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Prognosis of patients with primary malignant brain tumors admitted to the intensive care unit: a two-decade experience

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ABSTRACT *(250 words)*

Introduction. To describe the reasons for ICU admission and to evaluate the outcome and prognostic factors of patients with primary malignant brain tumors (PMBT) admitted to the intensive care unit (ICU).

Patients and methods. Retrospective observational cohort study of 196 PMBT patients admitted to two ICUs over a 19-year period.

Results. Acute respiratory failure was the main reason for ICU admission (45%) followed by seizures (25%) and non-epileptic coma (14%). Seizures were more common in patients with glial lesions (84% vs. 67%), whereas patients with primary brain lymphoma were more frequently admitted for shock (42% vs. 18%). Overall ICU and 90-day mortality rates were 23% and 50%, respectively. Admission for seizures was independently associated with lower ICU mortality (odds ratio [OR] 0.06), whereas the need for mechanical ventilation (OR 6.85), cancer progression (OR 7.84), respiratory rate (OR 1.11) and Glasgow coma scale (OR 0.85) were associated with higher ICU mortality. Among the 95 patients who received invasive mechanical ventilation, ICU mortality was 37% (n=35). For these patients, admission for seizures was associated with lower ICU-mortality (OR 0.050) whereas cancer progression (OR 7.49) and respiratory rate (OR 1.08) were associated with higher ICU-mortality.

Conclusion. The prognosis of PMBT patients admitted to the ICU appears relatively favorable compared to that of hematologic malignancies or solid tumors, especially when the patient is admitted for seizures. The presence of a PMBT therefore does not appear to be sufficient for refusal of ICU admission. Predictive factors of mortality may help clinicians make optimal triage decisions.

INTRODUCTION

Admission of cancer patients to intensive care units (ICU) has increased steadily over the past two decades and these patients now account for 10 to 20% of all ICU admissions [1]. Concomitantly, the mortality of critically ill cancer patients has decreased [2]. Consequently, a recent consensus of world experts emphasized that the existence of a hematologic malignancy or a solid tumor, even when metastatic, should not be considered a sufficient reason for ICU refusal [3].

Primary malignant brain tumors (PMBT) are rare tumors. In 2012, they represented less than 2% of all new cancer cases in Europe [4]. Although the prognosis of patients with hematologic malignancies or solid tumors admitted to the ICU has been well documented, only limited data are available concerning the prognosis of PMBT in the ICU [5-7]. One of the most likely reasons for this lack of data is the low prevalence of these tumors in the general population. However, it could also be due to the high ICU refusal rate of these patients, as the poor cancer prognosis [8], the severe impact on quality of life [9] or cognitive function [10] and the low survival of these patients in the case of clinical worsening [5] may explain the reluctance to admit these patients to the ICU [11]. However, PMBTs are very heterogeneous tumors in terms of their aggressiveness and patients with low-grade tumors, especially low-grade gliomas can be expected to have a much better prognosis [12]. In addition, therapeutic progress has contributed to a significant improvement of survival [13-16]. Finally, as for other malignancies, the reason for ICU admission and the number and intensity of life-supporting therapies initiated in the ICU may have a variable impact on each patient's prognosis [17].

A better knowledge of the risk factors for survival of patients with PMBT when admitted to the ICU could help to improve the quality of triage and management decisions. This study was designed to describe the profile of PMBT patients admitted to the ICU, assess the ICU and 90-day mortality rates and identify factors associated with ICU and 90-day mortality in a large cohort of PMBT patients.

PATIENTS AND METHODS

Study design and settings

The study was conducted in two ICUs: a 16-bed medical ICU in a respiratory medicine department (about 1,100 admissions per year) and a 16-bed ICU in a neurology department (about 300 admissions per year). The two ICUs are located in a 1600-bed university hospital with a strong neurological orientation including a specific neuro-oncology department (about 450 new patients each year). The study period extended from March 1996 to May 2014. The study was approved by the Institutional Review Board of the French Intensive Care Society.

Patient selection

A retrospective search of all cases of "primary brain tumor" was conducted on the database of the two ICUs (Fusion, Varimed, France). This database is prospectively managed and comprehensively describes all patient stays. The database comprised 12,890 records corresponding to 100% of admissions over the study period. After analysis of each patient's record, patients meeting the criteria of PMBT according to the 2007 World Health Organization (WHO) Classification of Tumors of the Central Nervous System [18] were included in this study. Patients with primary central nervous system (CNS) lymphomas were also included. Patients with brain metastases of solid cancers, secondary CNS lymphomas and benign brain tumors were excluded. Patients with a recent neurosurgical operation (< 2 weeks) and patients under the age of 18 years were also excluded. For patients with several ICU admissions, only the first stay was included in the analysis.

Data collection

Data such as age, gender, Performance Status (PS) during the week preceding ICU admission according to the Eastern Cooperative Oncology Group Scale [19] and comorbidities using the Charlson Comorbidity Index (CCI) [20] were collected for each patient. The tumor type was determined either by histological examination or by a highly suggestive clinical and radiologic presentation when the tumor was inaccessible to biopsy or surgery [21]. Tumors were further classified into four categories adapted from the 2007 WHO grading system [18, 22] since the more recent guidelines were available only in 2016, two years after the last inclusion: primary CNS lymphomas, high-grade gliomas (Grade III and IV), low-grade gliomas (Grade II) and other tumors. Cancer disease status was classified as newly diagnosed (when the tumor was diagnosed after ICU admission), in progression, controlled (partial response, complete response or stable disease) or unknown in the absence of reliable information. Assessment of cancer progression was based on multidisciplinary consultations reports prior to ICU admission, tumor volume and perilesional edema on magnetic resonance imaging (MRI) or CT-scan reports when MRI was not available and on the appearance of a new focal neurological deficit. The reason for admission was determined retrospectively from the conclusions of the medical records. The admission diagnosis of seizures was adopted when abnormal movements highly suggestive of seizures were observed, with or without electroencephalographic confirmation, or in the absence of suggestive movements, by disorders of consciousness with electroencephalographic confirmation of seizures. Severity on admission was assessed by the Simplified Acute Physiology Score (SAPS) II [23] and the Sequential Organ Failure Assessment (SOFA) [24].

Physiological variables such as body temperature, respiratory rate, heart rate, systolic blood pressure and Glasgow coma scale (GCS) were recorded. Blood gas analysis, leukocyte count with leukopenia defined by a leukocyte count $< 1,500/mm^3$ and serum creatinine were recorded. Advanced life support measures taken during the ICU stay, such as invasive (IMV) or noninvasive mechanical ventilation (NIV) were recorded. Vasopressors and renal replacement therapy were also recorded. Finally, ICU, hospital and 90-day mortality rates as well as length of ICU and hospital stay were also recorded.

Statistical analysis

Continuous variables are expressed as median (interquartile range) and categorical variables are expressed as absolute and relative frequencies. Continuous variables were analyzed by Mann-Whitney test and categorical variables were analyzed by Chi-square test or Fisher's exact test, as appropriate. Potential changes in mortality rates over the study period were analyzed using a Chi-square test. Potential changes of severity over time were analyzed by Spearman's correlation.

Multivariate logistic regression was used to identify factors associated with ICU and 90-day mortality. Each potential risk factor for ICU or 90-day mortality was first evaluated in univariate analysis. Factors yielding p values ≤ 0.20 or considered clinically pertinent ("tumor type") were then considered for logistic regression. Because SAPS II and SOFA scores were highly correlated (Rho = 0.65), SAPS II was not entered in the model. Continuous variables were not dichotomized. Multivariate analysis was performed by both imputing missing data with the nearest neighbor method and excluding patients with missing data (less than 3%). The final models were determined using a forward or backward stepwise logistic regression. All tests were two-tailed and p values < 0.05 were considered statistically significant. The Hosmer-Lemeshow Chi-square test [25] was used to check the goodness-of-fit of the final model. Odds ratios (ORs) and their 95% confidence intervals were calculated for significant factors. The area under the receiver operating characteristic (ROC) curve [26] was used to evaluate the ability of the models to discriminate between patients who survived and those who died. Accuracy was considered good when the area under the ROC curve ranged from 0.70 to 0.80 and excellent when it was greater than 0.80. Analyses were performed using Matlab™ (Natick, MA, USA) version 8.5.0.197613 (R2015a) and its Statistics Toolbox version 10.0.

RESULTS

Figure 1 displays the study flow chart. A total of 196 patients were included: 132 (67%) admitted to the medical ICU and 64 (33%) admitted to the neurological ICU.

Patient characteristics

All patients had a diagnosis of primary malignant brain tumor, which was confirmed histologically for 174 patients (88%) and based on a strong clinical and radiological suspicion for 23 patients (12%) in whom a biopsy could not be safely performed. Figure 2 displays the type of PMBT in this population. The main characteristics of the 196 patients are displayed in Table 1. Prior to admission, surgical resection had been performed in 63 patients (32%), 84 (43%) had received brain radiotherapy, 129 (66%) had received chemotherapy and 150 (79%) had received high-dose corticosteroid therapy.

Acute respiratory failure (ARF) was the main reason for ICU admission, mostly due to acute pneumonia (79%) and pulmonary embolism (8%). Admission for seizures was more common in patients with glial tumors than in patients with other types of tumors (84% vs. 67%, p = 0.019). Patients with primary CNS lymphoma were more frequently admitted to the ICU for shock (42% vs. 18%, p = 0.015). Leukopenia on admission was more commonly observed in patients with a primary CNS lymphoma than in patients with other types of tumors (50% vs. 19%, p = 0.005).

A neurosurgical procedure was performed during the ICU stay in 9 cases (5%) and chemotherapy was administered to 8 patients (4%).

Outcome analysis

Changes in mortality over the study period are reported in Figure 3. The ICU mortality rate (p=0.79) and the 90-day mortality rate (p=0.89) did not vary according to the admission period. SAPS II and SOFA scores did not vary according to the admission periods (p=0.36 and p=0.53, respectively). Mortality did not vary between primary CNS lymphoma, high grade glioma, low grade glioma and other tumor (respectively 24, 24, 26 and 13% p=0.856 in ICU and 45, 43, 58 and 53% p=0.481 at 90 days).

Table 2 shows the factors associated with ICU mortality identified by univariate analysis. Multivariate forward or backward logistic regression analysis with missing data imputations showed that five of these factors independently predicted ICU mortality. One factor, admission for seizures, was independently associated with lower ICU mortality (odds ratio [OR] 0.06, 95% confidence interval [CI] 0.01-0.33, p<0.001). Four factors were independently associated with higher mortality: need for MV (OR 6.85, 95%CI 2.18-21.50, p<0.001), cancer progression (OR 7.84, 95%CI 3.03-20.28, p<0.001), respiratory rate (OR 1.11, 95%CI [1.05-1.17], p<0.001 and

Glasgow coma scale (OR 0.85; 95%CI 0.77-0.94, p=0.002). The same five factors were identified after excluding patients with missing data. Among the ICU deaths, patients presented a cancer progression on admission in 52% of cases (24/46). Among these 24 patients, the death could be related to tumor progression in 50% of cases (12/24).

Table 3 displays the factors associated with 90-day mortality identified by univariate analysis. Multivariate forward or backward logistic regression analysis with missing data imputations showed that six of these factors independently predicted 90-day mortality. One factor, admission for seizures, was independently associated with lower 90-day mortality (OR 0.18, 95%CI 0.07-0.47, p<0.001). Five factors were independently associated with higher day-90 mortality: need for MV (OR 6.88, 95%CI 3.01-15.73, p<0.001), cancer progression (OR 7.87, 95%CI 3.26-18.99, p<0.001), Charlson Comorbidity Index (OR 1.44, 95%CI 1.10-1.88, p=0.007), systolic blood pressure on ICU admission (OR 1.02 95%CI 1.00-1.03, p=0.025) and respiratory rate (OR 1.05, 95%CI 1.00-1.10, p=0.041). The same seven factors were identified after excluding patients with missing data.

Subgroup of patients requiring invasive mechanical ventilation

Among the 108 patients who received MV, 18 (17%) received noninvasive ventilation (NIV) as first-line ventilatory support and 90 (83%) received invasive ventilation. Among the 18 patients who received NIV, 4 (22%) were intubated within 24 hours due to NIV failure. Among the 94 patients who finally received invasive mechanical ventilation (IMV), ICU mortality and 90-day mortality were 37% (n=35) and 60% (n=56), respectively.

Table 4 displays the factors associated with ICU mortality among patients who received IMV identified by univariate analysis. Multivariate forward or backward logistic regression analysis with missing data imputations showed that three of these factors independently predicted ICU mortality. Admission for seizures was the only factor independently associated with lower ICU mortality in patients who received IMV (OR 0.05, 95%CI 0.01-0.41, p=0.005), whereas two factors were associated with higher ICU mortality: cancer progression (OR 7.49, 95%CI 2.37-23.67, p<0.001) and respiratory rate (OR 1.08, 95%CI 1.01-1.15, p=0.022). The same three factors were identified after excluding patients with missing data.

DISCUSSION

The salient results of this study are: 1) mortality of PMBT patients admitted to the ICU was relatively low and has remained stable over the last 19 years, 2) cancer progression and the need for MV were associated with a poorer prognosis, 3) admission for seizures was a predictor of survival, even when invasive MV was required.

To the best of our knowledge, this is the largest cohort of neuro-oncological patients admitted to medical ICUs focusing on their short-term and medium-term prognosis [27].

The mortality of PMBT patients did not improve significantly during the study period, in contrast with the dramatic improvement of ICU survival rates observed in cancer patients over the last two decades [3]. This lack of improved survival cannot be attributed to increased severity of patients, as the SAPS II score of patients admitted to the ICU did not increase significantly over the study period. However, this mortality rate was similar to, if not lower than, that reported in patients with hematologic malignancies [17] and solid tumors [2]. The simple presence of a PMBT therefore should not be a sufficient argument for refusal of ICU admission. There are four possible explanations for this low mortality. First, the young age and limited comorbidities observed in PMBT patients may be protective factors. Second, since only patients with the best prognosis were considered for ICU admission, our population may be highly selected. Third, there was a high proportion of rapidly reversible causes of admission such as seizures. Fourth, progress in the management of malignancies over the past two decades [3], particularly in the subgroup of patient with primary CNS lymphoma, may also be beneficial for patients with PMBT.

In the present study, seizures appeared to be a predictive factor of short-term and medium-term survival, even in mechanically ventilated patients. Although the prognosis of tumor-associated status epilepticus appears to be poorer than that of status epilepticus due to other causes [28], it generally has a good prognosis and is associated with low mortality [29]. It should be stressed that the incidence of epilepsy is particularly high in gliomas, ranging from 60 to 100% for low-grade gliomas and 40 to 60% for high-grade gliomas [30]. A recent study reported similar results in PMBT patients admitted to the medical ICU: admission for a neurological cause (mainly seizures) was predictive of better ICU survival than non-neurological causes of ICU admission [27]. In contrast, in our study, cancer progression was a strong predictor of ICU and 90-day mortality regardless of the severity of the patients at the time of ICU admission. In most reports on cancer patients in the ICU, cancer progression appears to be an independent predictor of mortality [1, 17, 31, 34], highlighting the fact that cancer status is a crucial element that must be defined before any discussion regarding ICU admission.

Initiation of mechanical ventilation was an independent factor of poor prognosis, confirming numerous reports demonstrating the deleterious impact of mechanical ventilation on the prognosis of ICU patients with hematologic malignancies [17] or solid tumors [32, 33], particularly lung cancer [31, 32, 34]. In contrast with these series that reported a mean ICU mortality rate of 65% in mechanically ventilated patients [17, 31, 36], the ICU mortality rate in our PMBT patients was only 37%. This lower mortality in PMBT patients seemed to be directly related to the good prognosis of patients intubated for status epilepticus or seizure-related coma, as, when patients admitted for seizures were excluded, ICU mortality in mechanically ventilated patients increased to 49% (34/70). Interestingly, very few patients were treated by NIV. Although the potential benefit of NIV in cancer patients remains a matter of debate [37], NIV does not appear to be indicated in PMBT patients due to loss of upper airway control induced by disorders of consciousness and swallowing disorders [38]. Finally, the use of vasopressors was not an independent predictor of higher mortality, as previously reported in other types of cancer [31, 32, 34, 35], which could suggest that very brief use of vasopressors, for example to treat severe sepsis, should not be discouraged.

The present study has several limitations. First, this was a retrospective study, which involves a potential bias in patient selection or data collection. However, the rarity of the disease remains a major obstacle to prospective studies, even with a multicenter design. In addition, data were extracted from a prospectively managed database, which offers a higher reliability of data collection than simple chart examination. Second, the relevance of mortality as an outcome measure in this very specific population can be questioned in view of the potentially increased impairment of functional status and quality of life after an ICU stay. Unfortunately, such information was not available in our database. However, the vast majority of PMBT patients appeared to exhibit a stable or improved Karnofsky Performance Status after ICU discharge [27]. Third, the WHO classification of brain tumors has been updated in 2016, and without data regarding the molecular testing, further misclassification has been possible for the 2 patients with oligoastrocytoma of our cohort. 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.

In conclusion, patients with PMBT have a fairly good prognosis after ICU admission, as compared to patients with hematologic malignancies or solid tumors, especially when they are admitted for seizures. The presence of a PMBT therefore does not appear to be sufficient for ICU refusal. Prognostic factors such as cancer progression need for MV or seizures may help clinicians to make optimal triage decisions. In any case, ICU

transfer must always be based on multidisciplinary discussion between neuro-oncologists, intensivists, the patient and relatives, respecting the patient's autonomy and willingness.

DECLARATIONS SECTION

Ethical standards

Consent were not collected because of retrospective design

The study was approved by the Institutional Review Board of the French Intensive Care Society.

Author's contributions to the manuscript:

Conception and design: Maxens Decavèle, Nicolas Weiss, Isabelle Rivals, Alexandre Demoule.

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Final approval: All authors

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Tables

Table 1. Characteristics of the 197 patients included in the study

Variables	
Age, *years*	58 (47-66)
Gender (male) *n (%)*	132 (67)
Comorbidities	
Chronic heart failure, *n (%)*	11 (6)
Chronic obstructive pulmonary disease, *n (%)*	14 (7)
Functional status	
Performance Status 3-4, *n (%)*	114 (58)
Charlson Comorbidity Index	2 (2-3)
Mode of admission	
Intra-hospital transfer, *n (%)*	119 (61)
Transfer via emergency services, *n (%)*	62 (31)
Transfer from another hospital, *n (%)*	15 (8)
Disease status on admission	
Newly diagnosed, *n (%)*	17 (9)
In progression *n (%)*	53 (27)
Controlled *n (%)*	101 (51)
Unknown, *n (%)*	25 (13)
Reason for admission	
Acute respiratory failure, *n (%)*	88 (45)
Seizures, *n (%)*	50 (26)
Coma without seizures, *n (%)*	28 (14)
Shock, *n (%)*	24 (12)
Other, *n (%)*	6 (3)
Severity	
SAPS II	46 (31-59)
SOFA	5 (3-7)
Physiological variables	
Systolic blood pressure, *mmHg*	120 (103-136)
Heart rate, *b.p.m.*	100 (81-120)
Respiratory rate, *cycles/min*	24 (20-30)
Glasgow Coma Scale	11 (6-15)
Temperature, *°C*	37.7 (37.0-38.7)
Laboratory parameters	
Leukocytes, */mm³*	7670 (4548-12143)
Leukopenia, *n (%)*	18 (9)
Serum creatinine, *µmol/l*	72 (53-97)
Arterial Blood Gases	
pH	7.43 (7.39-7.48)
$PaCO_2$, *mmHg*	37 (31-42)
PaO_2/FiO_2	231 (139-303)
Bicarbonate, *mmol/l*	24 (20-30)
Life-supporting interventions	
Mechanical ventilation, *n (%)*	108 (55)
Non-Invasive Ventilation only, *n (%)*	14 (7)
Invasive Ventilation only, *n (%)*	95 (48)
Total duration of mechanical ventilation, *days*	6 (2-11)
Vasopressors, *n (%)*	45 (23)
Renal replacement therapy, *n (%)*	3 (2)
End-of-life decision, *n (%)*	43 (22)

Mortality	
ICU mortality, *n (%)*	46 (23)
Hospital mortality, *n (%)*	84 (43)
90-day mortality, *n (%)*	92 (50)

SAPS II, Simplified Acute Physiology Score II; SOFA, Sequential Organ Failure Assessment.

Continuous variables are expressed as median (interquartile range) and categorical data are expressed as number (%).

Table 2. Univariate analysis: factors associated with ICU mortality

Variables	ICU mortality		
	Survivors (n=150)	Non-survivors (n=46)	*P* value
Data before ICU admission			
Age, *years*	58 (48-66)	58 (45-64)	0.964
Performance status 3-4, *n (%)*	82 (55)	32 (70)	0.073
Chronic heart failure	3 (2)	8 (17)	<0.001
COPD, *n (%)*	9 (6)	5 (11)	0.324
Charlson Comorbidity Index	2 (2-3)	2 (2-3)	0.918
Corticosteroid therapy, *n (%)*	111 (74)	39 (85)	0.165
Cancer progression, *n (%)*	29 (19)	24 (52)	<0.001
Reason for admission			
Seizures, *n (%)*	48 (32)	2 (4)	<0.001
Coma without seizures, *n (%)*	16 (11)	12 (26)	0.009
Acute respiratory failure, *n (%)*	63 (42)	25 (54)	0.141
Shock, *n (%)*	18 (12)	6 (13)	0.850
Severity			
SAPS II	41 (28-54)	63 (46-71)	<0.001
SOFA	4 (2-7)	8 (5-10)	<0.001
Physiological variables			
Respiratory rate, *(cycles/min)*	23 (20-30)	28 (20-33)	0.034
Glasgow Coma Scale	12 (7-15)	6 (3-13)	<0.001
Laboratory parameters			
Leukopenia, *n (%)*	11 (7)	7 (15)	0.402
PaO_2/FiO_2	242 (162-324)	171 (106-252)	<0.001
Life-supporting interventions			
Mechanical ventilation, *n (%)*	71 (47)	37 (80)	<0.001
Vasopressors, *n (%)*	22 (15)	23 (50)	<0.001

Continuous variables are expressed as median (interquartile range) and categorical data are expressed as number (%).

ICU, Intensive Care Unit; COPD, Chronic obstructive pulmonary disease; SAPS II, Simplified Acute Physiology Score II; SOFA, Sequential Organ Failure Assessment.

Table 3. Univariate analysis: factors associated with 90-day mortality

| Variables | 90-day mortality | | |
	Survivors (n=92)	Non survivors (n=92)	*P* value
Data before ICU admission			
Age, *years*	57 (47-65)	59 (48-66)	0.789
Performance status 3-4, *n (%)*	45 (49)	61 (66)	0.025
Chronic heart failure, *n (%)*	3 (3)	8 (9)	0.220
COPD, *n (%)*	7 (8)	7 (8)	0.971
Charlson Comorbidity Index	2 (2-3)	3 (2-4)	0.003
Corticosteroid therapy, *n (%)*	61 (66)	79 (85)	0.003
Cancer progression, *n (%)*	11 (12)	39 (42)	<0.001
Reason for admission			
Seizures, *n (%)*	34 (37)	11 (12)	<0.001
Coma without seizures, *n (%)*	9 (10)	19 (21)	0.040
Acute respiratory failure, *n (%)*	34 (37)	49(53)	0.026
Shock, *n (%)*	10 (11)	11 (12)	1.000
Severity			
SAPS II	37 (26-52)	52 (35-65)	<0.001
SOFA	4 (2-6)	6 (4-9)	<0.001
Physiological variables			
Respiratory rate, *(cycles/min)*	22 (19-28)	25 (20-31)	0.031
Glasgow Coma Scale	12 (6-15)	9 (4-14)	0.025
Laboratory parameters			
Leukopenia, *n (%)*	8 (9)	10 (11)	0.467
PaO_2/FiO_2	247 (186-314)	200 (110-281)	0.014
Life-supporting interventions			
Mechanical ventilation, *n (%)*	38 (41)	63 (69)	<0.001
Vasopressors, *n (%)*	12 (13)	30 (33)	0.001

COPD, Chronic obstructive pulmonary disease; SAPS II, Simplified Acute Physiology Score II; SOFA, Sequential Organ Failure Assessment.

Continuous variables are expressed as median (interquartile range) and categorical data are expressed as number (%).

Table 4. Univariate analysis: factors associated with ICU-mortality among invasively ventilated patients.

	ICU mortality		
	Survivors (n=59)	**Non survivors (n=35)**	*P* value
Data before ICU admission			
Age, *years*	59 (48-68)	58 (42-64)	0.743
Performance status 3-4, *n (%)*	30 (51)	23 (66)	0.223
Chronic heart failure, *n (%)*	3 (5)	3 (9)	0.587
COPD, *n (%)*	2 (2)	4 (11)	0.191
Charlson Comorbidity Index	2 (2-3)	2 (2-3)	0.587
Corticosteroid therapy, *n (%)*	41 (69)	29 (83)	0.151
Cancer progression, *n (%)*	12 (20)	19 (54)	<0.001
Reason for admission			
Seizure, *n (%)*	24 (41)	1 (3)	<0.001
Coma without seizures, *n (%)*	7 (12)	11 (31)	0.020
Acute respiratory failure, *n (%)*	23 (39)	16 (46)	0.512
Shock, *n (%)*	5 (8)	6 (17)	0.319
Severity			
SAPS II	51 (38-59)	63 (52-72)	0.004
SOFA	6 (5-8)	8 (6-11)	0.007
Physiological variables			
Heart rate, *beats/min*	100 (79-115)	100 (86-130)	0.468
Glasgow Coma Scale score	7 (3-12)	6 (3-10)	0.237
Biological variables			
Leukopenia, *n (%)*	1 (2)	5 (14)	0.009
PaO_2/FiO_2	231 (146-322)	167 (103-273)	0.096
Life supporting interventions			
Vasopressors, *n (%)*	17 (29)	20 (57)	0.041
Renal replacement therapy, *n (%)*	0 (0)	3 (9)	0.049

ICU, Intensive Care Unit; COPD, Chronic obstructive pulmonary disease; SAPS II, Simplified Acute Physiology Score II; SOFA, Sequential Organ Failure Assessment.

Continuous variables are expressed as median (interquartile range) and categorical data are expressed as number (%).

FIGURE LEGENDS

Figure 1. Study flow chart

ICU, intensive care unit.

Figure 2. Distribution of primary malignant brain tumor types

ICU, intensive care unit.

[a] other tumors included: 5 medulloblastomas, 3 malignant meningeal tumors, 2 germinomas and 5 gliomas with unknown malignancy grade because of missing data.

Figure 3. Changes in the number of admissions and death during the study period

Bars represent the number of admissions during each 2-year period. Solid line with filled circles represents the intensive care unit mortality rates during each 2-year period. Dashed line with open circles represents 90-day mortality rates during each 2-year period.

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┌─────────────────────────┐
│ 12,890  ICU admissions  │
└─────────────────────────┘
            │
┌─────────────────────────┐
│   302 ICU admissions    │
│     of patients with    │
│   primary brain tumor   │
└─────────────────────────┘
            │
            ├──────────┌──────────────────────────────────────┐
            │          │ 48 excluded for multiple admissions  │
            │          └──────────────────────────────────────┘
            │
            ├──────────┌──────────────────────────────────────┐
            │          │ 38 excluded for missing data         │
            │          └──────────────────────────────────────┘
            │
            │          ┌──────────────────────────────────────┐
            │          │ 19 excluded:                         │
            │          │   -6 metastatic lymphoma             │
            │          │   -4 brain metastases of solid tumors│
            │          │   -3 meningiomas                     │
            │          │   -1 benign ganglioglioma            │
            ├──────────│   -1 benign hemangiopericytoma       │
            │          │   -1 invasive sarcoma                │
            │          │   -1 invasive Erdheim-Chester        │
            │          │ disease                              │
            │          │   -1 brainstem stroke                │
            │          │   -1 cerebral toxoplasmosis          │
            │          └──────────────────────────────────────┘
            │
┌─────────────────────────┐
│   197 patients with     │
│   primary malignant     │
│  brain tumor included   │
└─────────────────────────┘
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