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Etiology and prognosis of acute respiratory failure in patients with primary malignant brain tumors admitted to the intensive care unit

Maxens Decavèle^{1,2}  · Isabelle Rivals^{1,3} · Clémence Marois² · Marie Cantier² · Nicolas Weiss⁴ · Léa Lemasle² · Hélène Prodanovic² · Khe Hoang-Xuan⁵ · Ahmed Idbaih⁵ · Thomas Similowski^{1,2} · Alexandre Demoule^{1,2}

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Abstract

Purpose Acute respiratory failure (ARF) is common and potentially fatal in patients with primary malignant brain tumors (PMBT). However, few data are available regarding its precipitating factors and prognosis. We sought to: (1) compare the causes of ARF and the outcome between patients with PMBT and patients with other peripheral solid tumors (PST), (2) identify the factors influencing ICU survival in PMBT patients.

Methods Two-center retrospective case-control study from March 1996 to May 2014. Primary central nervous system lymphomas were also included.

Results Eighty-four patients with PMBT and 133 patients with PST were included. Acute infectious pneumonia was more frequent in PMBT than PST patients (77 vs. 36%, $p < 0.001$). Pulmonary embolism was also more frequent in PMBT patients (13% vs. 5%, $p = 0.042$), while cardiogenic pulmonary edema and acute-on-chronic respiratory failure were more frequent in PST patients (37 vs. 10%, $p < 0.001$). Among acute infectious pneumonia, *Pneumocystis* pneumonia and aspiration pneumonia were more frequent in PMBT patients (19 vs. 2%, $p < 0.001$ and 19 vs. 8%, $p < 0.001$, respectively). ICU mortality was similar between PMBT and PST patients (24% vs. 24%, $p = 0.966$). In multivariate analysis, cancer progression (OR 7.25 95% CI 1.13–46.45, $p = 0.034$), need for intubation (OR 7.01 95% CI 1.29–38.54, $p = 0.022$), were independently associated with ICU mortality in PMBT patients.

Conclusions The cause of ARF in patients with PMBT differs significantly than those with PST and up to 50% may have been prevented. Mortality did not differ between the two groups. These results suggest that PMBT alone is not a relevant criterion for ICU refusal.

Keywords Malignant brain tumors · Prognosis · Intensive care unit · Acute respiratory failure · *Pneumocystis* pneumonia · Critical care

Previous presentation: Preliminary results were presented at the most recent congress of the French Intensive Care Society, Paris, 2018.

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✉ Maxens Decavèle
maxencesar@hotmail.fr

Extended author information available on the last page of the article

Introduction

Acute respiratory failure (ARF) is the main cause for intensive care unit (ICU) admission of cancer patients [1, 2]. In these patients, acute infectious pneumonia is the leading cause of ARF, ranging from scarce infiltrates to life-threatening acute respiratory distress syndrome [3]. While abundant data are available on the etiological spectrum [4] and prognosis of ARF among patients with hematologic malignancies [2] or other solid tumors [1], very little is known about patients with primary malignant brain tumors (PMBT).

In two recent reports describing the diagnosis and prognosis of PMBT patients admitted to the ICU [5, 6], ARF

represented 16% and 45% of the reasons for admission, respectively, but the causes of ARF were not extensively described. Many findings suggest that the precipitating factors of ARF may differ between PMBT patients and those with other solid tumors. Firstly, PMBT patients are more severely immunocompromised than patients with other solid tumors as a result of both higher doses and more prolonged steroid therapy in addition to adjuvant radiotherapy and chemotherapy [6]. These factors are likely to contribute to the pathogenesis of opportunistic infections such as *Pneumocystis jirovecii* pneumonia (PCP) [7]. Secondly, as PMBT patients have fewer comorbidities [6], they are less likely to experience exacerbations of underlying cardiac or respiratory disease. Finally, at some time during the clinical course, PMBT are responsible for swallowing disorders [8, 9], subsequently predisposing to aspiration pneumonia.

As it has been clearly demonstrated that early identification of the cause of ARF is associated with better outcome in immunocompromised patients [2, 10], a better knowledge of the etiologic spectrum of ARF in PMBT patients is important. In addition, clear identification of the factors associated with the survival of these patients could improve the quality of triage and management decisions.

We hypothesized that the causes of ARF in PMBT patients differ significantly from the causes encountered in patients with other solid tumors and that factors associated with the prognosis of ARF in PMBT could be identified. To address these issues, we conducted the present case-control study to (1) compare the causes of ARF between PMBT patients and patients with other solid tumors, particularly focusing on PCP and (2) assess the factors associated with ICU mortality in PMBT patients.

Patients and methods

Study design and settings

The study was conducted from March 1996 to May 2014 in two medical ICUs: a 16-bed ICU in a pulmonology department (about 1,100 admissions per year) and a 16-bed ICU in a neurology department (about 300 admissions per year). Both ICUs are located in a 1600-bed university hospital with a strong neurological orientation including a specific neuro-oncology department (about 500 newly diagnosed patients each year) and the national reference center for high-grade oligodendroglioma (i.e. POLA Network) and primary central nervous system lymphoma (i.e. LOC Network). According to the French Public Health Code (L.1121-1 paragraph 1 and R1121-2), informed consent is unnecessary for anonymous extraction and analysis of data from patients' medical charts. The study was approved by the Institutional

Review Board of the French Intensive Care Society. Data from this cohort have been previously published [6].

Patient selection

Data were extracted from the ICU database (FusionF, Varimed, France). This prospectively managed database comprehensively describes all ICU stays. The database of the two ICUs comprised 12,890 records, corresponding to 100% of admissions over the study period. For both cases and controls, when the same patient presented several ICU admissions, only the first stay was included in the analysis.

PMBT selection (cases)

This set of 12,890 records was retrospectively searched for all cases of PMBT according to the 2016 World Health Organization (WHO) Classification of Tumors of the Central Nervous System [11]. Patients with primary central nervous system lymphomas were also included. Patients with brain metastases from solid cancers, secondary central nervous system lymphoma, benign brain tumor and patients with another cause of immunodeficiency than cancer (i.e. organ transplantation, human immunodeficiency virus infection and/or associated hematologic malignancies) were excluded, as these conditions may directly influence the etiology of ARF. Patients who had recently undergone a neurosurgical operation (< 2 weeks) or any other recent surgery (< 4 weeks) were also excluded.

Patients included in the study were those admitted to the ICU for ARF, defined as follows: (1) in spontaneously breathing patients (either standard oxygen or high-flow nasal cannula), ARF was defined by a respiratory rate > 20 breaths/min with $\text{PaO}_2/\text{FiO}_2 < 300$ mmHg, (2) in mechanically ventilated patients (either noninvasive or invasive ventilation), ARF was defined by $\text{PaO}_2/\text{FiO}_2 < 300$ mmHg regardless of respiratory rate.

Selection of controls with peripheral solid tumor (PST)

The same set of 12,890 records was retrospectively searched for all cases of "solid malignant tumor" other than PMBT. This control group was called the "peripheral solid tumor (PST)" group. To ensure that the two groups were as comparable as possible in terms of factors that potentially influence the causes and prognosis of ARF, patients with metastatic solid tumors, patients with tumors in complete remission for more than 5 years, patients with hematologic malignancies, recent postoperative patients (< 4 weeks) and patients with other types of immunodeficiency or chronic ventilator dependency were excluded. PST patients admitted to ICU for ARF, defined according to the same criteria as in PMBT patients, were included in this control group.

Definitions and data collection

Tumour type was determined by histological examination and, in the PMBT group, by a highly suggestive clinical and radiological presentation when the tumor was not accessible to biopsy or surgery [12]. Grade I/II and Grade III/IV gliomas were considered as low-grade and high-grade gliomas respectively. 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. Performance status (PS) during the week preceding ICU admission according to the Eastern Cooperative Oncology Group Scale [13] and the Charlson comorbidity index (CCI) [14] were collected for each patient. Physiological variables, such as body temperature, respiratory rate, heart rate, systolic blood pressure and Glasgow coma scale (GCS), were recorded. Arterial blood gases, lymphocyte count and leukopenia (defined by leukocyte count $< 1,500/\text{mm}^3$) were also recorded. Severity on admission was assessed by the simplified acute physiology score (SAPS) II [15] and the sequential organ failure assessment (SOFA) [16]. Three experienced critical care and respiratory physicians (A.D, H.P and M.D) determined the precipitating factor of ARF based on a set of clinical, laboratory, radiological and microbiological features. Microbial agents responsible for infectious pneumonia were also reported when identified. The diagnosis of PCP was based on high clinical suspicion and a microscopic visualization of *Pneumocystis jirovecii* cysts or trophozoites in bronchoalveolar lavage. Advanced life support measures taken during the ICU stay were recorded in PMBT patients. The ICU and hospital mortality were determined in all patients.

Statistical analysis

Continuous variables are expressed as median (interquartile range) and categorical variables are expressed as number (percentage). Between-group comparisons were performed using Mann–Whitney test (continuous variables) and Chi square test or Fisher's exact test as appropriate (categorical variables). Potential changes in mortality rates over the study period were analyzed using a Mann–Whitney test. Potential changes of severity over time were analyzed by Spearman's correlation.

Multivariate logistic regression was used to identify factors associated with ICU mortality in PMBT patients. Each potential risk factor for ICU mortality was first evaluated in univariate analysis. Factors yielding p values ≤ 0.20 were entered in the logistic regression, except for SAPS II and SOFA, which were redundant with other variables. Continuous variables were not dichotomized. Missing data were imputed by the nearest neighbor method (1.1%). The final

model was determined using a backward stepwise logistic regression. All tests were two-tailed and p values < 0.05 were considered statistically significant. The Hosmer–Lemeshow Chi square test 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. Analyses were performed using Matlab™ (Natick, MA, USA) version 9.3.0.713579 (R2017b) and its Statistics and Machine Learning Toolbox version 11.2.

Results

Figure 1 displays the study flow chart for both cases and controls. A total of 84 patients with PMBT were included. Tumor type was confirmed histologically in 74 (88%) patients and was based on a strong clinical and radiological suspicion for the remaining ten patients and was distributed as follows: 18 (22%) primary central nervous system lymphomas, 35 (42%) high-grade gliomas, 27 (32%) low-grade gliomas and 4 (4%) other tumors (see also Table S1 in the Online Supplement). These PMBT patients were compared to 133 PST patients, distributed as follows: 27 (20%) breast, 21 (16%) lung, 17 (13%) prostate, 14 (11%) larynx, pharynx and oral cavity, 14 (11%) urinary tract, 10 (7%) colorectal, 8 (6%) stomach, 7 (5%) thyroid, 5 (4%) liver, 4 (3%) pancreas and 6 (4%) other cancers (2 uterus, 2 ovary 1 melanoma and 1 gallbladder).

Comparison of the causes of ARF between PMBT and PST patients

Table 1 describes the main characteristics of PMBT and PST patients.

Acute infectious pneumonia was more frequent in PMBT patients, while acute cardiogenic pulmonary edema and acute-on-chronic respiratory failure were more frequent in PST patients (Fig. 2). The prevalence of pulmonary embolism as the primary cause of ARF was similar between the two groups. Of note, pulmonary embolism was observed in two PMBT patients and one PST patient, in whom the precipitating factor of ARF was pneumonia, resulting in an overall prevalence of pulmonary embolism of 13% ($n = 11$) in PMBT patients and 5% ($n = 7$) in PST patients ($p = 0.042$). Among the other causes of ARF, upper airway obstruction by tumor and hemoptysis were exclusively observed in PST patients (see Table S2 in the Online Supplement).

Among the various forms of acute infectious pneumonia, PCP and aspiration pneumonia were more frequent in PMBT patients than in PST patients (Fig. 3). Similar proportions of documented or undocumented bacterial pneumonia, viral pneumonia and Aspergillus pneumonia were observed between the two groups (see also Table S2 in the Online

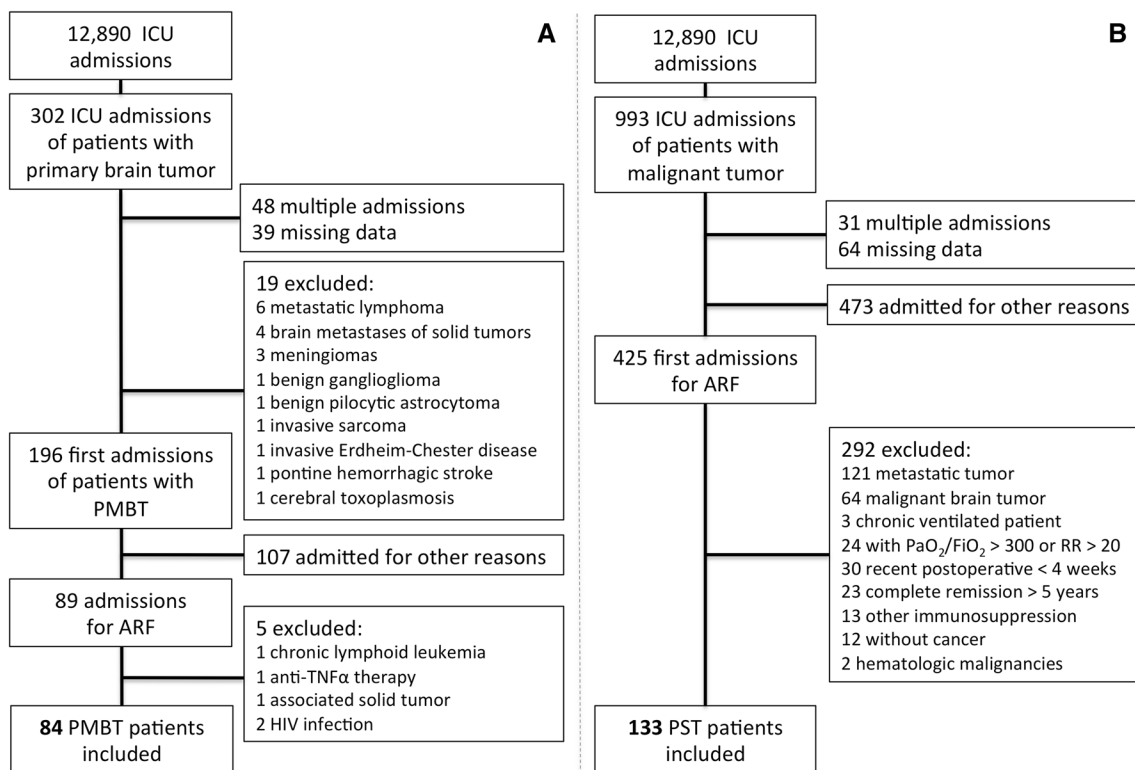


Fig. 1 Study flow chart of primary malignant brain tumor (PMBT, panel A) and peripheral solid tumor (PST, panel B) patients. *ICU* intensive care unit; *ARF* acute respiratory failure; *TNF α* tumor necrosis factor alpha; *HIV* human immunodeficiency virus; *RR* respiratory rate

Supplement). The microbial agents documented in cases of acute infectious pneumonia are shown in Table S3 in the Online Supplement.

PMBT patients with PCP had a lower blood lymphocyte count than those with other causes of ARF (335 [170–666]/mm³ vs. 608 [325–1000]/mm³, $p=0.017$). None of the patients with a diagnosis of PCP had received prophylaxis prior to admission. The date of admission did not influence the incidence of PCP ($p=0.950$), aspiration pneumonia ($p=0.992$) or pulmonary embolism ($p=0.601$).

Prognosis of PMBT patients

ICU mortality, hospital mortality and SAPS II in PMBT patients did not vary according to the date of admission ($p=0.447$, $p=0.451$ and $p=0.543$, respectively).

Table 2 shows the factors associated with ICU mortality identified by univariate analysis. ICU mortality rates was similar in patients with primary central nervous system lymphoma, high-grade glioma, low-grade glioma and other tumors ($p=0.856$). Multivariate logistic regression analysis showed that four variables were significantly associated with higher ICU mortality: cancer progression (OR 7.25, 95% CI 1.14–46.46, $p=0.033$), need for MV (OR 7.06 95% CI 1.29–38.54, $p=0.022$), respiratory rate (OR 1.17 95%

CI 1.05–1.30, $p=0.003$) and heart rate (OR 1.03 95% CI 1.00–1.06, $p=0.034$).

Discussion

The main results of this study can be summarized as follows: (1) infectious pneumonia is the leading cause of ARF in PMBT patients admitted to the ICU, while cardiogenic pulmonary edema and acute-on-chronic respiratory failure are less frequent in PMBT patients than in PST patients, (2) PCP and aspiration pneumonia are observed more frequently in PMBT patients than in patients with other solid tumors, (3) ICU and hospital mortalities are not significantly different between PMBT and PST patients, (4) cancer progression, heart rate, respiratory rate and initiation of mechanical ventilation were independently associated with ICU mortality in PMBT patients. To our knowledge, this is the largest cohort of PMBT patients admitted to the ICU for ARF and the first study to focus on the etiologic spectrum of ARF.

As previously reported in critically ill cancer patients, we observed a high prevalence of acute infectious pneumonia in our patient population [1–4]. These results could be explained by the frequent use of high-dose corticosteroids in PMBT patients (84% in our study) [17]. In addition, in

Table 1 Patient characteristics

Variables	PMBT patients n = 84	PST patients n = 133	<i>p</i>
General characteristics			
Age, years	58 [50–66]	72 [62–78]	<0.001
Gender (male), <i>n</i> (%)	62 (74)	79 (59)	0.030
Chronic respiratory disease, <i>n</i> (%)	10 (12)	49 (37)	<0.001
Chronic heart failure, <i>n</i> (%)	6 (7)	44 (33)	<0.001
Corticosteroid therapy, <i>n</i> (%)	69 (84)	4 (3)	<0.001
Performance status 3–4, <i>n</i> (%)	59 (70)	39 (41)	<0.001
On admission			
SAPS II	46 [32–59]	39 [29–53]	0.534
Respiratory rate, breaths/min	30 [24–35]	27 [23–33]	0.472
PaO ₂ /FiO ₂ , mmHg	161 [101–233]	166 [120–232]	0.113
Leukocytes count, /mm ³	8100 [4200–	10,300 [7872–	0.009
Leukopenia, <i>n</i> (%)	12,330] 9 (11)	15,600] 6 (5)	0.079
Outcomes			
Invasive mechanical ventilation, <i>n</i> (%)	33 (39)	53 (40)	0.978
Noninvasive ventilation only, <i>n</i> (%)	14 (17)	25 (19)	0.691
ICU mortality, <i>n</i> (%)	20 (24)	32 (24)	0.966
Hospital mortality, <i>n</i> (%)	39 (46)	65 (49)	0.687
ICU length of stay, days	6 [4–10]	6 [4–10]	0.985
Outcomes in the subgroup of invasively mechanically ventilated patients			
ICU mortality, <i>n</i> (%)	n = 33 14 (42)	n = 53 26 (49)	0.548
Hospital mortality, <i>n</i> (%)	24 (73)	38 (72)	0.917

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

PMBT, primary malignant brain tumor; PST, peripheral solid tumor (non-PMBT localized solid malignant tumor); SAPS II, Simplified Acute Physiology Score II; SOFA, Sequential Organ Failure Assessment

patients with primary central nervous system lymphomas, high-dose combination chemotherapy also exposes patients to an increased risk of neutropenia [18, 19] and subsequent infection.

The high incidence of PCP observed in this series has been previously reported in PMBT patients [7, 20, 21], but has not been specifically determined among patients with ARF. Moreover these reports on PCP are old and regards to chemotherapy and immunodeficiency profiles changes along these last two decades, the PCP incidence needed to be revisited. In contrast with patients with other solid tumors, patients with PMBT are exposed to high-dose corticosteroids, a well-known risk factor for PCP [22]. In addition to corticosteroids, the following factors may also contribute to cell-mediated immunosuppression in PMBT patients: brain radiotherapy [23], temozolomide [24, 25], and methotrexate [26]. All of these factors can also cause lymphopenia, which was more severe in PMBT patients.

Aspiration pneumonia was also more frequent in PMBT patients in the present study. Dysphagia or swallowing dysfunction is common in PMBT patients and represents

a major cause of mortality in this population [27, 28]. Dysphagia is generally described in posterior fossa tumors and is related to impairment of anatomic structures extending from the brainstem nuclei to the laryngeal muscles, but can also occur in a context of supratentorial lesions or altered state of consciousness independently of the site of the tumor [29].

Acute cardiogenic pulmonary edema and acute-on-chronic respiratory failure were observed less frequently in PMBT patients than in PST patients. This difference was probably related to the younger age of PMBT patients, the lower prevalence of comorbidities in this population [6, 30], and possibly also the limited cardiotoxicity of chemotherapeutic agents used in PMBT.

Finally, pulmonary embolism was observed more frequently in PMBT patients, which is also consistent with previous studies showing that PMBT are associated with one of the highest rates of venous thromboembolism in cancer patients [31], as high as 20% [32]. The main proposed explanations for the high prevalence of venous thromboembolism are the procoagulant state induced by glioblastoma

Fig. 2 Causes of ARF in PMBT and PST patients. PMBT, primary malignant brain tumor; PST, peripheral solid tumor (non-PMBT localized solid malignant tumor); Acute/chronic, acute-on-chronic. Proportions in each category are expressed in relation to the total sample size of PMBT (n = 84) and PST (n = 133) patients, respectively. The symbol * denotes a significant difference (p < 0.05) between the two groups

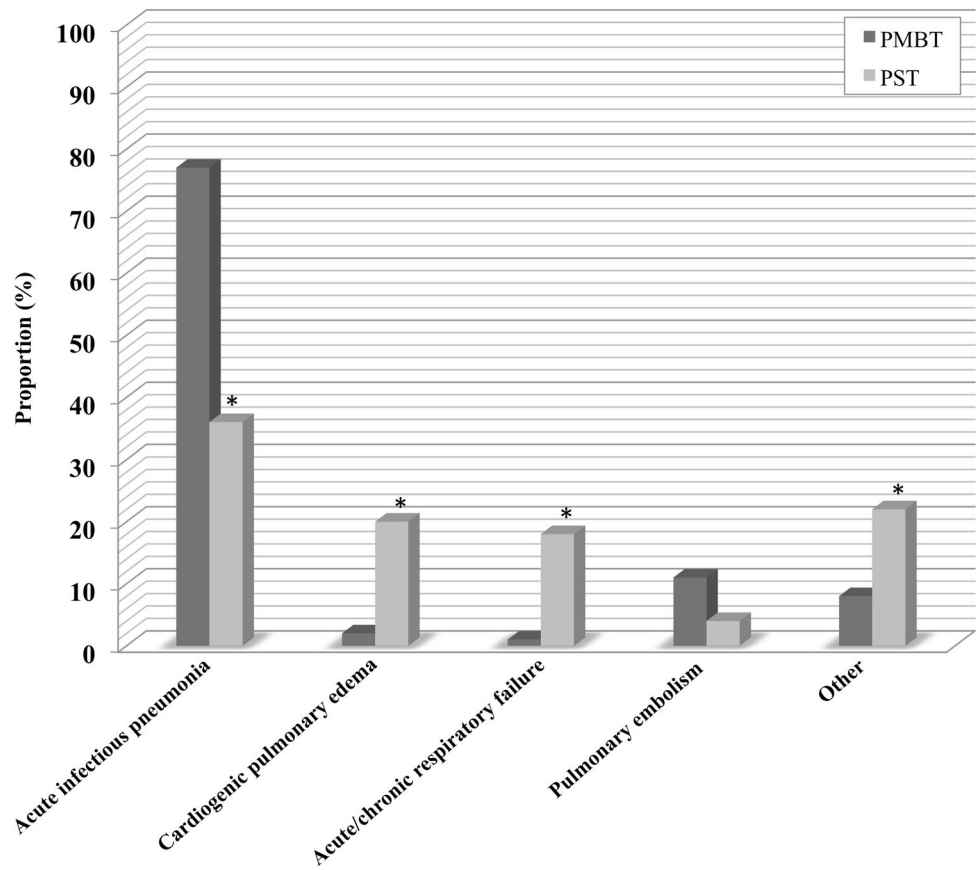


Fig. 3 Causes of acute infectious pneumonia in PMBT and PST patients. PMBT, primary malignant brain tumor; PST, peripheral solid tumor (other than PMBT). Proportions in each category are expressed in relation to the total sample size of PMBT (n = 84) and PST (n = 133) patients, respectively. The symbol * denotes a significant difference (p < 0.05) between the two groups

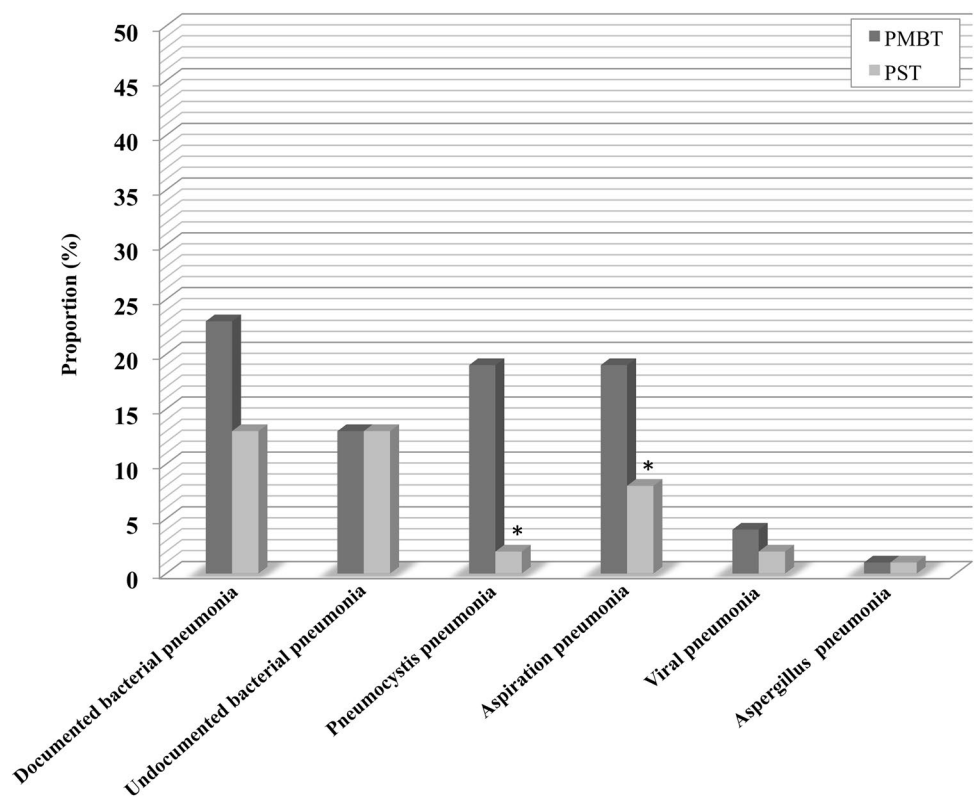


Table 2 Univariate analysis: factors associated with ICU mortality in patients with primary malignant brain tumor

Variables	ICU Mortality		<i>p</i> -value
	Survivors n = 64	Non survivors n = 20	
General characteristics			
Age, years	59 [49–65]	57 [50–66]	0.897
Gender (male), <i>n</i> (%)	49 (68)	13 (65)	0.712
Performance Status 3–4, <i>n</i> (%)	43 (67)	16 (80)	0.274
Charlson Comorbidity Index	2 [2–3]	3 [2–4]	0.483
Corticosteroid therapy, <i>n</i> (%)	52 (81)	17 (85)	0.534
Cancer progression	7 (11)	6 (30)	0.039
Cause of acute respiratory failure			
Acute infectious pneumonia, <i>n</i> (%)	51 (80)	14 (70)	0.366
Pulmonary embolism, <i>n</i> (%)	7 (11)	2 (10)	1.000
Cardiogenic pulmonary edema, <i>n</i> (%)	1 (2)	1 (5)	0.372
Acute-on-chronic respiratory failure, <i>n</i> (%)	1 (2)	0 (0)	0.423
Other, <i>n</i> (%)	5 (7)	2 (10)	0.297
Tumor type			
Primary CNS Lymphoma, <i>n</i> (%)	15 (23)	3 (15)	0.422
High-grade glioma, <i>n</i> (%)	26 (41)	11 (55)	0.258
Low-grade glioma <i>n</i> (%)	19 (30)	6 (30)	0.979
Other, <i>n</i> (%)	4 (6)	0 (0)	0.252
Severity scores			
SAPS II	41 [28–54]	62 [46–71]	<0.001
SOFA	4 [2–7]	8 [5–10]	<0.001
Physiological variables on ICU admission			
Respiratory rate, breaths/min	29 [23–35]	32 [29–40]	0.029
Heart rate, bpm	101 [89–120]	126 [116–137]	0.001
Glasgow coma scale	14 [11–15]	8 [5–13]	0.004
Laboratory variables on ICU admission			
Leukocyte count, /mm ³	7300 [4040–12,115]	8765 [4705–12,173]	0.325
Leukopenia, <i>n</i> (%)	6 (9)	3 (15)	0.477
pH	7.44 [7.41–7.48]	7.37 [7.18–7.44]	0.011
PaO ₂ /FiO ₂ , mmHg	177 [107–242]	111 [89–174]	0.017
Life-support interventions			
Mechanical ventilation, <i>n</i> (%)	31 (48)	16 (80)	<0.001
Vasopressor, <i>n</i> (%)	11 (17)	11 (55)	<0.001
Renal replacement therapy, <i>n</i> (%)	0 (0)	2 (10)	0.014

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

ICU, intensive care unit; CNS, central nervous system; SAPS II, Simplified Acute Physiology Score II; SOFA, Sequential Organ Failure Assessment

[33], limited postoperative mobility, motor deficits, steroid-induced myopathy and the use of bevacizumab [34] in gliomas.

A major finding of this study was that the cause of ARF in PMBT patients could have been prevented in many cases. Pneumocystis pneumonia can be efficiently prevented by chemoprophylaxis [35], but none of the PMBT patients with a diagnosis of PCP received prophylactic chemotherapy. Of note, PCP prophylaxis in PMBT is not

clearly recommended by guidelines after the initial phase of treatment [36, 37], despite the use of high-dose steroids in these patients. Pulmonary embolism can also be prevented by prophylactic anticoagulation [38]. Finally, swallowing disorders and their consequences (aspiration pneumonia) can also be prevented, although less effectively, by gastrostomy or enteral tube feeding, as in stroke patients [39], or by expiratory muscle training [40]. The epidemiologic knowledge gained from this study could

pave the way for future trials evaluating combined preventive strategies aiming at reducing the incidence of ARF in PMBT patients.

Another important finding, is the absence of any significant difference in mortality different between cases PMBT and PST patients, which is consistent with the findings of recent studies, showing that mortality is not higher in PMBT patients than in patients with other solid tumors admitted to the ICU [5, 6]. This is an important finding in terms of triage decisions, as it suggests that a diagnosis of PMBT alone should not preclude ICU admission of patients with ARF. However, as previously described in PMBT patients [5, 6] and in patients with other malignancies [1–4], initiation of mechanical ventilation and cancer progression are strongly associated with poor outcome.

This study has several limitations. First, the retrospective design implies a potential data collection bias. However, it would not be feasible to conduct prospective studies in this field due to the rarity of this disease. Of note, data were extracted from a prospectively managed database, which ensures a certain degree of reliability. Second, because PMBT are localized tumors, they were compared to non-metastatic solid tumors, which creates a selection bias. For instance, patients with lung and pleural metastases, known to predispose to ARF, were excluded. Finally, a matching procedure was not performed on variables likely to influence the causes of ARF (e.g. cardiovascular and respiratory comorbidities, corticosteroids), due to the many differences between PMBT and PST patients regarding such variables, which would limit matching. However, although SAPS II, SOFA and PaO₂/FiO₂ could certainly influence the mortality, all these three variables were similar in the two groups.

In conclusion, ARF in PMBT patients is due to a wide range of causes, different from those generally observed in other cancer patients. The high prevalence of preventable causes suggests the need for guidelines to help physicians institute prophylactic measures in these patients. Finally, the prognosis of ARF in PMBT patients does not appear to differ from that of patients with other solid tumors, and the identification of simple prognostic factors may help physicians to optimize triage decisions.

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Author Contributions MD: methodology, data curation, conceptualization, validation, writing - original draft, and writing - review and editing. NW: data curation, conceptualization, validation, writing - original draft. CM: data curation, validation. LL: validation, software. MC: data curation, validation. KH-X: validation. HP: data curation, conceptualization, validation, IR: methodology, software, validation, writing - original draft. AI: supervision, validation, AD: methodology, data curation, supervision, conceptualization, validation, writing - original draft, and writing - review and editing, TS: supervision, validation, conceptualization, writing - original draft.

Compliance with ethical standards

Conflict of interest Alexandre Demoule has signed research contracts with Covidien, Maquet, Philips and Ait Liquide Santé; he has also received personal fees from Covidien, Maquet and MSD. Ahmed Idbaih reports research funding from La Fondation ARC pour la recherche sur le Cancer, Carthera, Beta-Innov, and Intselchimos; travel funding from Hoffmann-La Roche; and personal fees from Novartis, La Lettre du Cancérologue, BMS, and Cipla unrelated to the submitted work. Nicolas Weiss has signed research contracts with Eumedica, BMS, Med-Day pharmaceuticals; he has also received personal fees from Norgine and Alpha-Wasserman. Thomas Similowski has received grant research from Covidien, Philips, Pierre Fabre Médicaments, Air Liquide Medical Systems; he has also received personal fees from Takeda, Teva Pharma, Lungpacer Inc, Almirall France, Pierre Fabre Médicaments, Novartis, Mundipharma, Invacare, Astra Zeneca, Boehringer Ingelheim and GlaxoSmithKline. Hélène Prodanovic, Khê Hoang-Xuan, Clémence Marois, Isabelle Rivals, Marie Cantier, Léa Lemasle and Maxens Decavèle all declare that they have no conflict of interest.

Research involving human participants and/or animals and informed consent. According to the French Public Health Code (L.1121-1 paragraph 1 and R1121-2.), informed consent is unnecessary for anonymous extraction and analysis of data from patients' medical charts. The study was approved by the Institutional Review Board of the French Intensive Care Society.

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Affiliations

Maxens Decavèle^{1,2}  · Isabelle Rivals^{1,3} · Clémence Marois² · Marie Cantier² · Nicolas Weiss⁴ · Léa Lemasle² · Hélène Prodanovic² · Khe Hoang-Xuan⁵ · Ahmed Idbaih⁵ · Thomas Similowski^{1,2} · Alexandre Demoule^{1,2}

¹ Sorbonne Universités, UPMC Univ Paris 06, INSERM, UMRS_1158 Neurophysiologie respiratoire expérimentale et clinique, Paris, France

² AP-HP, Groupe Hospitalier Pitié-Salpêtrière Charles Foix, Service de Pneumologie et Réanimation Médicale (Département “R3S”), F-75013 Paris, France

³ Equipe de Statistique Appliquée, ESPCI Paris, PSL Research University, UMRS 1158 Neurophysiologie Respiratoire Expérimentale et Clinique, Paris, France

⁴ Sorbonne Université, Brain Liver Pitié-Salpêtrière (BLIPS) Study Group, INSERM UMR_S 938, Centre de Recherche Saint-Antoine, Assistance Publique - Hôpitaux de Paris, Groupement Hospitalier Pitié-Salpêtrière Charles

Foix, Département de Neurologie, Unité de réanimation neurologique, Paris, France

Universitaires La Pitié Salpêtrière - Charles Foix, Service de Neurologie 2-Mazarin, 75013 Paris, France

⁵ Sorbonne Université, Inserm, CNRS, UMR S 1127, Institut du Cerveau et de la Moelle épinière, ICM, AP-HP, Hôpitaux