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Other authors had no conflict of interest to declare.

Ethics approval

The study was approved by the French Intensive Care Society Institutional Review Board (CE SRLF 20-15) and information was given to the patients or their relatives.

Availability of data and material

Our data are available to ensure transparency.

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ABSTRACT

Introduction. To describe the reasons for intensive care unit (ICU) admission and to evaluate the outcomes and prognostic factors of patients with primary central nervous system lymphoma (PCNSL) admitted to the ICU.

Patients and Methods. Retrospective observational cohort study of 101 PCNSL patients admitted to three ICUs over a two-decade period.

Results. Acute respiratory failure, mainly secondary to aspiration pneumonia and *Pneumocystis jirovecii* pneumonia, was the leading reason for ICU admission (33%). Aspiration pneumonia was more common in patients with brainstem tumor (67% vs. 0%, $p<0.001$), whereas patients with intracranial hypertension were more frequently admitted for coma without seizures (61% vs. 9%, $p=0.004$). Hospital and 6-month mortality were 47% and 53%, respectively. In multivariate analysis, admission for coma without seizures (OR 7.28), cancer progression (OR 3.47), mechanical ventilation (OR 6.58) and vasopressors (OR 4.07) were associated with higher 6-month mortality. Karnofsky performance status prior to ICU admission was independently associated with lower 6-month mortality (OR 0.96).

Discussion. Six-month survival of PCNSL patients admitted to the ICU appears to be relatively favorable (around 50%) and the presence of PCNSL alone is not a relevant criterion for ICU refusal. Predictive factors of mortality may help clinicians to make optimal triage decisions.

INTRODUCTION

Primary central nervous system lymphoma (PCNSL) is characterized by large B-cell proliferation limited to the central nervous system and the eyes, with no evidence of concomitant systemic disease [1]. Although PCNSL is a rare cancer that accounts for less than 5% of all newly diagnosed primary malignant brain tumors, the incidence of PCNSL is increasing in immunocompetent patients, especially in older people [2-4].

Cancer patients account for 20% of all intensive care unit (ICU) admissions [5, 6, 8] and it has been estimated that 5% of all cancer patients will require ICU admission at some point [2]. Because PCNSL patients are at high risk of life-threatening complications, they present a high probability of ICU admission. Reasons for ICU admission include, but are not limited to, neurological disorders related to the site of the brain tumor (e.g. seizures or coma secondary to intracranial hypertension,) and chemotherapy toxicity, such as acute renal failure [8] and sepsis [9-11].

Only limited data are currently available concerning the prognosis of PCNSL patients admitted to the ICU. Most data are derived from case series comprising patients with gliomas as well as patients with PCNSL [9, 12, 13]. However, compared to gliomas, especially high-grade gliomas, PCNSL is highly sensitive to chemotherapy [14]. Over recent decades, considerable progress in anticancer therapies [15-17] has improved the outcome of PCNSL patients [11]. A better understanding of the precipitating factors leading to ICU admission and the determinants of the outcome of PCNSL patients admitted to the ICU could help to improve the quality of triage and management decisions.

The primary objective of our study was to describe the clinical features of PCNSL patients admitted to the ICU, especially by analyzing the reasons for ICU admission. The secondary objective was to assess the hospital mortality and 6-month mortality rates and to identify factors associated with hospital mortality and 6-month mortality. These analyses were conducted on a large cohort of PCNSL patients.

METHODS

This retrospective observational multicenter cohort study was carried out from February 1998 to June 2019 in three French medical ICUs: a 16-bed ICU in a respiratory department (circa 1,200 admissions per year), a 16-bed ICU in a neurology department (circa 300 admissions per year) and a 25-bed ICU in a cardiology department (circa 1,000 admissions per year). These three ICUs are part of a 1600-bed university hospital with a strong neurological orientation, including a specific neuro-oncology department and the national reference center for PCNSL (i.e. LOC Network) that manages about 40 new patients per year. The study was approved by the

French Intensive Care Society Institutional Review Board (CE SRLF 20-15) and patients or their relatives were provided with information about the study. Data from part of this cohort have been previously published [9, 12].

Patient selection

Data were extracted from the ICU database (FusionF, Varimed, France). This database is prospectively managed and comprehensively describes all patient stays. The database of the three ICU comprised 25,672 records, corresponding to 100% of admissions over the study period. This set of 25,672 records was retrospectively searched for all consecutive cases of "primary brain tumor" and "non-Hodgkin's lymphoma" during the study period. After analysis of each selected record, patients meeting the criteria of PCNSL according to the 2016 World Health Organization Classification of Tumors of the Central Nervous System [18] were included in this study. Patients with previous or concurrent systemic lymphoma, another type of primary malignant brain tumor (e.g. glioma), benign brain tumor, or brain metastases from solid cancers were excluded. Patient who had recently undergone neurosurgery (< 2 weeks) or any other type of surgery (< 4 weeks) and patients under the age of 18 years were also excluded. For patients with several ICU admissions, only the first ICU stay was included in this analysis

All patients had histologic (stereotactic brain biopsy) or cytologic (cerebrospinal fluid cytology) confirmation of PCNSL [4, 19].

Data collection

At the time of ICU admission, demographic data such as gender, age, pre-existing immunosuppression and comorbidities according to the Charlson Comorbidity Index [20], physiologic variables such as body temperature, respiratory rate, heart rate, systolic blood pressure and Glasgow coma scale and various laboratory variables were recorded. Neutropenia was defined by a neutrophil count less than 0.5 10^9/L. Cerebrospinal fluid levels of protein, interleukin (IL)-6 and IL-10 were also recorded. The reason for ICU admission was determined by consensus of two experienced senior intensivists (M.D. and J.M.), based on the main symptoms at the time of ICU admission and a set of clinical, laboratory, radiologic and microbiologic features recorded during the ICU stay, as previously reported [9] and detailed in the online supplement. The clinical severity of the patients was assessed by the Simplified Acute Physiology Score (SAPS) II [21] and the Sequential Organ Failure Assessment (SOFA) score [22]. The functional status was assessed during the week before ICU admission, using the Karnofsky Performance Status Scale [23]. Cancer-related therapies (chemotherapy, brain radiation, and autologous stem cell transplantation) were recorded. The disease status was classified according to international definitions [24] as: 1) newly diagnosed, when the tumor was diagnosed during the four weeks preceding or

during the ICU stay and when no anticancer therapy had yet been delivered, 2) complete or partial response, or 3) progression. The site of the brain tumor and the presence of intracranial hypertension on admission were also recorded. Intracranial hypertension was defined as headache or altered level of consciousness associated with cerebral edema, midline shift and/or brain herniation on brain CT-scan or magnetic resonance imaging [25, 26].

Life-sustaining interventions, hospital mortality and mortality six months after ICU admission (6-month mortality) were recorded.

Statistical analysis

Data were expressed as number and percentage (n, %) for categorical variables, and as median (0.25 – 0.75 interquartile interval) for continuous variables. Categorical variables were compared using the Chi-square test or Fisher's exact test and continuous variables were compared using the Mann-Whitney test. All tests were two-sided, and the significance level was set at 0.05. Multivariate logistic regression was used to identify factors associated with hospital and 6-month mortality, adjusted for all other variables identified by univariate analysis with $p < 0.20$, except for SAPS II, which was redundant with other variables. Missing data were imputed by the nearest neighbor method (1.5%). Odds ratios (ORs) and their 95% confidence intervals were calculated for significant factors. Kaplan-Meier survival curves according to disease status and reason for ICU admission were computed for 6-month mortality. The study period was subdivided into two periods (1998 to 2008 and 2009 to 2019) and changes in mortality rates and severity over periods were analyzed using a Chi-square test and a Mann-Whitney test, respectively. All analyses were performed with R software version 3.5.2.

RESULTS

Figure 1 displays the study flow chart. Of the 101 patients included in the study, 71 (70%) were admitted to the respiratory department ICU, 22 (22%) were admitted to the neurological ICU and 8 (8%) were admitted to the cardiology department ICU.

Patient characteristics

The diagnosis of PCNSL was based on stereotactic biopsy in 91 (90%) patients and cytological analysis of cerebrospinal fluid in the remaining 10 (10%) patients. Ninety-seven (97%) patients had diffuse large B-cell lymphoma and the remaining four (4%) patients had T-cell lymphoma. The main characteristics of the 101 patients are displayed in Table 1. Seventeen patients (17%) had pre-existing immunosuppression, 12 (12%) of whom had undergone solid organ transplantation and 5 (5%) of whom had human immunodeficiency virus (HIV) infection. Prior to admission, 82 (82%) patients had received chemotherapy, 14 (14%) had received brain

radiotherapy, 11 (11%) had received autologous stem cell transplantation and 84 (84%) had received high-dose corticosteroid therapy. Cerebrospinal fluid protein, IL-6 and IL-10 assays during the three months prior to ICU admission were available for 57 (57%), 35 (35%) and 35 (35%) patients, respectively. Median CSF protein was 0.7 (0.5-1.2) g/L, median CSF IL-6 was 6 (3-24) pg/mL and median CSF IL-10 was 8 (1-42) pg/mL. IL-6 and IL-10 were undetectable in 9 (26%) and 9 (26%) patients, respectively (not necessarily the same patients). For the 88 (88%) patients in whom the diagnosis of PCNSL was established prior to admission, the median time interval between diagnosis and ICU admission was 4 (1-11) months.

Reasons for ICU admission

Reasons for ICU admission are reported in Table 1. Coma was the main reason for ICU admission (47%). Among the patients admitted for coma, intracranial hypertension was more common in comatose patients without seizures than in comatose patients with seizures (61% vs. 9%, p=0.004). Admission for coma without seizures was more common among patients with newly diagnosed or progressive disease than in patients with complete or partial response (33% vs. 9%, p = 0.003).

Acute respiratory failure (ARF) was the second leading reason for ICU admission (32%), mostly secondary to acute infectious pneumonia (27/33 [82%]), with a substantial proportion of cases of aspiration pneumonia (9/27) and *Pneumocystis jirovecii* pneumonia (7/27). More details on the causes of ARF are listed in Table S1 in the Online Supplement. The Glasgow coma scale score on admission was significantly lower in patients with aspiration pneumonia than in patients with other causes of ARF (7 [6-11] vs. 14 [13-15], p=0.016). Brainstem tumor was more frequently observed in patients with aspiration pneumonia than in patients with other causes of ARF (67% vs. 0%, p<0.001).

Hospital and 6-month mortality

Intensive care unit, hospital and 6-month mortality were 26%, 47% and 53%, respectively. Hospital mortality, 6-month mortality and SAPS II were not significantly different between the two periods of admission (p = 0.637, p= 0.835 and p = 0.785, respectively). Lengths of ICU and hospital stay were 6 (3-10) days and 19 (8-44) days, respectively.

Table 1 shows the factors associated with hospital mortality identified by univariate analysis. Multivariate logistic regression analysis identified four variables significantly associated with higher hospital mortality: pre-existing immunosuppression (Odds ratio [OR] 5.35, 95% confidence interval [95%CI] 1.07-30.79, p=0.047), Charlson comorbidity index (OR 1.44, 95%CI 1.08-1.99, p=0.017), mechanical ventilation (OR 9.74, 95%CI 3.09-36.15, p<0.001), and vasopressors (OR 4.71, 95%CI 1.41-17.49, p=0.015).

Table 2 shows the factors associated with 6-month mortality identified by univariate analysis. Multivariate logistic regression analysis identified five variables significantly associated with 6-month mortality. Admission for coma without seizures (OR 7.28, 95%CI 1.48-51.40, p=0.025), cancer progression (OR 3.47, 95%CI 1.09-12.46, p=0.042), mechanical ventilation (OR 6.58, 95%CI 2.13-22.76, p=0.002) and vasopressors (OR 4.07, 95%CI 1.16-16.04, p=0.034) were associated with higher 6-month mortality, while one factor, Karnofsky performance status prior to ICU admission, was independently associated with lower 6-month mortality (OR 0.96, 95%CI 0.93-0.99, p=0.027).

Figure 2 displays the 6-month survival probability according to the reasons for ICU admission and disease status. The highest 6-month survival probability was observed in patients with responsive disease admitted for coma with seizures or sepsis. More details on Figure 2 are reported in the Online Supplement.

DISCUSSION

The main results of this study can be summarized as follows. In PCNSL patients admitted to the ICU: 1) ARF, mainly due to aspiration pneumonia, was the leading reason for ICU admission, 2) aspiration pneumonia was associated with the presence of brainstem tumor, 3) medium-term survival was relatively high and 4) admission for coma without seizures, need for life-supporting intervention (mechanical ventilation, vasopressors) and presence of pre-existing immunosuppression were independently associated with mortality. To the best of our knowledge, this is the largest published cohort of PCNSL patients admitted to the ICU.

Comparison with existing data

ARF is the leading reason for ICU admission of cancer patients [27, 28] and is generally related to opportunistic or non-opportunistic lung infections, secondary to neutropenia [29]. In our study, ARF was the leading reason for ICU admission, mainly secondary to acute infectious pneumonia. Due to the association of polychemotherapy and high-dose corticosteroids used to treat PCNSL, these patients are at increased risk of neutropenia and subsequent infection. Compared to patients with other primary malignant brain tumors [9, 12, 13] or other solid cancers [30, 31], we found a relatively high proportion of patients with neutropenia, similar to that observed in critically ill patients with other systemic hematologic malignancies (e.g. leukemia, lymphoma, myeloma) [28]. Dysphagia and swallowing dysfunction are also commonly reported in PCNSL patients and in patients with other primary malignant brain tumors [32], predisposing to aspiration and subsequent pneumonia. Finally, we observed a high rate of *Pneumocystis jirovecii* pneumonia, probably related to CD4+ cell-mediated immunosuppression (corticosteroids, brain radiotherapy, methotrexate), as reported in similar settings [33].

Tumor site had an impact on the reasons for ICU admission, as the higher rate of aspiration pneumonia observed in patients with brainstem tumor suggest direct impairment of anatomic structures extending from the brainstem nuclei to nerves innervating laryngeal muscles. The relatively low proportion of ICU admissions for coma with seizures (11%) observed in PCNSL patients, compared to patients with other primary malignant brain tumors, especially gliomas (26% to 41%) [12, 13], could also be explained by a higher rate of subcortical tumor sites [34, 35]. Tumor stage also had an impact on the reasons for ICU admission, as patients with progressive disease were more frequently admitted for coma secondary to intracranial hypertension without seizures (e.g. tumor swelling, perilesional edema, tumor bleeding) or a direct mass-effect on the brainstem (in the case of infratentorial tumor).

Hospital and 6-month mortality observed in PCNSL patients were similar to those observed in patients with other systemic hematologic malignancies [28] or other solid cancers [29, 30, 36, 37], suggesting that, as for other types of cancer, the mere presence of PCNSL does not constitute sufficient reason to deny ICU admission. Because patients with PCNSL have a better prognosis than patients with high-grade glioma [6, 7, 17], we could have expected better survival of PCNSL patients. However, the mortality observed in our study was similar to that observed in series including high-grade glioma patients [13]. Despite the better prognosis of PCNSL compared to high-grade glioma, we did not observe better ICU survival in the PCNSL patients of our series. This could be explained by the lower proportion of admission for seizures in PCNSL compared to gliomas [12]. If the prognosis of comatose patients with seizures admitted to the ICU is generally good [38], in our study, the absence of seizures constituted clearly an independent risk factor for mortality. Indeed, only 17% of patients admitted for coma without seizures are still alive at 6 months vs. 54% when admitted for coma with seizures. This is an important finding in terms of triage decisions for ICU admission in comatose patients, in whom prompt discrimination between seizures or intracranial hypertension as the cause of the coma would avoid futile use of ICU resources. Initiation of mechanical ventilation and use of vasopressors were independent predictors of mortality, confirming numerous reports demonstrating the deleterious impact of mechanical ventilation and vasopressors on the prognosis of ICU patients with hematologic malignancies [28] or solid tumors [27, 35, 36].

Finally, we found that the presence of a pre-existing immunosuppression in PCNSL was a strong predictor of hospital mortality, confirming accumulated evidence that critically ill immunocompromised patients are exposed to a roughly two-fold increased risk of mortality compared to critically ill immunocompetent patients, especially in the presence of ARF. More specifically, this result is in line with a recent report showing

that HIV-positive patients with PCNSL, compared to HIV-negative patients, have a lower probability of complete remission and overall survival [37].

Pictured summary for clinical practice

Based on evidence provided by our results and based on our experience as a national reference center, we thought that a real-life clinical picture-based approach might provide a simple visualization of a kind of hierarchy between typical patients, with higher and lower survival probabilities (Figure 3). These various scenarios are designed to practically address the most relevant variables to determining the goal of care in a given patient when ICU admission is considered. These relevant variables include: (1) performance status, (2) reasons for ICU admission (seizures or sepsis vs. coma without seizures), (3) number of organ failures (one vs. two or more), (4) disease status (responsive vs. progressive, and also various less quantifiable variables, such as quality of life or patient willingness).

Limitations

The present study has several limitations. First, it was a retrospective study, which involves a potential bias in patient selection or data collection. However, data were extracted from a prospectively managed database and the rarity of the disease remains a major obstacle to prospective studies, even with a multicenter design. Second, although these patients exhibited a relatively high survival probability six months after ICU discharge, no information was available concerning their functional status and quality of life, which is likely to be altered in this setting. Third, we did not report any information on possible maintenance of anticancer therapy after ICU discharge, which may influence 6-month survival. Finally, we only considered patients admitted to the ICU. Patients who were not considered for ICU admission for any reason, such as poor prognosis or performance status, were therefore not included in this analysis.

Conclusion

In conclusion, in this study, we report that almost one-half of all PCNSL patients admitted to the ICU were alive 6 months after ICU discharge, suggesting that the simple presence of PCNSL should not preclude patients from the potential benefits of ICU admission. Simple and easily identifiable factors, such as reasons for ICU admission, disease status and Karnofsky performance status at ICU admission, are strong independent predictors of medium-term mortality that may help clinicians to optimize triage decisions.

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Table legends

Table 1. Univariate analysis: factors associated with hospital mortality

Table 2. Univariate analysis: factors associated with 6-month mortality

Figure Legends

Figure 1. Study flow chart

Figure 2. Kaplan-Meier survival curves (6-month mortality) according to the reason for intensive care unit (ICU) admission (left panel) and disease status (right panel).

Figure 3. Experience-based typical clinical situations with which neuro-oncologists and intensivists must be familiar when considering transfer of a primary central nervous system lymphoma patient to the intensive care unit (ICU).

These seven scenarios are classified from the best (*scenario 1*) to the worst (*scenario 7*) survival probability after ICU admission.

ICU, intensive care unit; KPS, Karnofsky performance status; HIV, human immunodeficiency virus; IH, intracranial hypertension

Supplementary data

Details on the definitions and criteria used for the diagnosis of the cause of acute respiratory failure.

*Acute-on-chronic respiratory failure generally corresponds to an acute exacerbation of COPD (AECOPD) or asthma. AECOPD may have a sudden or progressive onset and last several days to several weeks. In a patient with known COPD, the diagnosis of AECOPD is based on the presence of worsening of respiratory symptoms beyond daily variations (dyspnea, cough, sputum volume and/or purulence), requiring a change of treatment (including a simple increase in bronchodilator doses. In this case, exacerbation is defined by increased doses for > 24 h). The diagnosis of AECOPD requires the exclusion of community-acquired pneumonia (CAP), pulmonary embolism and acute cardiogenic pulmonary edema. In particular, chest-X ray must be inconclusive with no lobar consolidation and ARF is likely to be hypercapnic. The mere presence of ARF in a COPD patient is not sufficient to conclude on AECOPD. For example, if a COPD patient presented typical features of CAP with rapid onset of lobar consolidation, chest pain, fever and marked asthenia, the cause of ARF was classified as Acute Infectious Pneumonia and not Acute-on-chronic respiratory failure.
*Acute infectious pneumonia was defined according to the Guidelines [Woodhead M, Clin Microbiol Infect, 2011] by an acute illness with cough and at least one of: new focal chest signs, fever or dyspnea/tachypnea, with no other obvious cause, associated with a new radiological infiltrate (< 7 days) likely to be localized in a lung lobe or segment.
*Pulmonary embolism was defined by the presence of at least one segmental obstruction on the contrast-enhanced chest CT scan. Contrast-enhanced chest CT scan was performed in all patients with pulmonary embolism.
*Cardiogenic pulmonary edema was defined according to Guidelines and included underlying chronic heart failure, ARF without fever, clinical signs of congestion (peripheral edema, rapid weight gain, bilateral crackles, orthopnea, systemic arterial hypertension), echocardiographic signs of left ventricular dysfunction or increased preload pressure, and elevated serum biomarkers such as natriuretic peptides (BNP and NT-proBNP).

Details on the definitions and criteria used for the diagnosis of the two main etiologies of acute infectious pneumonia: *Pneumocystis jirovecii* pneumonia and aspiration pneumonia.

**Pneumocystis jirovecii* pneumonia: the first step in the diagnosis of Pneumocystis infection is the presence of a high clinical suspicion. High clinical suspicion in our study included a compatible clinical history (e.g. corticosteroid therapy, radiation therapy, T-cell immunodeficiency), compatible clinical presentation (e.g. progressive dyspnea or severe subacute [one week] respiratory failure, with fever, with no other organ failure [no shock]) and suggestive radiological presentation with alveolo-interstitial infiltrates presenting as bilateral ground glass opacities. Diagnostic chest CT scan was performed in all PCP patients in our study around the time of ICU admission.
Bronchoalveolar lavage was performed in all PCP patients. PCP was confirmed when *P. jirovecii* cysts or trophozoites were identified by standard staining or immunofluorescence in BAL fluid.
Different stains were used during the study to identify trophic (Wright-Giemsa or modified Papanicolaou stains) or cystic forms (Gomori methenamine silver or toluidine blue). Over the last 10 years, an additional immunofluorescence staining technique using fluorescein-conjugated monoclonal antibodies has been systematically performed. Our laboratory now systematically uses three different staining techniques: Giemsa, silver (Musto) and immunofluorescence.
BAL fluid of HIV-negative PCP patients compared to HIV-positive patients contains numerous inflammatory cells (mainly neutrophils), but may contain very few or even no *Pneumocystis jirovecii* bodies, which is why PCR testing of BAL fluid has been developed. The high sensitivity of PCR testing of BAL fluid is therefore very helpful, particularly as quantitative PCR can help to distinguish infection from colonization (cut-off of 10,000 copies/mL in our center). However, as this cut-off has not been clearly established in the literature, we prefer not to use this cut-off for the diagnosis of PCP in our study.

*Aspiration pneumonia was defined according to the Guidelines [*Woodhead M, Clin Microbiol Infect, 2011*] by acute lower respiratory tract infection in patients with suspected or obvious swallowing difficulties. Aspiration pneumonia is generally localized in the lower region of the lung, predominantly the right lower and middle lobes.

Table S1. Details on the diagnosis of acute respiratory failure

Diagnosis of acute respiratory failure	**n = 33**
Acute-on-chronic respiratory failure, *n (%)*	**0 (0)**
Acute infectious pneumonia	**27 (82)**
Documented bacterial pneumonia, *n (%)*	4 (15)
Undocumented bacterial pneumonia, *n (%)*	6 (22)
Aspiration pneumonia, *n (%)*	9 (33)
Pneumocystis jirovecii pneumonia, *n (%)*	7 (26)
Viral pneumonia (influenza pneumonia), *n (%)*	1 (4)
Pulmonary embolism, *n (%)*	**1 (3)**
Cardiogenic pulmonary edema, *n (%)*	**2 (7)**
Other, *n (%)*	**3 (9)**
Methotrexate-induced hypersensitivity pneumonitis, *n (%)*	2 (66)
Acute interstitial pneumonia after autologous stem cell transplantation, *n (%)*	1(34)

Details on Figure 2. Two-by-two comparisons of six-month cumulative survival probability according to the reasons for intensive care unit (ICU) admission and disease status.

Cumulative survival probability according to disease status, Log-rank p-value:

- Partial or complete response vs. newly diagnosed, p = 0.169
- Partial or complete response vs. progression, p = 0.002
- Progression vs. newly diagnosed, p = 0.325

Cumulative survival probability according to the reason for admission, Log-rank p-value

- Coma with seizures vs. Sepsis or septic shock, p = 0.903
- Coma with seizures vs. Acute respiratory failure, p = 0.825
- Coma with seizures vs. Coma without seizures, p = 0.026
- Sepsis or septic shock vs. acute respiratory failure, p = 0.321
- Sepsis or septic shock vs. Coma without seizures, p = 0.009
- Acute respiratory failure vs. Coma without seizures, p = 0.063

Supplementary data

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- Sepsis or septic shock vs. Coma without seizures, p = 0.009
- Acute respiratory failure vs. Coma without seizures, p = 0.063

Table 1 Univariate analysis: factors associated with hospital mortality

Variables	Hospital Mortality			*P-value*
	All (n = 101)	**Survivors (n = 54)**	**Non-survivors (n = 47)**	
Age, *years*	60 [54-69]	61 [54-70]	60 [53-69]	0.966
Gender (male), *n (%)*	63 (62)	32 (59)	31 (66)	0.488
Charlson comorbidity index	4 [3-6]	4 [2-5]	4 [3-6]	0.055
Pre-existing immunosuppression, *n (%)*	17 (17)	5 (9)	12 (26)	0.029
KPS at admission, %	60 [50-70]	70 [60-75]	60 [40-70]	**0.021**
Disease status at admission				
Progression, *n (%)*	45 (45)	18 (33)	27 (57)	**0.026**
Newly diagnosed, *n (%)*	13 (13)	6 (9)	7 (15)	0.383
Partial/complete response, *n (%)*	43 (43)	29 (54)	14 (30)	**0.015**
Tumor site				
Infratentorial site, *n (%)*	25 (25)	9 (17)	16 (34)	**0.044**
Brainstem site, *n (%)*	17 (17)	5 (9)	12 (26)	**0.029**
Orbital involvement, *n (%)*	9 (9)	7 (13)	2 (4)	0.170
Intracranial hypertension, *n (%)*	27 (27)	10 (19)	17 (36)	**0.046**
Reason for admission				
Acute respiratory failure, *n (%)*	33 (33)	18 (33)	15 (32)	0.880
Sepsis/Septic shock, *n (%)*	24 (24)	14 (26)	10 (21)	0.584
Coma without seizures, *n (%)*	23 (23)	9 (17)	14 (30)	0.117
Coma with seizures, *n (%)*	11 (10)	7 (13)	4 (9)	0.537
Other, *n (%)*	10 (10)	6 (11)	4 (8)	0.678
Simplified Acute Physiology Score II	47 [34-60]	42 [30-52]	52 [45-67]	**< 0.001**
Physiological variables at admission				
Glasgow coma scale	13 [7-15]	14 [11-15]	9 [4-13]	**< 0.001**
Heart rate, *beats/min*	101 [80-117]	97 [81-117]	103 [80-117]	1.000
Systolic blood pressure, *mmHg*	122 [109-140]	121 [108-137]	124 [110-143]	0.538
Respiratory rate, *cycle/minute*	22 [19-28]	23 [19-29]	22 [19-27]	0.281
Temperature, *°C*	38 [37-38]	38 [37-39]	37 [37-38]	0.318
Laboratory variables at admission				
Leukocyte count, $10^9/L$	7.1 [0.9-12.4]	6.5 [0.3-11.2]	8.3[1.4-13.3]	0.334
Neutropenia, $< 500/mm^3$, *n (%)*	24 (24)	13 (24)	11 (23)	0.937
Serum creatinine, *µmol/L*	90 [57-142]	76 [53-108]	107 [66-189]	**0.012**
Serum lactate dehydrogenase, *U/L*	497 [378-671]	440 [345-626]	565 [426-778]	**0.023**
Life-sustaining intervention				
Mechanical ventilation, *n (%)*	50 (50)	17 (32)	33 (70)	**< 0,001**
Vasopressor, *n (%)*	30 (30)	9 (17)	21 (45)	**0.002**
Renal replacement therapy, *n (%)*	9 (9)	3 (6)	6 (13)	0.297

Data are expressed as number and percentage (n, %) for categorical variables, and median (interquartile interval) for continuous variables

KPS, Karnofsky performance status

Table 2. Univariate analysis: factors associated with 6-month mortality

Variables	6-month mortality		*P-value*
	Survivors (n = 42)	**Non-survivors (n = 59)**	
Age, *years*	60 [53-69]	61 [56-70]	0.372
Gender (male), *n (%)*	23 (55)	40 (68)	0.183
Charlson comorbidity index	4 [3-6]	4 [3-6]	0.891
Pre-existing immunosuppression, *n (%)*	4 (10)	13 (22)	0.216
KPS at ICU admission, %	70 [60-80]	60 [50-70]	0.008
Disease status at admission			
Cancer progression, *n (%)*	12 (29)	33 (56)	0.008
Newly diagnosed, *n (%)*	5 (12)	8 (14)	0.757
Controlled, *n (%)*	24 (57)	18 (31)	0.012
Tumor site			
Infratentorial site, *n (%)*	7 (17)	18 (31)	0.212
Brainstem site, *n (%)*	4 (10)	13 (22)	0.097
Orbital involvement, *n (%)*	6 (14)	3 (5)	0.158
Intracranial hypertension *n (%)*	7 (17)	20 (34)	0.054
Reason for admission			
Acute respiratory failure, *n (%)*	13 (31)	20 (34)	0.756
Sepsis/Septic shock, *n (%)*	13 (31)	11 (19)	0.152
Coma without seizures, *n (%)*	4 (10)	19 (32)	0.008
Coma with seizures, *n (%)*	6 (14)	5 (8)	0.519
Other, *n (%)*	6 (14)	4 (7)	0.312
Simplified Acute Physiology Score II	39 [28-50]	52 [43-67]	< 0.001
Physiological variables at admission			
Glasgow coma scale	15 [12-15]	10 [6-14]	< 0.001
Heart rate, *beats/min*	90 [79-114]	104 [83-120]	0.201
Systolic blood pressure, *mmHg*	119 [105-135]	125 [112-143]	0.148
Respiratory rate, *cycle/minute*	22 [19-28]	23 [20-28]	0.956
Temperature, *°C*	38 [37-39]	37 [37-38]	0.512
Laboratory variables at admission			
Leukocyte count, */mm^3*	6.5 [0.5-11.1]	8.0 [1.4-13.7]	0.385
Neutropenia, *< 500 / mm^3*, *n (%)*	10 (24)	14 (24)	0.993
Serum creatinine, *µmol/L*	76 [56-112]	100 [61-169]	0.193
Serum lactate dehydrogenase, *U/L*	438 [353-573]	563 [405-789]	0.031
Life-sustaining intervention			
Mechanical ventilation, *n (%)*	11 (26)	39 (66)	< 0.001
Vasopressor, *n (%)*	7 (17)	23 (39)	0.016
Renal replacement therapy, *n (%)*	3 (7)	6 (10)	0.732

Data are expressed as number and percentage (n, %) for categorical variables, and median (interquartile interval) for continuous variables

KPS, Karnofsky performance status

25,672 intensive care unit admissions

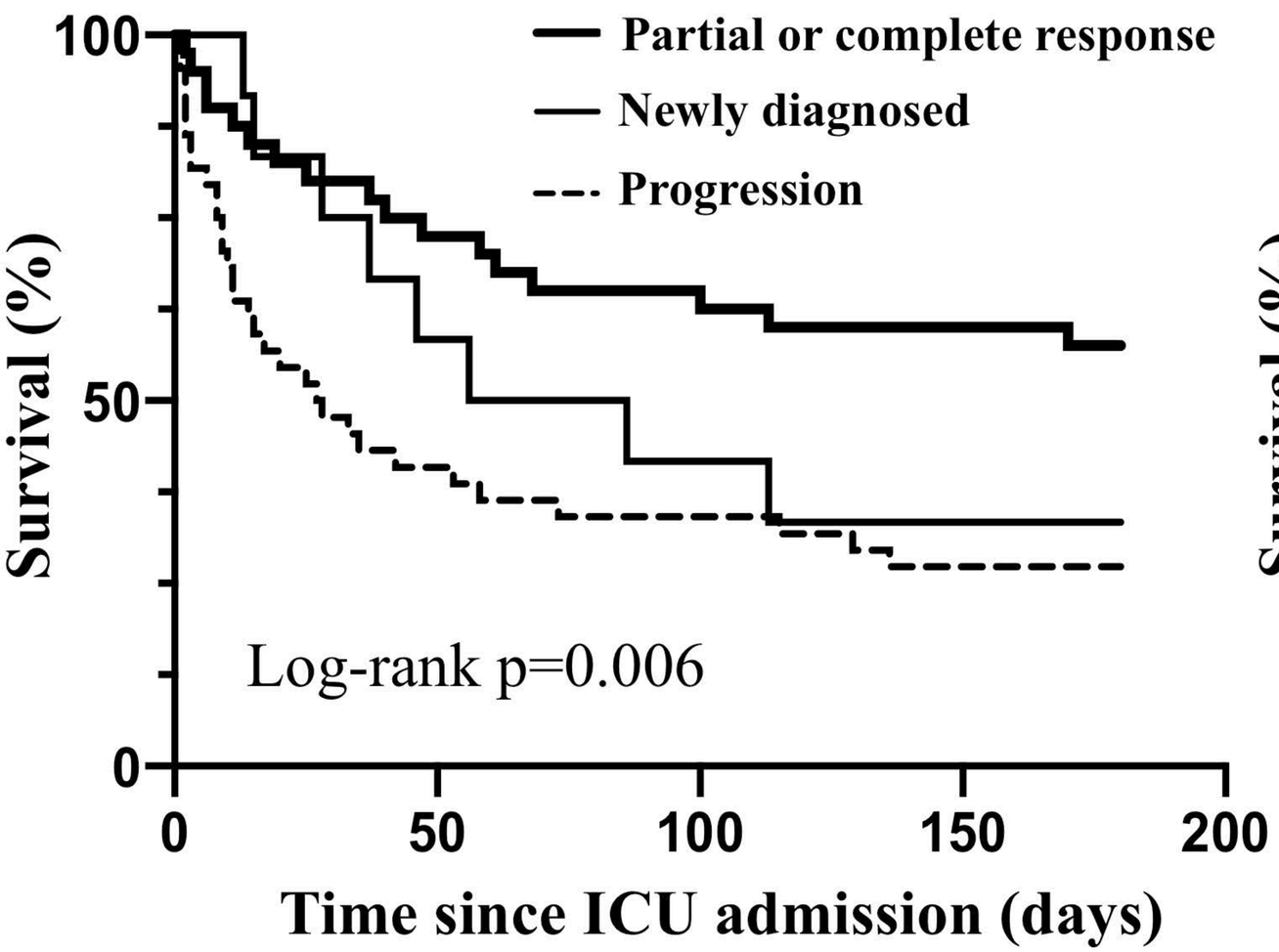
936 admissions of patients with "primary brain tumor" or "non Hodgkin's lymphoma"

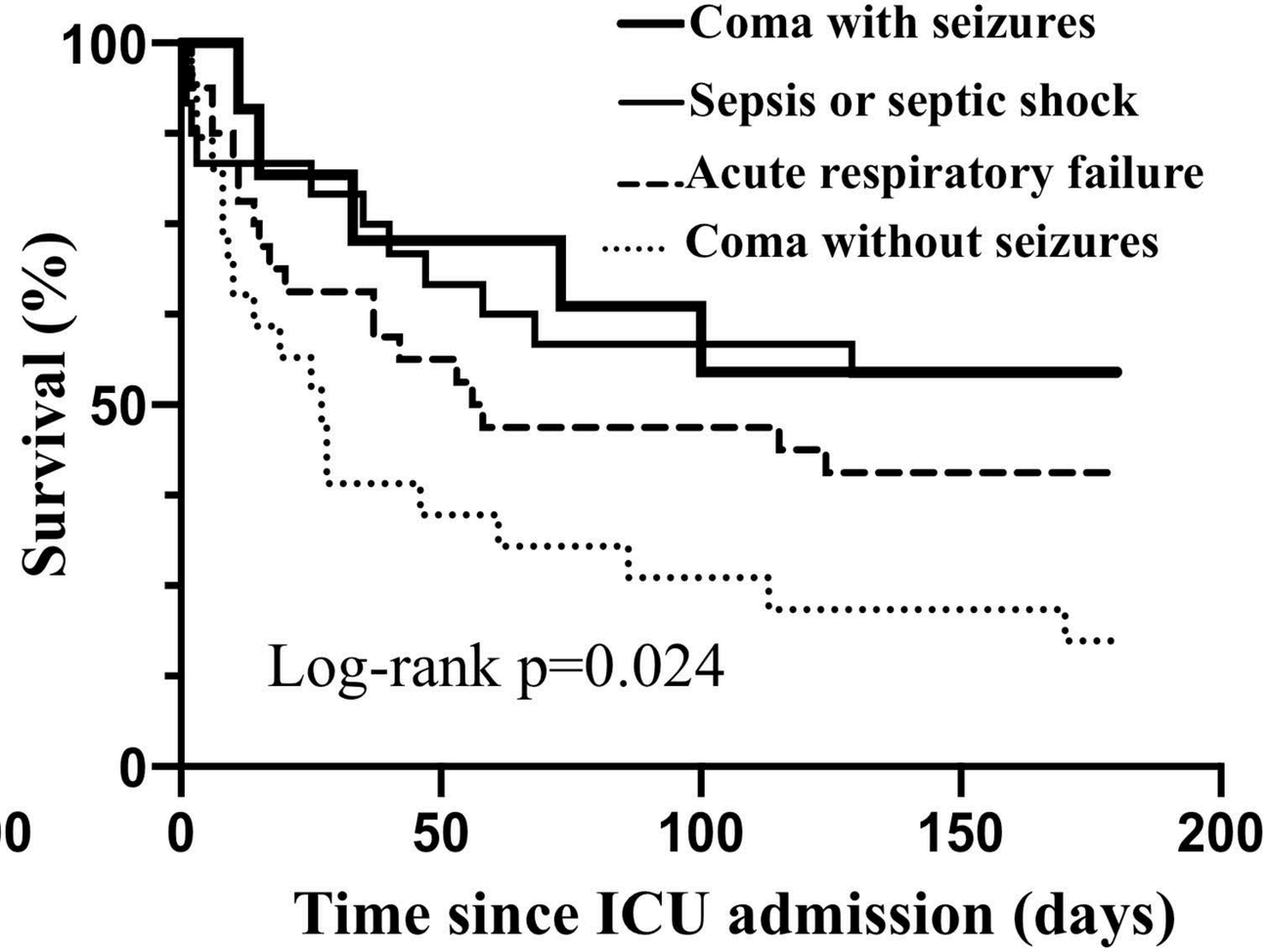
828 excluded:
-444 systemic lymphoma
-316 gliomas (high and low grade)
-35 other malignant brain tumors
-19 benign brain tumors
-9 brain metastases of solid tumors
-5 other

108 first admissions of patients with primary central nervous system lymphoma

7 excluded:
4 multiple admissions
2 no histological confirmation
1 recent neurosurgery

101 primary central nervous system lymphoma patients included

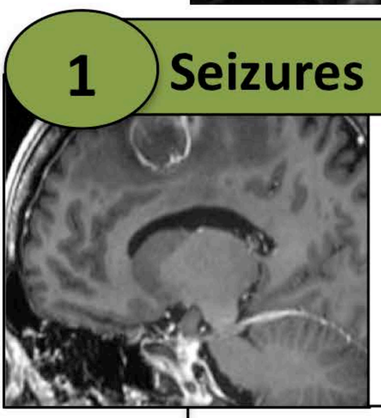

100
50
0
Survival (%)
Partial or complete response
Newly diagnosed
Progression
Log-rank p=0.006
0
50
100
150
200
Time since ICU admission (days)


100
50
0
Survival (%)
Coma with seizures
Sepsis or septic shock
Acute respiratory failure
Coma without seizures
Log-rank p=0.024
0
50
100
150
200
Time since ICU admission (days)

2 Sepsis

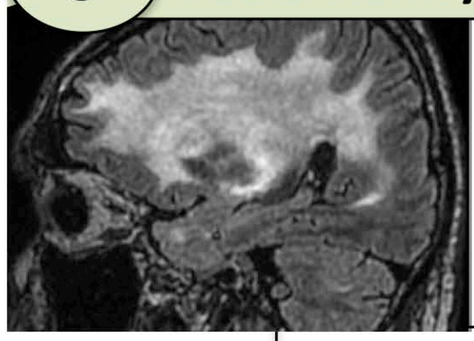
Vasopressors encouraged even with neutropenia or progressive disease, especially if infection is rapidly reversible *(catheter or urinary tract infection)*

1 Seizures

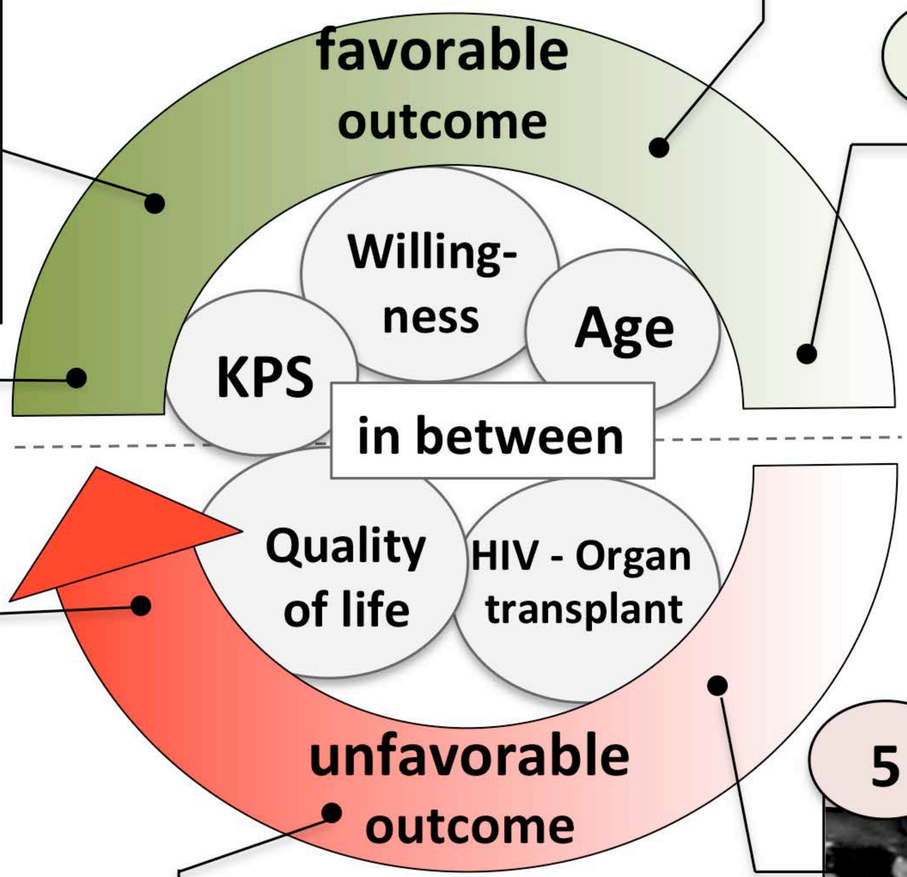


Intubation encouraged even with progressive disease, especially if no other organ failure is associated

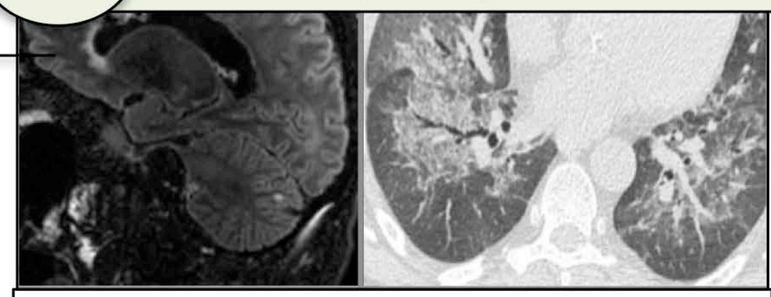
3 Acute kidney failure



Renal replacement therapy encouraged. Kidney failure is generally related to high dose MTX, combined with sepsis or antibiotic toxicity

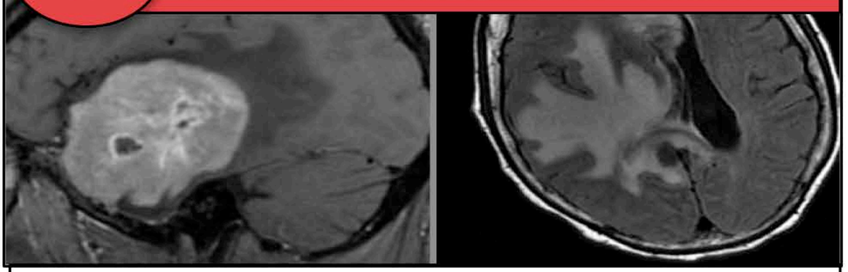


4 *Pneumocystis* pneumonia



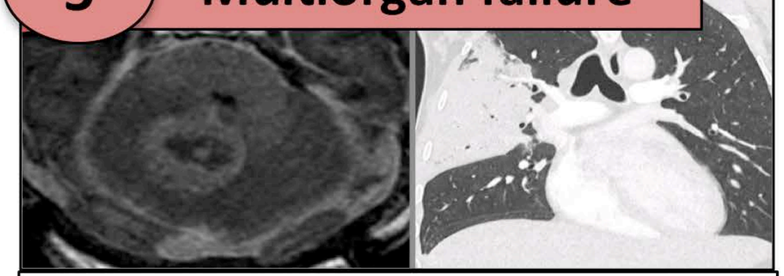
Intubation could be proposed especially with responsive disease. Generally, no other organ failure is associated

5 Coma unrelated to seizures



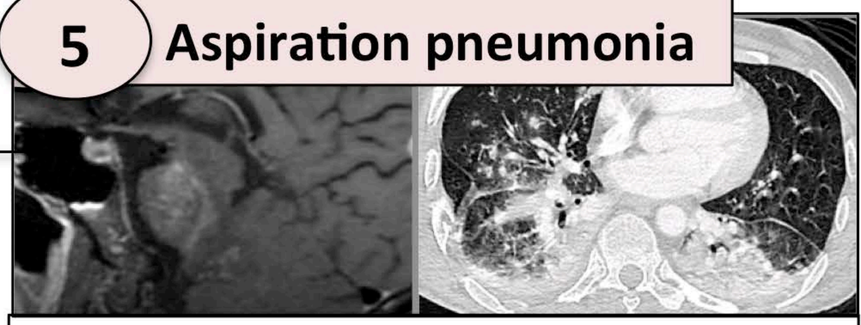
ICU admission not encouraged. Coma is generally related to IH in context of progressive disease and is often associated with respiratory failure and/or sepsis (aspiration)

5 Multiorgan failure



3-day ICU trial could be proposed, especially if disease is responsive with good performance status

5 Aspiration pneumonia



Intubation not encouraged, especially with progressive disease or poor performance status.
Aspiration is generally recurrent and related to brainstem involvement