Brain Biopsy for Neurological Diseases of Unknown Etiology in Critically Ill Patients

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Brain Biopsy for Neurological Diseases of Unknown Etiology in Critically Ill Patients: Feasibility, Safety and Diagnostic Yield

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ABSTRACT

Objectives: Brain biopsy is a useful surgical procedure in the management of patients with suspected neoplastic lesions. Its role in neurological diseases of unknown etiology remains controversial, especially in ICU patients. This study was undertaken to determine the feasibility, safety and the diagnostic yield of brain biopsy in critically ill patients with neurological diseases of unknown etiology. We also aimed to compare these endpoints to those of non-ICU patients who underwent a brain biopsy in the same clinical context.

Design: Monocenter, retrospective, observational cohort study.

Setting: A French tertiary center.

Patients: All adult patients with neurological diseases of unknown etiology under mechanical ventilation undergoing in-ICU brain biopsy between January 2008 and October 2020 were compared to a cohort of non-ICU patients.

Interventions: None.

Measurements and Main Results: Among the 2,207 brain-biopsied patients during the study period, 234 biopsies were performed for neurological diseases of unknown etiology, including 29 who were mechanically ventilated and 205 who were not ICU patients. Specific histological diagnosis and final diagnosis rates were 62.1% and 75.9%, respectively, leading to therapeutic management modification in 62.1% of cases. Meningitis on prebiopsy CSF analysis was the sole predictor of obtaining a final diagnosis (2.3 [1.4-3.8]; *p*=0.02). ICU patients who experienced therapeutic management modification after the biopsy had longer survival (*p*=0.03). The grade 1 to 4 (mild to severe) complication rates were: 24.1%, 3.5%, 0% and 6.9%, respectively. Biopsy–related mortality was significantly higher in ICU patients compared to non-ICU patients (6.9% vs. 0%, *p*=0.02). Hematological malignancy was associated with biopsy-related mortality (1.5 [1.01-2.6]; *p*=0.04).

Conclusions: Brain biopsy in critically ill patients with neurological disease of unknown etiology is associated with high diagnostic yield, therapeutic modifications and postbiopsy survival advantage. Safety profile seems acceptable in most patients. The benefit/risk ratio of brain biopsy in this population should be carefully weighted.

KEYWORDS
Coma
Mechanical ventilation
Intensive care unit
Cryptogenic neurological diseases
Diagnostic workup
Biopsy

INTRODUCTION

Brain biopsy is a surgical procedure used to obtain histopathological diagnosis and guide the management of patients with suspected neoplastic lesions, for which its diagnostic yield exceeds 95%(1, 2). As an invasive procedure associated with potentially severe complications, its role in the diagnosis of nonneoplastic neurological diseases remains controversial. The reported diagnostic yield for this indication was low in the before year 2000, ranging from 20 to 30%(3, 4) and was associated with high frequency of complications(5). Recent evidence in both adults and children reported better results (68%-83%) (6–9), leading to reappraise of the role of brain biopsy in the diagnosis and therapeutic algorithm of patients with neurological diseases of unknown etiology(10).

In critically-ill patients, invasive procedures are associated with a higher risk of complication, especially in the setting of altered hemostasis(11). To the best of our knowledge, no study specifically addressed the role of brain biopsy in neurological diseases of unknown etiology in this population.

We conducted a retrospective monocenter study to investigate brain biopsy feasibility, diagnostic yield, and safety in critically ill adults with neurological diseases of unknown etiology. We also aimed to compare these endpoints to those of non-ICU patients who underwent a brain biopsy in the same clinical context. This study therefore explores the critical care population and updates our previously published cohort of non-ICU patients (6).

MATERIALS AND METHODS

Patients

We retrospectively reviewed the medical records and histology reports of all adults brain-biopsied at our tertiary medical center, between January 2008 and October 2020. Patients meeting the following criteria were included: 1) patients in ICU under mechanical ventilation; 2) neurological disease of unknown etiology or atypical cerebral evolution of systemic and/or neurological underlying diseases; 3) negative comprehensive less-invasive diagnostic work-up including physical examination, laboratory tests including cerebrospinal fluid (CSF) examination obtained by lumbar puncture, radiological examinations and extra-neurological histological findings; and 4) indication for brain biopsy validated by a multidisciplinary team.

Patients were not included if the brain biopsy had been obtained before ICU admission or after discharge. Patients who underwent brain biopsy for histological confirmation of an obvious primary or secondary cerebral neoplasm, or brain abscess were not included.

We then compared variables regarding diagnostic yield and safety between the ICU patients included in this study and a cohort of non-ICU patients with neurological diseases of unknown etiology who underwent a brain biopsy during the study period at our institution. The latter met the above-mentioned criteria 2,3 and 4.

Study variables and outcomes

The primary endpoint was the frequency of obtaining a specific histological diagnosis. Secondary endpoints were frequency of obtaining a final diagnosis, the occurrence of any brain biopsy–related complications, and postbiopsy survival. Histological results of brain biopsies were categorized into 3 groups: specific lesion, nonspecific lesion, normal brain. Obtaining a specific histological diagnosis was defined as brain biopsy findings of a specific lesion sufficient by itself to make a diagnosis. The final diagnosis was reached by combining the brain biopsy findings integrated with the patient's medical history and the results of the less-invasive diagnostic work-up. Brain biopsies containing specific lesion(s) were classified as contributory to the final diagnosis. Brain biopsies with nonspecific lesion(s) could nonetheless be classified as contributing to a final diagnosis. A multidisciplinary discussion determined whether a brain biopsy with nonspecific lesion(s) contributed to a final diagnosis. During these discussions, participants systematically and comprehensively reviewed each patient's medical history, neurological and extra-neurological findings, less-invasive diagnostic work-up, brain biopsy microbiology and histology results. The treating physician's main hypothetical diagnosis and treatment at the time of biopsy and changes made thereafter were noted. Two senior neuroradiologists analyzed all the imaging studies, including available 3.0 Tesla magnetic resonance imaging (MRI) sequences and multiparametric imaging data. Two senior neuropathologists examined all histological slides. During the multidisciplinary discussion, participants had to agree unanimously that the brain biopsy contributed to making the final diagnosis.

Complications related to brain biopsy were monitored during the 30 days following the intervention. In view of existing literature on complications in neurosurgery, we used a previously published grading severity scale tailored for diagnostic intracerebral procedures (6, 12):

- grade 1: complication visible only on postoperative computed-tomography (CT) scan (asymptomatic hemorrhage) or transient event that did not require treatment;
- grade 2: transient complication that resolved completely but required treatment;
- grade 3: persistent neurological deficit >6 months postbiopsy;
- grade 4: biopsy-related death.

Surgical methodology and neuropathological protocol

The biopsies were taken under general anesthesia. A stereotactic biopsy technique was used for deep-seated lesions with patients positioned in a Leksell stereotactic frame. An enhanced CT scan or 3D gadolinium-enhanced and FLAIR sequences 1.5 Tesla MRI were performed. When a stereotactic CT was performed, the images were merged with those of the reference MRI. Once these images were acquired, the trajectory and depth were planned according to the lesion to be targeted. Stereotactic coordinates were calculated with Framelink (Medtronic, Minneapolis, MN) software. The biopsy procedures were then performed as previously described (6). We collected up to 10 tissue samples, ~1 x 10 mm (2).

For cortical and/or meningeal lesions, biopsies were obtained via open craniotomy or a burr hole. We considered a gold standard diagnostic open biopsy to be 1 cm3 of leptomeninges and cortex including grey and white matter. For MRI-negative patients, the biopsy was preferentially taken from the right middle frontal lobe gyrus, unless history, examination or imaging asymmetry suggested another location would provide a higher diagnostic yield.

Postoperative CT scan was then performed immediately after the end of biopsy to rule out complications, before transfer to the ICU (12, 13).

The tissue samples collected were divided into several parts for neuropathological, bacteriological, parasitological and virological investigations. When the differential diagnosis included infection, tissue was set aside for microbiology studies. The management of samples in the neuropathology lab relied on the previously described protocol (6). Since 2016, in case of negativity of the first and second-line panels, the remaining samples were used for metagenomic next-generation sequencing (NGS) analysis in patients with encephalitis (14, 15).

Statistical analyses

Results for categorical variables, expressed as number (%), were compared with $\chi2$ tests; those for continuous variables, expressed as mean ± standard deviation or median [25th–75th percentile interquartile range (IQR)], were compared using Student's t-test or Wilcoxon's rank test. Normality of continuous variable distribution was assessed with the Shapiro–Wilk test and nonnormally distributed continuous variables were compared using Wilcoxon's rank test. Patients' demographic, clinical and biological characteristics were tested in univariable analyses for association with the primary and secondary endpoints. We compared variables regarding diagnostic yield and safety between ICU and non-ICU patients using appropriated tests. Survival between groups were analyzed with the log-rank test. $P<0.05$ defined statistical significance. Analyses were computed with IBM SPSS Statistics v22.0 software (IBM Corp, Armonk, NY).

Standard Protocol Approvals, Registrations, and Patient Consents

In accordance with the ethical standards of our hospital's institutional review board (N°2214386 - CNIL), the Committee for the Protection of Human Subjects, informed consent was not obtained for demographic, physiologic, and hospital-outcome data analyses because this observational study did not modify existing diagnostic or therapeutic strategies. The manuscript was prepared in accordance with the STrengthening the Reporting of Observational studies in Epidemiology (STROBE) statement.

RESULTS

Study population and characteristics

During the study period, 2,207 patients underwent a brain biopsy, of which 234 (10.6%) were performed to investigate a neurological disease of unknown etiology. Twenty-nine were critically ill and 205 were non-ICU patients. The study flowchart is reported in **Figure 1**. The general characteristics of the study patients and their brain biopsies are reported in **Supplemental Digital Content 1 (Table)**. The male-to-female ratio was 2.6 and the mean age on biopsy-day was 49.4±15.4 years. Clinical manifestations included altered consciousness (100.0%), neurological deficit (55.2%), extra-neurological symptoms (37.9%) and seizures (27.6%). Elevated CSF proteins and meningitis were reported in 70.4% and 44.4%, respectively. Most patients had multifocal (69%), bilateral (69%) or gadolinium-enhanced (58.6%) lesions. The biopsy-targeted lesion was exclusively supratentorial. One patient had no lesion on MRI. The most frequent biopsy technique was stereotaxic (65.5%), with MRI-guidance (57.9%). Patient's clinical characteristics and organ failures on ICU admission-day and brain biopsy-day are reported in **Table 1**. Patients were mainly admitted in ICU for coma (79.3%) or status epilepticus (17.2%). Brain biopsy-day organ failure supports were mechanical ventilation 100%, renal replacement therapy 17.2%, vasopressors 10.3%, while no patient was under extracorporeal membrane oxygenation. The median pre-biopsy SOFA score was 4 [4-6]. The median ICU-admission-to-biopsy interval was 11 [6-19] days.

Diagnoses and diagnostic yield-associated factors

Brain biopsy analysis showed a specific lesion, nonspecific lesion or normal brain, in 18 (62.1%), 10 (34.5%) and 1 (3.4%) patients, respectively. A final diagnosis could be made in 22 (75.9%) patients, with most common diagnoses including infection (44.8%), autoimmune or inflammatory disease (13.8%), malignancy (13.8%) and demyelinating disease (6.9%) (**Supplemental Digital Content 2 - Table**). One patient had multiple diagnoses(16). Of note, diagnostic yield did not differ significantly between ICU patients and non-ICU patients (75.9% vs. 74.1%, respectively, p=0.8). Comparisons between ICU patients according to contribution of the biopsy to the final diagnosis are presented in **Table 2**. The univariate analysis retained only the meningitis on pre-biopsy cerebrospinal fluid analysis as being a predictor of obtaining a final diagnosis (odds ratio (OR) [95% confidence interval (CI)], 2.3 [1.4-3.8]; p=0.02).

Complications and factors associated with them

During the month following the biopsy, 10 (34.5%) patients developed a complication (**Supplemental Digital Content 3 - Figure)**. Seven (70%) were grade-1 asymptomatic and diagnosed on systematic post biopsy CT scan. Nine complications (90%) were biopsy site hemorrhages, none leading to surgical evacuation, and one was brain edema requiring corticosteroid administration (grade 2). Two biopsy site delayed hemorrhages were fatal (grade 4): one in a patient with acute myeloid leukemia and persistent severe thrombopenia (30 G/L) 20 day after the biopsy, and another in a patient with multiple myeloma and hemodialysis on day 3 postbiopsy. Rates of overall complications and mortality were significantly higher in ICU patients compared to non-ICU patients: 34.5% vs. 17.6%, p=0.03 and 6.9% vs. 0%, p=0.02, respectively. In the ICU patient group, no variable was associated with the occurrence of postbiopsy complication, while history of hematological malignancies was significantly associated with biopsy-related mortality (OR 1.5 [1.01-2.6]; p=0.04).

Postbiopsy outcomes

Brain biopsy findings led to a therapeutic modification in 62.1% of the ICU-patients; significantly less than in non-ICU patients (79.1%, p=0.04). Twelve patients (41.4%) died in the ICU and a total of 14 (48.3%) within the first year postbiopsy (**Fig. 2A**). The univariate analysis retained low prebiopsy hemoglobin rate (p=0.01), high SOFA score on biopsy day (p=0.04) and history of hematological malignancies (p=0.02) as being associated with in-ICU mortality. In-ICU mortality was significantly lower in patients in whom the biopsy had led to therapeutic changes (22.2% vs. 63.6%, 0.2 [0.03-0.9]; p=0.048). Obtaining of a final diagnosis was not significantly associated with overall survival ($p_{\text{Log-Rank}}$ = 0.39, **Fig. 2B**). Patients with therapeutic management modification after biopsy had a higher probability of survival (72.2% vs. 27.2% at 1-year postbiopsy, $p_{Log\text{-}Rank}$ =0.03, **Fig. 2C**).

DISCUSSION

Most neurological diseases in ICU patients do not require brain biopsy for their diagnosis and management. Nevertheless, in some patients with neurological disease of unknown etiology, obtaining a pathological brain sample can be decisive. To the best of our knowledge, we report the first series on the safety and diagnostic yield of brain biopsy in critically ill patients.

Owing the retrospective nature of this study, to maximize the identification of brain biopsy-related complications, we used a severity grading scale that also took into account silent hemorrhagic complications. Our rate of postbiopsy asymptomatic hemorrhages (24.1%) is consistent with the rates previously reported in non-ICU patients (7-67%)(17). However, the overall complication and mortality rates (34.5% and 6.9%, respectively) were higher in ICU patients. Hematologic malignancies were the only factor associated with biopsy-related mortality in our series despite these patients had normal hemostasis parameters value on biopsy-day. Indeed, pre-biopsy platelet transfusions do not prevent the risk of delayed biopsy-site hemorrhage. One patient had a very delayed (up to 20 days postbiopsy) hemorrhagic complication while having severe thrombopenia (30 G/L). Under exceptional circumstances, we thereby think that the patient's platelet count should be maintained over >100 G/L for at least 3 weeks after the biopsy. For ICU patients with hematologic malignancies who are candidates for brain biopsy, the benefit/risk ratio must be therefore carefully weighted. We demonstrated that multiple organ dysfunction or failure do not impede the conduction and high diagnostic yield of brain biopsy. However, based on our own experience, patients on ECMO support are not good candidates for brain biopsy as these devices are associated with profound hemostatic disturbances(18, 19), and therefore were excluded from being considered for brain biopsy.

The rate of final diagnosis established with brain biopsy in ICU patients was high in our series (75.9%) and comparable to that obtained in our control group of non-ICU patients (74.9%) and even with recent studies published in non-ICU patients(6–8). Furthermore, although 24.1% of the biopsies were non-contributory for a diagnosis, they excluded infectious diseases or malignancies, thereby enabling therapeutic management to be adapted accordingly(20–23). Since the mid-2010's, the progress of metagenomic next generation sequencing on brain samples has enabled diagnoses that could not be achieved with usual microbiological analyses. In our study, metatranscriptomics identified sequences of viral infections in brain tissues from 3 immunocompromised patients with clinical and pathological signs of encephalitis. The 3 identified pathogens were measles(24), rubella and a novel zoonotic virus called umbre orthobunyavirus(25). Nonetheless, we did not significantly improve our rate of positive biopsies since the introduction of metagenomics (76.5% vs. 75%, respectively), because our growing expertise probably led to retain wider indication of brain biopsy in challenging cases. A systematic literature review compiled 22 patients with encephalitis in which a next generation sequencing analysis on brain tissue provided a previously unsuspected diagnosis(14). The authors reported a diagnostic yield of brain tissue analysis of 50% versus only 20% for CSF. The vast majority of the positive results from brain samples was in immunocompromised patients suggesting that metagenomics may be best applied to a targeted population in whom it will be most rewarding. Introduced in the diagnostic algorithm of encephalitis of unknown etiology, including in ICU patients, this new technique opens perspective for comprehensive and unbiased detection of pathogens and paves the way to further improving in the diagnostic yield of brain biopsy(15, 26). The sole factor associated with obtaining a diagnosis on the brain biopsy was the detection of a meningitis on pre-biopsy CSF analysis. Indeed, brain biopsy was contributory to a final diagnosis in all patients who had a meningitis. This major finding should be borne in mind when evaluating the expected brain biopsy diagnostic yield in a critically ill patient potentially eligible for a brain biopsy. In addition, we confirmed that small or non-contrast-enhanced lesions, and even negative-MRI in immunocompromised patients, were not associated with a low diagnosis rate.

Comparing the diagnostic yields in ICU patients, brain biopsy appears to be as effective compared to other solid-organ biopsies. In the literature, percutaneous renal biopsy establish a diagnosis in 69-71% of patients (27, 28), while transvenous renal biopsy obtain a diagnosis in 96% of patients (29). On their side, open lung biopsies contained a specific lesion for 44% of patients in the 2006 study of Kao et al (30), while Philipponnet et al, in 2018, reported a 80% diagnostic-yield (31). The 62%-rate of therapeutic management changes following brain biopsy observed in our study is in the range with those reported for other organs: 73–78% for open lung biopsies (30, 31) and 21-71% for renal biopsies (27–29). Regarding the safety profile of biopsies, although it is difficult to compare the severity of biopsy-related complications between different organs, brain biopsies do not appear to carry any excessive risks for critically ill patients compared to other biopsies. Thus, previous works reported complications following 7.5% to 22% of renal biopsies (27–29) and 20% to 35% of lung biopsies (30, 31). As we report for brain biopsies, fatal complications were observed both in percutaneous renal biopsies (28) and in open lung biopsies (31).

Interestingly, we demonstrated that patients with therapeutic management modification linked to the brain biopsy results had higher probability of survival. Altogether, our results suggest that the contribution of brain biopsy to diagnosis and treatment is undeniable but may be at the cost of complications although most of them were asymptomatic. In that sense, the risk of postbiopsy serious complications should always be weighed against the risks borne by the natural course of an undiagnosed and untreated acute neurological disease. The latter is more often life-threatening than the former, as supported by the 2 biopsy-attributable deaths versus 14 because of disease-attributed deaths.

In the end, it appears fundamental that the indication and feasibility of brain biopsy are evaluated and retained after multidisciplinary discussion between intensivists, neurosurgeons, anesthesiologists and external physicians (neurologists, internal medicine physicians, hematologists…) weighting the benefit-risk balance in every patient. Based on these results and our experience, we propose a decision-making algorithm for the indication and management of brain biopsy in ICU patients with neurological disease of unknown etiology (**Fig. 3**). This underscores that a number of elements must be needed to consider a brain biopsy in this context. When these criteria are met together, we advocate that this intervention be considered as early as possible in the diagnostic management of these patients.

Our study has limitations and strengths. First, it is retrospective, single-center design with a small number of ICU patients, but this is the first series to report on this procedure in critically ill patients. Second, while we compared ICU and non-ICU patients, it was not possible to select relevant matching criteria. Third, we could not provide data on the optimal timing of biopsy as many patients were referred to our institution from distant centers after very variable previous management duration. Last, brain biopsy safety and efficacy in this study relies on the experience of our neurosurgeons, intensivists and neuropathologists, and those results may not be immediately reproducible in every center.

CONCLUSIONS

Brain biopsy in critically ill patients with neurological disease of unknown etiology has high diagnostic yield and is associated with frequent therapeutic modifications. Safety profile seems acceptable in most patients, but fatal post biopsy cerebral hemorrhage occurred in two patients with hematologic malignancies. The benefit/risk ratio of brain biopsy in this indication should be carefully weighted.

FIGURE LEGENDS

Fig. 1. Flowchart of patient inclusion in this study on brain biopsy contribution to diagnosis.

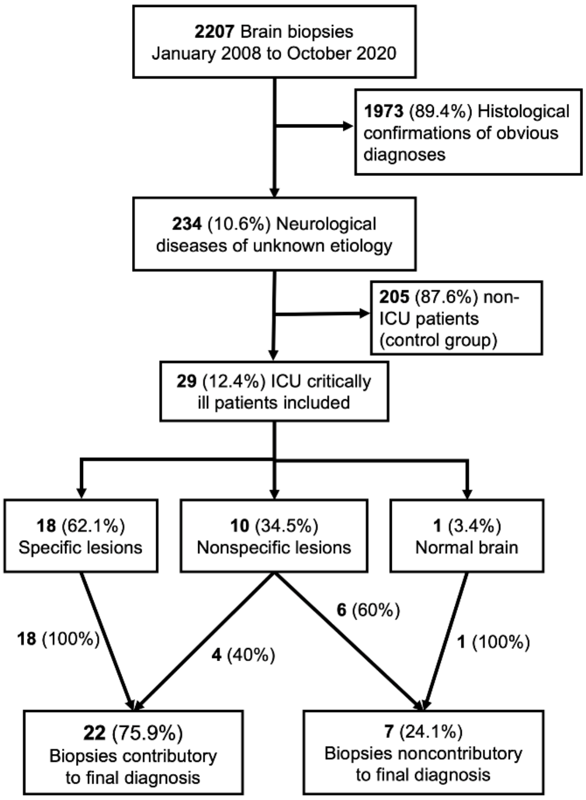

Fig. 2. Comparisons of postbiopsy survival between ICU patients and non-ICU patients (**A**). Overall survival of the 29 ICU critically ill patients according to the brain biopsy findings (**B**) and the biopsy-related therapeutic management changes (**C**).

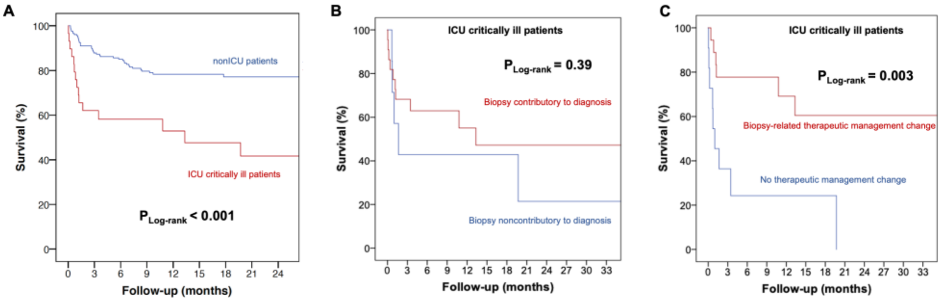

Fig. 3. Decision-making algorithm for the indication and management of brain biopsy in critically ill patients with neurological disease of unknown etiology.

The red color indicates that brain biopsy is not recommended/contra-indicated in the present situation.

APTT, activated partial thromboplastin time; *CSF, cerebrospinal fluid; DTI, direct thrombin inhibitors; INR,* international normalized ratio; *LMWH, low-molecular-weight heparin; UFH, unfractionated heparin.*

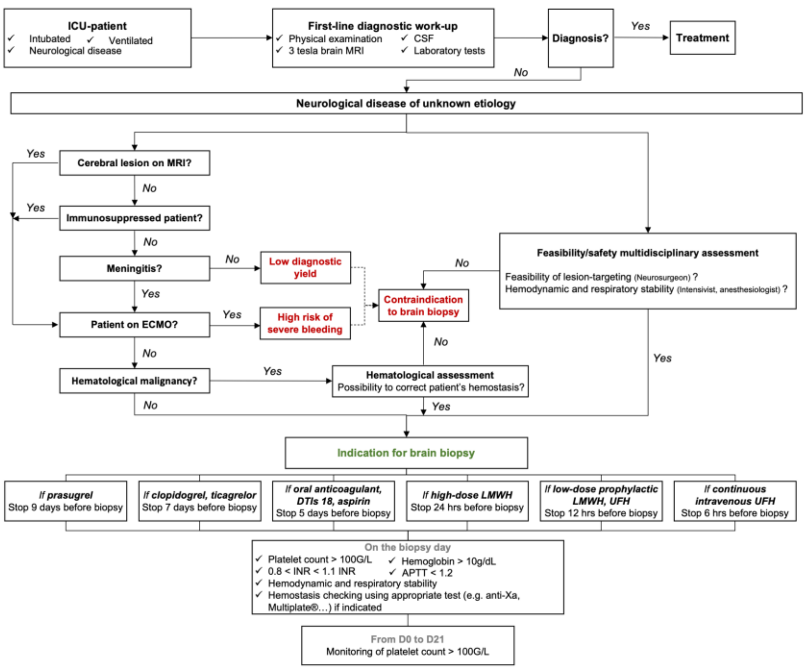

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Table 1. Clinical characteristics of the 29 ICU critically ill patients with brain biopsies.

Characteristics	**Value**
Age, years	49.4 ± 15.4
Reason for ICU admission	
Disorders of consciousness	23 (79.3%)
Status epilepticus	5 (17.2%)
Acute kidney injury	1 (3.4%)
Admission-day SAPS II score	39 [26-48]
Admission-day SOFA score	4 [3-6]
Biopsy-day SOFA score	4 [4-6]
In-ICU organ-failure support or monitoring on biopsy day	
Mechanical ventilation	29 (100%)
Renal replacement therapy	5 (17.2%)
Vasopressor use	3 (10.3%)
External ventricular drain	3 (10.3%)
Intracranial pressure monitoring	2 (6.9%)
Extracorporeal membrane oxygenation	0 (0%)
Pre-biopsy length of ICU stay, d	11 [6-19]
Post-biopsy length of ICU stay, d	20 [7-34]
Mortality	
In-ICU	12 (41.4%)
Day-90	12 (41.4%)
Day-180	13 (44.8%)
Day-365	14 (48.3%)

Abbreviations: D, days; ICU, intensive care unit; SAPS II, Simplified Acute Physiology Score II; SOFA, Sequential Organ Failure Assessment.
Continuous variables are expressed as mean ± SD or median [25–75th percentile interquartile range]; categorical variables are expressed as n (%).

Table 2. Univariable Analysis of Variables Associated with Brain Biopsy Contributory to Final Diagnosis in the 29 ICU Critically Ill Patients.

Variables	**All patients *n* = 29**	**Biopsy Contributory to Final Diagnosis *n* = 22**	**Biopsy Noncontributory to Final Diagnosis *n* = 7**	***P***	**OR 95%CI**
Male	21 (72.4)	16 (72.7)	5 (71.4)	1.0	
Comorbidity					
Immunocompromised	17 (58.6)	12 (54.5)	5 (71.4)	0.67	
Cardiovascular	8 (27.6)	5 22.7)	3 (42.9)	0.36	
Autoimmune diseases	3 (10.3)	3 (13.6)	0 (0.0)	0.56	
HIV infection	6 (20.7)	4 (18.2)	2 (28.6)	0.61	
Hematological malignancies	6 (20.7)	4 (18.2)	2 (28.6)	0.61	
Organ transplantation	5 (17.2)	4 (18.2)	1 (14.3)	1.0	
Solid-organ tumor	2 (6.9)	1 (4.5)	1 (14.3)	0.43	
Clinical findings before biopsy					
Admission-day SOFA score	4.3±1.8	4.3±1.8	4.4±1.8	0.89	
Biopsy-day SOFA score	4 [4-6]	4 [3.8-6.3]	4 [4-6]	1.0	
Admission-day SAPS II score	39 [25-47.5]	39 [24-48]	47 [31-48]	0.67	
Extra-neurological symptoms	11 (37.9)	9 (40.9)	2 (28.6)	0.68	
Laboratory findings before biopsy					
Meningitis	12/27 (44.4)	12/27 (57.1)	0/27 (0)	**0.02**	**2.3 (1.4-3.8)**
Elevated CSF proteins	19/27 (70.4)	15/21 (71.4)	4/6 (66.7)	1.0	
White blood cell count, G/L	9 [6.5-11]	9.4 [6.3-11.4]	7.6 [6.5-10.6]	0.39	
C-reactive protein, >10 mg/L	17/28 (60.7)	12/21 (57.1)	5/7 (71.4)	0.67	
MRI findings before biopsy					
Multifocal lesions	20 (69)	15 (68.2)	5 (71.4)	1.0	
Bilateral lesions	20 (69)	15 (68.2)	5 (71.4)	1.0	
Gadolinium enhancement	17 (58.6)	14 (63.6)	3 (42.9)	0.40	
Meningeal involvement	4 (13.8)	2 (9.1)	2 (28.6)	0.24	
Largest lesion diameter, mm	14.8 [7.5-30.5]	14.9 [9.5-28.3]	11.1 [4.5-36.7]	1.0	

Biopsy-targeted lesion characteristics				
Subcortical	10 (34.5)	8 (36.4)	2 (28.6)	1.0
Deep-brain	12 (41.4)	10 (45.5)	2 (28.6)	0.67
Cortical	5 (17.2)	2 (9.1)	3 (42.9)	0.08
Size >1 cm	18 (62.1)	16 (72.7)	2 (28.6)	0.07
Gadolinium-enhanced	16 (55.2)	13 (59.1)	3 (42.9)	0.67
Biopsy technique				
Stereotaxic	19 (65.5)	16 (72.7)	3 (42.9)	0.19
MRI-guided	11/19 (57.9)	9/16 (56.3)	2/3 (66.7)	1.0
Cortico-meningeal	2 (6.9)	2 (9.1)	0 (0.0)	1.0

Abbreviations: CI = confidence interval; CSF = cerebrospinal fluid; GCS = Glasgow coma score; MRI = magnetic resonance imaging; OR = odds ratio; SAPS II, Simplified Acute Physiology Score II; SOFA, Sequential Organ Failure Assessment. Continuous variables, expressed as mean ± SD or median [interquartile range (IQR)], were compared with Student's *t*-test or Wilcoxon's rank test; categorical variables, expressed as *n* (%), were compared with Fisher's exact tests.

Supplemental Digital Content 1 - Table. Patient, Biopsy and Outcome Characteristics with Comparison According to Patients' Clinical Status

Characteristic	**All patients** ***n*** **= 234**	**ICU patients** ***n*** **= 29**	**Non-ICU patients** ***n*** **= 205**	***p-value***
Male	149 (63.7)	21 (72.4)	128 (62.4)	0.30
Age on biopsy day, years	48 [36-60]	53 [34.5-59.5]	48 [36.5-60]	0.35
Comorbidity				
Immunocompromised	101 (43.2)	17 (58.6)	84 (41.0)	0.07
Cardiovascular	53 (22.6)	8 (27.6)	45 (22.0)	0.5
Autoimmune diseases	41 (17.5)	3 (10.3)	38 (18.5)	0.28
HIV infection	32 (13.7)	6 (20.7)	26 (12.7)	0.24
Hematological malignancies	28 (12.0)	6 (20.7)	22 (10.7)	0.12
Organ transplantation	23 (9.8)	5 (17.2)	18 (8.8)	0.15
Solid-organ tumor	22 (9.4)	2 (6.9)	20 (9.8)	0.62
Clinical findings before biopsy				
Neurological defect	163/231 (70.6)	16 (55.2)	147/202 (72.8)	0.052
Altered consciousness (GCS <15)	76/231 (32.9)	29 (100.0)	47/202 (23.3)	**<0.001**
Seizure	64 (27.4)	8 (27.6)	56 (27.3)	0.98
Extra-neurological symptoms	76/230 (33.0)	11 (37.9)	65/201 (32.3)	0.55
Fever	38/231 (16.5)	14 (48.3)	24/202 (11.9)	**<0.001**
Laboratory findings before biopsy				
Meningitis	67/198 (33.8)	12/27 (44.4)	55/171 (32.2)	0.21
Elevated CSF proteins	101/197 (51.3)	19/27 (70.4)	82/170 (48.2)	**0.03**
White blood cell count, G/L	6.8 [4.8-10.3]	9 [6.5-11]	6.6 [4.7-9.6]	**0.02**
Hemoglobin, g/dL	12.2 [10.2-13.8]	9.3 [8.2-11.9]	12.4 [10.6-13.9]	**0.001**
Platelet count, G/L	249 [193-309]	267 [192-358]	246 [193-301]	0.23
<150 G/L	36/225 (16.0)	5 (17.2)	31/196 (15.8)	0.85
<100 G/L	12/225 (5.3)	2 (6.9)	10/196 (5.1)	0.69
C-Reactive protein >10 mg/L	64/225 (28.4)	17/28 (60.7)	47/197 (23.9)	**<0.001**
MRI findings before biopsy				
Multifocal lesions	146/233 (62.7)	20 (69.0)	126/204 (61.8)	0.45

Bilateral lesions	124/233 (53.2)	20 (69.0)	104/204 (51.0)	0.07
Hydrocephalus	18/232 (7.8)	4 (13.8)	14/203 (6.9)	0.19
Gadolinium enhancement	143/232 (61.6)	17 (58.6)	126/203 (62.1)	0.72
Meningeal involvement	33/232 (14.2)	4 (13.8)	29/203 (14.3)	0.94
Largest lesion diameter, mm	18.4 [11-29.9]	14.8 [7.5-30.5]	19 [11.2-29.9]	0.31
<10 mm	53/226 (23.5)	8/28 (28.6)	45/198 (22.7)	0.50
>10 mm	173/226 (76.5)	20/28 (71.4)	153/198 (77.3)	0.50
>20 mm	107/226 (47.3)	11/28 (39.3)	96/198 (48.5)	0.36
>50 mm	18/226 (8.0)	5/28 (17.9)	13/198 (6.6)	**0.04**
Biopsy-targeted lesion characteristics				
Subcortical	89/232 (38.4)	10 (34.5)	79/203 (38.9)	0.65
Deep-brain	90/232 (38.8)	12 (41.4)	78/203 (38.4)	0.76
Cortical	38/232 (16.4)	5 (17.2)	33/203 (16.3)	0.89
Supratentorial	212 (90.6)	29 (100)	183 (89.3)	0.06
Cerebellum	10 (4.3)	0 (0.0)	10 (4.9)	0.22
Brainstem	10 (4.3)	0 (0.0)	10 (4.9)	0.22
Size >1 cm	166/232 (71.6)	18 (62.1)	148/203 (72.9)	0.23
Gadolinium-enhanced	143/232 (61.6)	16 (55.2)	127/203 (62.6)	0.44
Biopsy technique				
Stereotaxic	172/233 (73.8)	19 (65.5)	153/204 (75.0)	0.28
MRI-guided	136/172 (79.1)	11/19 (57.9)	125/153 (81.7)	**0.02**
Cortico-meningeal	15/232 (6.5)	2 (6.9)	13/203 (6.4)	0.92
Biopsy-related histology				
Specific lesion	161 (68.8)	18 (62.1)	143 (69.8)	0.40
Non-specific lesion	67 (28.6)	10 (34.5)	57 (27.8)	0.46
Normal brain	6 (2.6)	1 (3.4)	5 (2.4)	0.75
Biopsy-related diagnosis				
Diagnostic biopsy	174 (74.4)	22 (75.9)	152 (74.1)	0.84
Second biopsy	7 (3.0)	0 (0.0)	7 (3.4)	0.31
Biopsy-related complication				
Complication	46/233 (19.7)	10 (34.5)	36/204 (17.6)	**0.03**
Symptomatic complication	10/233 (4.3)	3 (10.3)	7/204 (3.4)	0.11

Biopsy-related mortality	2 (0.9)	2 (6.9)	0 (0.0)	**0.02**
Post-biopsy outcomes				
Therapeutic management change	177/230 (77.0)	18 (62.1)	159/201 (79.1)	**0.04**
Death during follow-up	57 (24.4)	16 (55.2)	41 (20.0)	**<0.001**
Follow-up, days	323 [107-703]	201 [28-646]	343 [140-712]	0.23

Abbreviations: CSF = cerebrospinal fluid; GCS = Glasgow coma score; MRI = magnetic resonance imaging. Continuous variables, expressed as median [interquartile range (IQR)], were compared with Wilcoxon's rank test; categorical variables, expressed as *n* (%), were compared with χ^2 tests.

Supplemental Digital Content 2 - Table. Features, diagnosis and outcome of the 29 ICU patients.

Patient (ref.)	Sex	Age, years	Medical history	Epilepsy	CSF	Target lesion >1cm	Gado+	Biopsy	Complication	Final diagnosis	Outcome
1	F	43	HIV	No	Meningitis	Yes	Yes	Stereo	Grade 1	CD8+ encephalitis	Dead day 400
2	M	64	Lung transplant	No		Yes	Yes	Stereo	None	Tuberculosis	Alive
3	M	58	0	No	Meningitis	Yes	No	Open	None	Lymphoma	Alive
4	F	30	HIV	Yes	High CSF proteins	Yes	No	Open	Grade 1	No	Alive
5	M	36	0	No	Meningitis	Yes	Yes	Open	None	Gliomatosis cerebri	Dead day 324
6	M	59	Hodgkin	Yes	Meningitis	Yes	Yes	Open	None	Cerebral vasculitis	Alive
7	M	64	HSCT	No	High CSF proteins	Yes	Yes	Open	Grade 4	No	Dead day 20
8	M	57	Myeloma	No	High CSF proteins	No	Yes	Stereo	Grade 4	Paracoccidioidomycosis	Dead day 1
9	M	53	Myeloma/ HSCT	Yes	High CSF proteins	No	Yes	Stereo	None	Lymphoma	Dead day 6
10	M	45	0	No	Normal	Yes	Yes	Stereo	None	HSV-1 encephalitis	Alive
11	M	60	Myeloma	Yes	High CSF proteins	No	Yes	Open	None	No	Dead day 30
12	M	28	HIV	No	Normal	Yes	Yes	Stereo	None	ADEM	Alive
13	M	55	HIV	No	Normal	No	No	Stereo	None	PML*	Dead day 21
14	M	69	0	Yes	Meningitis	No	Yes	Stereo	None	Lymphoma	Alive
15	F	76	Lung cancer	Yes	Normal	No	Yes	Open	None	No	Dead day 591
16	M	31	0	No	Meningitis	Yes	Yes	Stereo	Grade 1	Tuberculosis	Alive
17	M	21	Heart transplant	No		No	No	Stereo	None	No	Dead day 50
18	M	55	0	No	High CSF proteins	No	No	Stereo	None	No	Alive
19	M	54	Kidney transplant	No	Meningitis	Yes	Yes	Stereo	None	Aspergillosis	Dead day 3
20 (24)	F	28	HIV	Yes	Normal	Yes	No	Open	None	Measles encephalitis	Dead day 38

21 (25)	F	58	0	Yes	Meningitis	No lesion	No	Open	Grade 2	Bunyavirus encephalitis	Dead day 12
22	F	68	Liver Transplant	Yes	High CSF proteins	Yes	No	Open	None	Rubella encephalitis	Dead day 104
23	M	42	0	No	Meningitis	No	No	Stereo	None	Behçet’s disease	Alive
24	M	51	0	No	Meningitis	Yes	No	Stereo	None	ADEM	Dead day 25
25 (23)	M	37	Obesity	No	Meningitis	No	No	Stereo	Grade 1	Multiple angiopathy of Sars-Cov-2 infection	Dead day 37
26 (23)	M	50	Kidney transplant	No	High CSF proteins	No	Yes	Stereo	Grade 1	Multiple angiopathy of Sars-Cov-2 infection	Alive
27 (23)	F	77	Obesity, HBP	No	High CSF proteins	Yes	Yes	Stereo	Grade 1	Multiple angiopathy of Sars-Cov-2 infection	Dead day 35
28 (16)	F	31	HIV	No	Normal	Yes	Yes	Stereo	Grade 1	Toxoplasmosis + Lymphoma	Alive
29	M	33	0	No	Meningitis	Yes	No	Stereo	None	Behcet’s disease	Alive

Supplemental Digital Content 3 - Figure.