema $n = 3$

The median ICU stay was 12 [14–17] days. A decision to withhold or withdraw life-sustaining therapies was taken in 18 (21%) patients. In-ICU and day-90 mortality were 22% and 41%, respectively. One year after ICU discharge, six (7%) patients were alive and had complete remission of the malignancy, while ten (11%) required ongoing chemotherapy for relapsing diseases. The univariate analysis of factors associated with day-90 mortality is reported in Table 3. By multivariate analysis (Fig. 1), four factors were independently associated with a higher day-90 mortality: SOFA score at day 1 (as a proxy for baseline organ failure and/or life-sustaining therapies), age, sepsis and haemophagocytic syndrome.

Comparative outcomes between T cell phenotype and B cell phenotype

One hundred and thirty-two patients were included in the comparative analysis after the matching procedure (66 T cell NHLs versus 66 B cell NHLs; 21 T cell NHLs of the initial sample could not be matched to B cell NHLs patients based on the matching criteria (see "Methods" section for details)). Supplementary Table 1 and Supplementary Table 2 (in Electronic Supplementary Material) describe the matched population. Reasons for ICU admission were similar in the two groups except for haemophagocytic syndrome, which was more frequent in patients with T cell NHLs than in patients with B cell NHLS (35% versus 14%, $P = 0.008$). Day-90 mortality was 43% in patients with T cell NHLs and 54% in patients with B cell NHLs ($P = 0.21$).

The median follow-up was 24 [0–163] months. The overall survival rates of patients with T cell NHLs and B cell NHLs were 20% and 46%, respectively. The hazard ratio for death of patients with T cell NHLs was 2.00 [1.12–3.58] ($P = 0.02$) (Fig. 2). The univariate analysis of factors associated with overall survival is shown in Table 4. Seven factors were associated with a lower overall survival: T cell phenotype, higher age, HIV infection, higher SOFA score at day 1, shock, acute kidney injury, sepsis and haemophagocytic syndrome. By multivariate analysis, three factors were associated with overall mortality (Table 4): T cell lymphoma phenotype (HR 2.04 [1.21, 3.46]), HIV status (2.09 [1.08, 4.04]) and severity at ICU admission (SOFA score at ICU admission, HR 2.09 [1.08, 4.04]).

Table 3 Factors associated with mortality 90 days after ICU admission in patients with T cell NHLs (univariate analysis)

Variable	Survivors $N = 51$ N (%) or median [IQR]	Non-survivors $N = 36$ N (%) or median [IQR]	P value
Baseline characteristics			
Age (by year)[a]	45.5 [35–59.8]	53.5 [46.3–63.3]	0.045
Male gender	32 (64)	26 (72)	0.49
HIV infection	4 (8)	4 (11)	0.71
PS 3 or 4[a]	29 (58)	27 (75)	0.12
Chronic cardiovascular disease	4 (8)	3 (8)	1.00
Body mass index (kg/m^2)	23.7 [20.2–25.6]	21.48 [19.6–24.2]	0.48
B symptoms	28 (57)	21 (58)	1.00
IPI ≥ 2	31 (82)	26 (90)	0.50
Ann Arbor stages III–IV	46 (94)	33 (94)	1.00
Albumin < 30 g/l	24 (63)	22 (85)	0.09
Characteristics at ICU admission			
Neutropenia (≤ 1.0 G/L)	9 (18)	12 (33)	0.13
SOFA score at day 1[a]	5 [3–7.75]	8 [7–12.5]	<0.0001
Direct ICU admission	11 (22)	5 (14)	0.41
Acute respiratory failure	12 (24)	16 (44)	0.062
Shock	9 (18)	17 (47)	0.005
Acute kidney injury	20 (40)	19 (53)	0.28
Neurological impairment	9 (18)	10 (28)	0.30
Tumour lysis syndrome[a]	13 (26)	3 (8)	0.05
Haemophagocytosis[a]	15 (30)	17 (47)	0.13
Hypercalcaemia	7 (14)	1 (3)	0.11
Sepsis[a]	11 (22)	14 (38)	0.04
Life-sustaining therapies			
Invasive mechanical ventilation	19 (38)	20 (56)	0.13
Renal replacement therapy	16 (32)	18 (50)	0.12
Vasoactive drugs	11 (22)	22 (61)	0.0003

HIV human immunodeficiency virus, *ICU* intensive care unit, *SOFA* sequential organ failure assessment, *PS* performance status, *IPI* international pronostic index, *IQR* interquartile range

[a] These variables were included in the global multivariable model

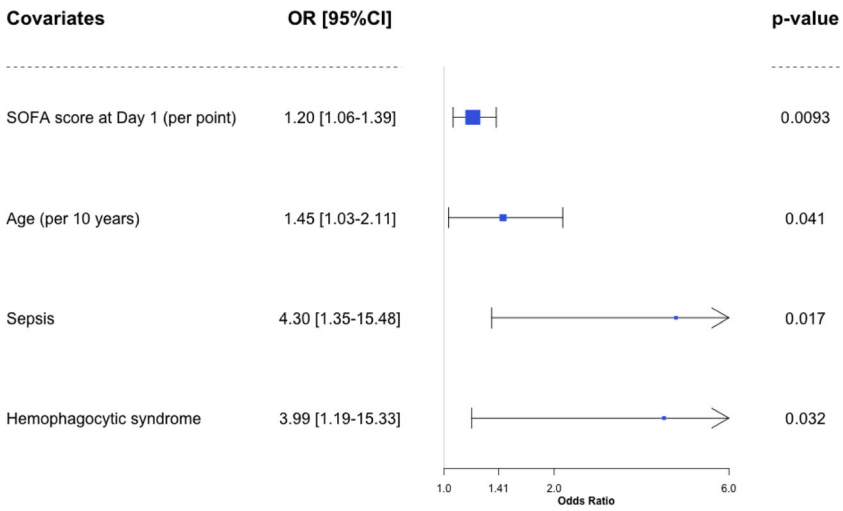

Fig. 1 Final prediction model of mortality 90 days after ICU admission in patients with T cell NHLs (multivariate analysis). Candidates entered in the multivariate analysis were: age, PS 3–4, SOFA score at day 1, haemophagocytosis, sepsis, and tumour lysis syndrome. Only the four variables with reported OR were selected in the final model as adding to each other predictive information. Goodness of fit (Le Cessie van Houweligen) P value = 0.99; calibration (AUC-ROC) 0.84. SOFA sequential organ failure assessment

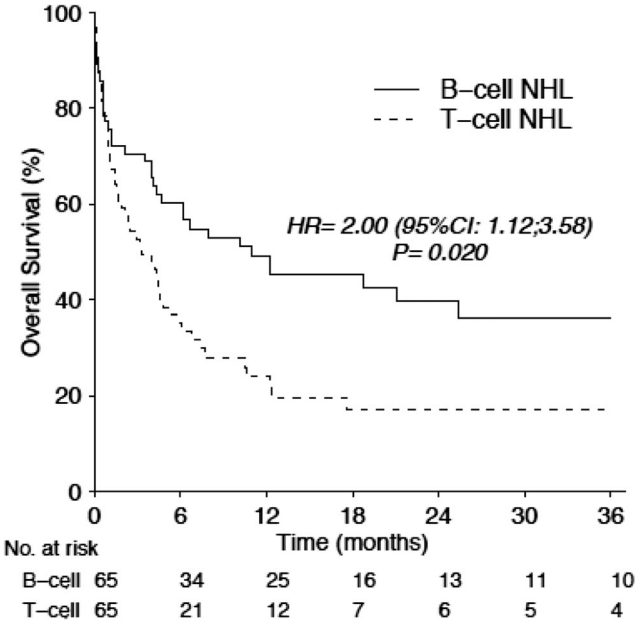

Fig. 2 Overall survival according to the NHL phenotype. B-NHL B cell non-Hodgkin lymphoma, T-NHL T cell non-Hodgkin lymphoma, HR hazard ratio, CI confidence interval

Discussion

Key findings

This study was designed to describe the clinical features and outcomes of patients with newly diagnosed T-NHLs admitted to the ICU for the management of life-threatening complications. We found that two-thirds of the patients had tumour-related complications, among which haemophagocytic syndrome and tumour lysis syndrome were the most common. Moreover, we observed that one in every seven patients developed invasive aspergillosis. The 78% ICU survival rate is encouraging, and a T cell phenotype did not seem to influence the short-term prognosis. Indeed, critically ill T-NHL patients and B-NHL patients shared a similar day-90 survival.

Relationship to previous studies

Patients with lymphomas are a group of particular interest as it is one of the most common HMs [2, 10]. Algrin et al. conducted a study in 190 ICU patients with Hodgkin lymphoma and different types of NHLs [14]. They reported a hospital survival rate of 63% and identified six independent predictors of mortality: age older than 50 years, poor PS (≥2), Burkitt lymphoma, primary cerebral lymphoma, haemophagocytic syndrome, severity of organ dysfunction at ICU admission (SOFA score) and admission before 2004. In our study, we confirmed that age, severity of organ dysfunction, and haemophagocytic syndrome were associated with a higher mortality. In contrast, although two-thirds of the T-NHL patients had a poor PS, it was not an independent predictor of mortality. PS is usually a robust predictor of survival in the ICU environment [15–18]. A possible explanation for this unexpected finding is that we focused on patients newly diagnosed with the malignancy. Consequently, we hypothesise that the poor PS was likely to be related to the aggressive malignancy itself (85% had an IPI score ≥ 2), and thus to be improved by early treatment, rather than explained by a combination of comorbidities, multiple lines of treatments, and relapsing or refractory diseases with limited treatment options. Although patients with poor PS are usually unlikely to benefit from ICU management, our results support the fact that ICU trial policy would be considered in this selected population.

Another interesting finding of our study is that sepsis was also an independent predictor of mortality. We observed a high rate of fungal infections in patients who had sepsis, with an unanticipated overrepresentation of invasive aspergillosis (6/9 IFIs). Invasive aspergillosis is known to be associated with a high mortality rate in the ICU environment [19, 20] but chiefly occurs in patients with prolonged neutropenia or in allogeneic stem cell recipients [21]. How early onset aspergillosis unexpectedly developed in patients newly diagnosed for T-NHLs remains to be investigated. We speculate that this specific category of NHLs might alter the normal immune response to fungi [22].

Wohlfarth et al. recently identified high IPI score and bulky disease as predictors of unplanned ICU admission and reported an ICU survival rate of 75.7% among 37 critically ill patients with diffuse large B cell lymphomas [23]. In our study, we found that the phenotype of the lymphoma (T cell versus B cell lymphoma) did not influence the likelihood of survival in the ICU. However, the overall survival rate of patients with B cell lymphomas was significantly higher than that of patients with T-NHLs, in accordance with previous studies [7, 8, 24].

Study implications

The findings of our study have three implications in clinical practice. Firstly, our results support ICU admission in patients with newly diagnosed T-NHLs. Indeed, a high rate of survival can reasonably be expected regardless of the patient's general condition. However, the potential benefit of an ICU admission should take into account the long-term survival, which was very low in our cohort. Thus, we believe that although an ICU trial is a reasonable option for patients newly diagnosed for the malignancy, extended multi-organ support or further readmission in the ICU should be considered only for selected patients responding to the haematological treatment.

Secondly, the assessment at ICU admission must include a comprehensive screening of malignancy related complications, such as haemophagocytic syndrome, tumour lysis syndrome, and organ compression or infiltration by the malignancy. These conditions are frequent and early recognition allows

Table 4 Factors associated with overall survival in a matched cohort of B cell NHL (univariate analysis)

Variable	Overall survival, *N* events/*N* total	Overall survival, HR [95%CI]	*P* value
Total (*N* = 130)[a]	87/130		
B cell NHL	35/65	1	
T cell NHL	52/65	2.0 [1.00–1.03]	0.02
Age (by 10 years)	–	1.18 [1.00–1.40]	0.048
Male gender	63/90	1.13 [0.68–1.88]	0.64
HIV infection	24/27	1.80 [1.12–2.90]	0.016
Chronic cardiovascular disease	10/15	1.05 [0.53–2.09]	0.88
Body mass index (kg/m^2)	–	0.98 [0.90–1.06]	0.54
Inaugural disease	27/40	1.06 [0.64–1.75]	0.83
IPI			
1	2/4	1	
2	25/45	1.31 [0.31–5.53]	
3	61/82	1.94 [0.47–7.98]	0.72
			0.36
Neutropenia at ICU admission (≤ 1.0 G/L)	16/21	1.72 [0.94–3.14]	0.078
SOFA score at day 1 (by point)	–	1.20 [1.13–1.28]	< 0.0001
Acute respiratory failure	30/41	1.35 [0.84–2.18]	0.22
Shock	27/30	2.97 [1.77–4.99]	< 0.0001
Acute kidney injury	39/53	1.61 [1.02–2.56]	0.043
Tumour lysis syndrome	22/35	0.93 [0.56–1.55]	0.79
Haemophagocytosis	25/32	1.64 [0.98–2.73]	0.058
Hypercalcaemia	9/13	0.95 [0.46–1.98]	0.89
Sepsis	31/39	2.16 [1.33–3.50]	0.002

B-NHL B cell non-Hodgkin lymphoma, *T-NHL* T cell non-Hodgkin lymphoma, *HIV* human immunodeficiency virus, *IPI* International Prognostic Index, *SOFA* sequential organ failure assessment, *HR* hazard ratio, *CI* confidence interval

[a] One matched pair excluded due to unavailable mortality data in one patient

the implementation of specific treatments. Finally, septic patients are at high risk for invasive aspergillosis. Thus, we advise prompt investigations, and consideration for an empirical antifungal treatment.

Strengths and limitations

This study has a number of strengths. To our knowledge, we report the largest study on the clinical features of critically ill patients with T-NHLs. Thus, we provide relevant and updated data for haematologists and intensivists. Moreover, our study is the first to investigate the impact of the lymphoma phenotype on ICU outcome. Finally, we identified some predictors of mortality, which may assist ICU admission triage.

This study also has some limitations. Firstly, the retrospective design may have introduced some selection bias. However, we used validated and robust criteria to identify T-NHL patients (the ICD-10 classification). Secondly, the study was conducted in a single institution. Therefore, the patient recruitment patterns may have significantly influenced our findings. Nonetheless, the standardised policy of ICU admission and the large number of patients with HMs treated in our institution suggest that our results may apply to other environments. Thirdly, we included patients over a 14-year period, during which treatment practices may have changed. However, our major findings are unlikely to be altered by these changes.

In conclusion, critically ill patients with newly diagnosed T-NHLs have advanced stage diseases, high IPI score and mostly experience tumour-related complications. The high rate of ICU survival (almost 80%) and the absence of deleterious impact of T cell phenotype on short-term prognosis support an ICU trial for patients newly diagnosed for the malignancy. However, the poor long-term survival must be taken into account. Thus, extended stay in the ICU or readmission later in the course of the disease should be considered only for selected patients with good response to the haematological treatment. Further studies are needed to confirm our results and to assess whether early treatment of sepsis and haemophagocytic syndrome can translate into better patient outcomes.

Acknowledgments We thank Victoria Mears for helping with English editing.

Compliance with ethical standards

This study was approved by our institutional review board (CECIC Clermont Ferrand – IRB no.5891; Ref. 2007-16). According to French law, informed consent was not required in this retrospective observational study in which the collected data were anonymised.

Conflict of interest GD, LB, CG, SA, LZ, VL, EM, CT and EC declare that they have no competing interests. EA declares the following statements: board member for Gilead, lectures for Alexion, MSD, Astellas, and research grants from MSD, Fisher & Payckle, Pfizer (2012).

Abbreviations AITL, angioimmunoblastic T cell lymphoma; ALCL, anaplastic large-cell lymphoma ALK+; ATLL, adult T cell leukaemia/lymphoma; AUC, area under the curve; COPD, chronic obstructive pulmonary disease; HIV, human immunodeficiency virus; HM, haematological malignancies; HSTCL, hepatosplenic T cell lymphoma; ICU, intensive care Unit; IFI, invasive fungal infection; IPI, international pronostic index; IQR, interquartile range; LDH, lactate dehydrogenase; NHL, non-Hodgkin's lymphoma; NK/TCL, NK/T cell lymphoma; PS, performance status; PTCL-NOS, peripheral T cell Lymphoma-Not otherwise specified; PTCL, peripheral T cell lymphomas; SOFA, sequential organ failure assessment

References

1. Perry AM, Jacques D, Nathwani BN et al (2015) Classification of non-Hodgkin lymphoma in seven geographic regions around the world: review of 4539 cases from the international non-Hodgkin lymphoma classification project. Blood 126:1484–1484
2. Armitage JO, Gascoyne RD, Lunning MA, Cavalli F (2017) Non-Hodgkin lymphoma. Lancet Lond Engl 390:298–310. https://doi.org/10.1016/S0140-6736(16)32407-2
3. Zafrani L, Azoulay E (2014) How to treat severe infections in critically ill neutropenic patients? BMC Infect Dis 14:512. https://doi.org/10.1186/1471-2334-14-512
4. Azoulay E, Pène F, Darmon M, Lengliné E, Benoit D, Soares M, Vincent F, Bruneel F, Perez P, Lemiale V, Mokart D, Groupe de Recherche Respiratoire en Réanimation Onco-Hématologique (Grrr-OH) (2015) Managing critically ill hematology patients: time to think differently. Blood Rev 29:359–367. https://doi.org/10.1016/j.blre.2015.04.002
5. Azoulay E, Mokart D, Pène F, Lambert J, Kouatchet A, Mayaux J, Vincent F, Nyunga M, Bruneel F, Laisne LM, Rabbat A, Lebert C, Perez P, Chaize M, Renault A, Meert AP, Benoit D, Hamidfar R, Jourdain M, Darmon M, Schlemmer B, Chevret S, Lemiale V (2013) Outcomes of critically ill patients with hematologic malignancies: prospective multicenter data from France and Belgium—a groupe de recherche respiratoire en réanimation onco-hématologique study. J Clin Oncol Off J Am Soc Clin Oncol 31:2810–2818. https://doi.org/10.1200/JCO.2012.47.2365
6. Benoit DD, Soares M, Azoulay E (2014) Has survival increased in cancer patients admitted to the ICU? We are not sure. Intensive Care Med 40:1576–1579. https://doi.org/10.1007/s00134-014-3480-8
7. Vose J, Armitage J, Weisenburger D, International T-Cell Lymphoma Project (2008) International peripheral T-cell and natural killer/T-cell lymphoma study: pathology findings and clinical outcomes. J Clin Oncol Off J Am Soc Clin Oncol 26:4124–4130. https://doi.org/10.1200/JCO.2008.16.4558
8. Abramson JS, Feldman T, Kroll-Desrosiers AR, Muffly LS, Winer E, Flowers CR, Lansigan F, Nabhan C, Nastoupil LJ, Nath R, Goy A, Castillo JJ, Jagadeesh D, Woda B, Rosen ST, Smith SM, Evens AM (2014) Peripheral T-cell lymphomas in a large US multicenter cohort: prognostication in the modern era including impact of front-line therapy. Ann Oncol Off J Eur Soc Med Oncol 25:2211–2217. https://doi.org/10.1093/annonc/mdu443
9. Swerdlow SH, Campo E, Pileri SA, Harris NL, Stein H, Siebert R, Advani R, Ghielmini M, Salles GA, Zelenetz AD, Jaffe ES (2016) The 2016 revision of the World Health Organization classification of lymphoid neoplasms. Blood 127:2375–2390. https://doi.org/10.1182/blood-2016-01-643569
10. Thiéry G, Azoulay E, Darmon M, Ciroldi M, de Miranda S, Lévy V, Fieux F, Moreau D, le Gall JR, Schlemmer B (2005) Outcome of cancer patients considered for intensive care unit admission: a hospital-wide prospective study. J Clin Oncol Off J Am Soc Clin Oncol 23:4406–4413. https://doi.org/10.1200/JCO.2005.01.487
11. Vincent JL, de Mendonça A, Cantraine F et al (1998) Use of the SOFA score to assess the incidence of organ dysfunction/failure in intensive care units: results of a multicenter, prospective study. Working group on "sepsis-related problems" of the European Society of Intensive Care Medicine. Crit Care Med 26:1793–1800
12. Henter J-I, Horne A, Aricó M, Egeler RM, Filipovich AH, Imashuku S, Ladisch S, McClain K, Webb D, Winiarski J, Janka G, for the Histiocyte Society (2007) HLH-2004: diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. Pediatr Blood Cancer 48:124–131. https://doi.org/10.1002/pbc.21039
13. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, Bellomo R, Bernard GR, Chiche JD, Coopersmith CM, Hotchkiss RS, Levy MM, Marshall JC, Martin GS, Opal SM, Rubenfeld GD, van der Poll T, Vincent JL, Angus DC (2016) The third international consensus definitions for Sepsis and septic shock (Sepsis-3). JAMA 315:801–810. https://doi.org/10.1001/jama.2016.0287
14. Algrin C, Faguer S, Lemiale V, Lengliné E, Boutboul D, Amorim S, Galicier L, Canet E, Thieblemont C, Azoulay E (2015) Outcomes after intensive care unit admission of patients with newly diagnosed lymphoma. Leuk Lymphoma 56:1240–1245. https://doi.org/10.3109/10428194.2014.922181
15. Normilio-Silva K, de Figueiredo AC, Pedroso-de-Lima AC, Tunes-da-Silva G, Nunes da Silva A, Delgado Dias Levites A, de-Simone AT, Lopes Safra P, Zancani R, Tonini PC, Vasconcelos de Andrade e Silva U, Buosi Silva T, Martins Giorgi J, Eluf-Neto J, Costa A, Abrahão Hajjar L, Biasi Cavalcanti A (2016) Long-term survival, quality of life, and quality-adjusted survival in critically ill patients with Cancer. Crit Care Med 44:1327–1337. https://doi.org/10.1097/CCM.0000000000001648
16. Zampieri FG, Bozza FA, Moralez GM, Mazza DDS, Scotti AV, Santino MS, Ribeiro RAB, Rodrigues Filho EM, Cabral MM, Maia MO, D'Alessandro PS, Oliveira SV, Menezes MAM, Caser EB, Lannes RS, Alencar Neto MS, Machado MM, Sousa MF, Salluh JIF, Soares M (2017) The effects of performance status one week before hospital admission on the outcomes of critically ill patients. Intensive Care Med 43:39–47. https://doi.org/10.1007/s00134-016-4563-5
17. Soares M, Salluh JIF, Carvalho MS, Darmon M, Rocco JR, Spector N (2006) Prognosis of critically ill patients with cancer and acute renal dysfunction. J Clin Oncol Off J Am Soc Clin Oncol 24:4003–4010. https://doi.org/10.1200/JCO.2006.05.7869
18. Park C-M, Koh Y, Jeon K, Na S, Lim CM, Choi WI, Lee YJ, Kim SC, Chon GR, Kim JH, Kim JY, Lim J, Rhee CK, Park S, Kim HC, Lee JH, Lee JH, Park J, Cho J, Koh SO, Suh GY, Validation of Simplified acute physiology score 3 in Korean Intensive care unit (VSKI) study group, Korean Study Group on Respiratory Failure (KOSREF) (2014) Impact of eastern cooperative oncology group

performance status on hospital mortality in critically ill patients. J Crit Care 29:409–413. https://doi.org/10.1016/j.jcrc.2014.01.016

19. Taccone FS, Van den Abeele A-M, Bulpa P et al (2015) Epidemiology of invasive aspergillosis in critically ill patients: clinical presentation, underlying conditions, and outcomes. Crit Care Lond Engl 19:7. https://doi.org/10.1186/s13054-014-0722-7
20. Bassetti M, Garnacho-Montero J, Calandra T, Kullberg B, Dimopoulos G, Azoulay E, Chakrabarti A, Kett D, Leon C, Ostrosky-Zeichner L, Sanguinetti M, Timsit JF, Richardson MD, Shorr A, Cornely OA (2017) Intensive care medicine research agenda on invasive fungal infection in critically ill patients. Intensive Care Med 43:1225–1238. https://doi.org/10.1007/s00134-017-4731-2
21. Lortholary O, Gangneux J-P, Sitbon K, Lebeau B, de Monbrison F, le Strat Y, Coignard B, Dromer F, Bretagne S, French Mycosis Study Group (2011) Epidemiological trends in invasive aspergillosis in France: the SAIF network (2005-2007). Clin Microbiol Infect Off Publ Eur Soc Clin Microbiol Infect Dis 17:1882–1889. https://doi.org/10.1111/j.1469-0691.2011.03548.x
22. Romani L (2011) Immunity to fungal infections. Nat Rev Immunol 11:275–288. https://doi.org/10.1038/nri2939
23. Wohlfarth P, Carlström A, Staudinger T, Clauss S, Hermann A, Rabitsch W, Bojic A, Skrabs C, Porpaczy E, Schiefer AI, Valent P, Knöbl P, Agis H, Hauswirth A, Jäger U, Kundi M, Sperr WR, Schellongowski P, Arbeitsgruppe für hämato-onkologische Intensivmedizin der Österreichischen Gesellschaft für Internistische und Allgemeine Intensivmedizin und Notfallmedizin (ÖGIAIN) (2016) Incidence of intensive care unit admission, outcome and post intensive care survival in patients with diffuse large B-cell lymphoma. Leuk Lymphoma 57:1831–1838. https://doi.org/10.3109/10428194.2015.1106537
24. Foss FM, Zinzani PL, Vose JM, Gascoyne RD, Rosen ST, Tobinai K (2011) Peripheral T-cell lymphoma. Blood 117:6756–6767. https://doi.org/10.1182/blood-2010-05-231548