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Original Article

Outcomes of intracranial hemorrhage in critically ill patients with acute leukemia: Results of a retrospective cohort study

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ABSTRACT

Background: Admission to the intensive care unit (ICU) is frequently required for patients with acute leukemia (AL) because of life-threatening complications such as intracranial hemorrhage (IH). In this study, we evaluated the impact of IH on survival and neurological outcomes in this population.

Methods: This was a single-center retrospective cohort study including adult patients with AL requiring ICU admission and experiencing IH between 2002 and 2019 at Saint Louis Hospital. Leukemia type was determined according to the French–American–British classification. Brain imaging (either computed tomography or magnetic resonance imaging) was available for all the patients. The primary endpoint of the study was to describe the clinical and biological characteristics and evaluate the mortality and neurological outcome of patients hospitalized in the ICU with newly diagnosed AL and IH. The secondary endpoint was to identify predictive factors of IH in these patients.

Results: Thirty-five patients with AL were included, median age of the patients was 59.00 (interquartile range [IQR]: 36.00–66.00) years. Twenty-nine patients (82.9%) had acute myeloid leukemia, including 12 patients with acute promyelocytic leukemia. Thrombocytopenia was constant, and 48.5% of patients had disseminated intravascular coagulation (DIC). At ICU admission, the median Sequential Organ Failure Assessment score was 5 (IQR: 3–9). The median time between AL onset and IH was 2.0 (IQR: 0.0–9.5) days. The ICU and hospital mortality rates were 60.0% (n =21) and 65.7% (n=23), respectively. In univariate analysis, mechanical ventilation and stupor were associated with mortality, but DIC and acute promyelocytic leukemia were not. Upon multivariate analysis, stupor or coma was the only factor significantly associated with a poor outcome (odds ratio = 8.56, 95 % confidence interval: 2.40 to 30.46).

Conclusion: IH is associated with a high mortality rate in AL patients, with stupor or coma at the onset of intracranial bleeding being independently associated with poor outcomes.

Introduction

Hematological malignancies account for 12% of cancers in France.[1] Acute leukemia (AL) is a hematological malignancy characterized by a monoclonal proliferation of myeloid acute myeloid leukemia (AML) or acute lymphocytic leukemia (ALL) precursor cells blocked at an early stage of differentiation. AL is characterized by the accumulation of immature hematopoietic cells, called blast cells, in the bone marrow, peripheral blood, and other tissues.

Patients with neoplastic diseases represent a significant proportion of intensive care unit (ICU) admissions (17.9%), [2] and their number is steadily increasing. Approximately 15% of patients with AL are admitted to the ICU, whether at diagnosis or during therapeutic course.[3,4] The most frequent complications presented by AL patients are sepsis (36%–49%) and respiratory failure (31%–82%).[5] Moreover, severe bleeding complications can also result in ICU admissions, given that 57 % of patients with AL are reported to have a bleeding event [6] and 23% have a life-threatening bleeding event.[7]

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Multiple factors such as thrombocytopenia and disseminated intravascular coagulation (DIC)[8] are particularly well-described in acute promyelocytic leukemia (APL)[9] but may also lead to clinically significant bleeding in all types of AL. Intracranial hemorrhages (IH) may alter the short-term and long-term prognosis of AL patients. There is little data regarding intracranial bleeding in mixed AL patients, but it may affect up to 4 % of AML patients.[10] Despite therapeutic advances, all-cause mortality remains high in patients with hematological malignancies admitted to the ICU. One study reported that AL patients had a 38 % ICU mortality rate, with only 25% of patients being alive at 12 months.[11] There are neither identified risk factors nor prognostic factors for IH in critically ill patients with AL. Therefore, the objective of this study was to describe the clinical and biological features, mortality, and neurological outcomes of patients admitted to the ICU with newly diagnosed AL and IH.

Methods

Patient selection criteria

We conducted a monocentric retrospective study in the ICU department of Saint Louis Hospital in Paris (France). All consecutive adult patients admitted to the ward from January 1, 2002, to December 31, 2019, were included if they presented with a recent diagnosis of AML or ALL confirmed by cytology (diagnosis made in the ICU or induction treatment in progress at the time of ICU admission) and an IH confirmed by brain imaging (computed tomography or magnetic resonance imaging).

Data collection and definitions

All anonymized data were abstracted from the medical charts of patients. We collected extensive data on patient history, drugs affecting hemostasis, hematological disease, IH, and ICU stay.

Hyperleukocytosis was defined by a white blood cell count of $>10 \times 10^9$/L for APL and $>50 \times 10^9$/L for other types of AL. Stupor or coma was defined respectively by the individual waking only to repeated vigorous stimuli and a Glasgow Coma Scale of <8.[12] Hemostasis perturbations were defined as platelets $<50 \times 10^9$/L, prothrombin rate <50 %, fibrinogen <1.5 g/L, and D-dimer >1000 μg/L. DIC was assessed based on the diagnostic algorithm of the International Society for Thrombosis and Hemostasis.[13] Biological tumor lysis syndrome (TLS) was defined by hyperuricemia, hyperkaliemia, hyperphosphatemia, hypocalcemia, and increased lactate dehydrogenase (LDH), and clinical TLS was defined by the combination of biological TLS and at least one organ involvement.

The ICU prognostic scores[14] were analyzed as follows: A Charlson Comorbidity Index (CCI) score on a scale of 0–6 excluding primary disease to estimate the 10-year survival probability,[15] Sequential Organ Failure Assessment (SOFA) score at admission on a scale of 0–20 to determine organ failures,[16] and Simplified Acute Physiology Score II (SAPS II) score on a scale of 0–164 to predict ICU mortality.[17,18] The modified Rankin score[19] (0–6) was measured at 3 months, 6 months, and 1 year after ICU discharge to evaluate the long-term functional impact of IH.

This retrospective study was approved by the Société de Réanimation de Langue Française ethical committee (N°19–08) and was conducted in accordance with the tenets of the Declaration of Helsinki.

Outcomes

The primary endpoint of the study was to describe the clinical and biological characteristics and evaluate the mortality and neurological outcome of patients hospitalized in the ICU with newly diagnosed AL and IH.

The secondary endpoint was to identify predictive factors of IH in these patients to optimize their diagnostic and therapeutic management.

Statistical analysis

Statistical analysis was carried out using R software (version 4.2.2). Sample characteristics were described as numbers and percentages for qualitative variables and as mean ± standard deviation or median and interquartile range (IQR) for quantitative variables (including Rankin scores), depending on the nature of data distribution. Continuous data were compared using independent samples *t*-tests and categorical data using the chi-squared test. The median follow-up was calculated using Kaplan–Meier analysis. Cumulative survival was estimated from ICU admission to death from any cause. Data were censored according to the time period for survival analysis. Survival probabilities were calculated using the Kaplan–Meier method. Log-rank tests and multivariate analyses were performed using Cox models with variable selection before analysis according to literature and clinical relevance. Modified Rankin scores were plotted against event occurrence. A two-sided *P*-value <0.05 was considered to indicate statistically significant differences.

Results

Study population

Among approximately 2300 patients diagnosed with AL (77.0% AML and 23.0% ALL) at Saint Louis Hospital between 2002 and 2019, all patients with cerebral hemorrhage (35/2300; 1.52%) were hospitalized in the ICU, regardless of the severity of the neurological disorders.

Patient characteristics

IH likely occurred around the time of diagnosis, with a median delay of 3 days. The sex ratio (male/female) was 1.69 and the median age of the patients was 59.00 (IQR: 36.00–66.00) years. Patients had few comorbidities with a median CCI score of 0 (IQR: 0–1.5): 12 patients (34.3%) had arterial hypertension and 5 (14.3%) had diabetes. The majority of patients (29/35, 82.9%) had AML, including 12 (34.3%) with APL (Supplementary Figure S1). The majority of patients had hyperleukocytic leukemia at diagnosis with a median white blood cell count of 106×10^9/L (IQR: 23–266)$\times 10^9$/L. Only one patient received prophylactic anticoagulation at the time of IH (Table 1). At ICU admission, more than half of the patients (54.3%) presented with non-severe mucocutaneous bleeding.

Patients were admitted to the ICU median 1 (IQR: 0–3) day after the diagnosis of IH. Upon ICU admission, the median global SOFA score was 5 (IQR: 3–9), and the median neurological component of SOFA score was 0 (IQR: 0–1). Hematological failure was marked with 91.4% of the patients presenting with thrombocytopenia and/or hypofibrinogenemia, and 45.7% with DIC (Table 1). Four patients (11.4%) had neutropenia at the time of ICU admission.

According to the current guidelines in promyelocytic leukemia, almost all patients underwent aggressive transfusion management.[20] They received fresh frozen plasma, fibrinogen, and platelet transfusions to reach a fibrinogen concentration and a platelet count above 1.0–1.5 g/L and 30–50 $\times$ 10^9/L, respectively. During the ICU stay, 91.4% (32/35) patients received chemotherapy: 51.5% (18/35) received high-dose daunorubicin + cytarabine, 11.4% (4/35) received induction polychemotherapy course according to the Group for Research in Adult Acute Lymphoblastic Leukemias 2014 protocol, [21] 34.3% (12/35) received all-trans retinoic acid (ATRA), 17.1% (6/35) received arsenic trioxide,[22] and 28.6% (10/35) received cytoreductive therapy with hydroxycarbamide. Following these treatments, 40.0% (14/35) of patients developed TLS, wherein six patients showed biological signs and eight showed clinical signs. In addition, 28.6% (10/35) of patients required vasopressors for hypotension unresponsive to fluid resuscitation, and 68.6% (24/35) required invasive mechanical ventilation. Coma was the main reason for intubation (15/24, 62.5%). One-third of the patients (11/35, 31.4%) presented with acute renal failure and half of them required renal replacement therapy (5/35, 14.3%) (Table 1).

Clinical symptoms of IH were variable, with a high incidence of stupor or coma (24/35, 68.6%). Few patients presented with seizures (1/35, 2.9%) or mydriasis (5/35, 14.3%), whereas focal neurological deficit was described in more than half of the patients (19/35, 54.3%). The site of the central nervous system hemorrhage was supratentorial in 27 (77.1%) patients. Massive bleeding with intraventricular hemorrhage was observed in four (11.4%) patients. Only two patients were diagnosed with cerebral venous thrombosis, and none of them received curative anticoagulation (Table 2). Only one patient underwent unsuccessful surgical treatment. The majority of patients had no indication for surgery or were deemed unsuitable for surgery owing to severe coagulopathy and poor prognosis of the underlying hematological malignancy.

Outcomes of ICU and after ICU discharge

In univariate analysis, stupor or coma at ICU admission (P <0.001) and mechanical ventilation in the ICU (P=0.004) were associated with mortality. The neurological component of SOFA score was lower in survivors (P=0.031). In contrast, age, sex, leukemia phenotype (myeloblastic or lymphoblastic), SOFA score, hyperleukocytosis, APL, platelet count, hemostasis abnormalities, hypofibrinogenemia, concomitant mucocutaneous bleeding, DIC, presence of a focal deficit on clinical examination, and IH location were not correlated with ICU mortality. Furthermore, we did not find any association between the worst values of the different hemostasis parameters and mortality (Table 3). Chemotherapy administration had no impact on ICU mortality (P=0.501). In multivariate analysis, the only factor significantly associated with mortality was stupor or coma (odds ratio=8.56, 95% confidence interval: 2.40 to 30.46, P <0.001) (Supplementary Table S1). When forcing APLs into sensitivity analysis, there was no impact on survival. The survival curves showed that stupor or coma (P <0.001) and the use of mechanical ventilation (P=0.002) during ICU stay had a significant impact on mortality. The phenotype of AL, the promyelocytic phenotype of AML, presence of hyperleukocytosis, or DIC

Table 1
Clinical and biological characteristics of patients with IH.

Variables	Patients (n=35)
Demographic characteristics	
Age (years)	59.00 (36.00–66.00)
Male	22 (62.9)
Charlson score	0 (0–1.5)
Type of hematological malignancy	
AML	29 (82.9)
APL	12 (34.3)
ALL	6 (17.1)
Time from diagnosis of AL to IH (days)	3 (1–10)
Time from IH to ICU admission (days)	1 (0–3)
SOFA score at ICU admission	5 (3–9)
Supportive care in ICU	
Invasive mechanical ventilation	24 (68.6)
Vasopressors	10 (28.6)
RRT	5 (14.3)
Biological parameters at diagnosis of IH	
Leukocytes ($\times10^9$/L)	106 (23–266)
Platelets ($\times10^9$/L)	42 (22–81)
Abnormalities of hemostasis	32 (91.4)
PR (%)	54.00 (44.75–61.50)
APTT, P/C ratio	1.13 (1.00–1.20)
Fibrinogen (g/L)	1.44 (0.99–2.30)
DIC	
Presence of DIC	16 (45.7)
ISTH score	4 (2–6)
Chemotherapy during ICU stay	32 (91.4)
Outcome	
ICU mortality	21 (60.0)
Hospital mortality	23 (65.7)
1 year-mortality	28 (80.0)

Data were expressed as n (%) or median (interquartile range).
AL: Acute leukemia; ALL: Acute lymphocytic leukemia; AML: Acute myeloid leukemia; APL: Acute promyelocytic leukemia; APTT: Activated partial thromboplastin; DIC: Disseminated intravascular coagulation; ICU: Intensive care unit; IH: Intracranial hemorrhage; ISTH: International Society on Thrombosis and Hemostasis; P/C ratio: Prothrombin/control ratio; PR: Prothrombin rate; RRT: Renal replacement therapy; SOFA: Sequential Organ Failure Assessment.

Table 2
Clinical and radiological characteristics of intracranial hemorrhage.

Variables	Patients (n=35)
Clinical signs	
Focal motor deficiency	19 (54.3)
Mydriasis	5 (14.3)
Seizure	1 (2.9)
Confusion	9 (25.7)
Stupor or coma	24 (68.6)
Cerebral location and types of hemorrhage	
Infratentorial hematoma	12 (34.3)
Supratentorial hematoma	27 (77.1)
Parenchymal hematoma	23 (65.7)
Ventricular hemorrhage	4 (11.4)
Subdural hematoma	5 (14.3)
Extradural hematoma	1 (2.9)
Cerebral thrombophlebitis	2 (5.7)

Data were expressed as n (%).

Table 3
Factors associated with ICU mortality in patients with AL and intracranial hemorrhage (univariate analysis).

Variables	ICU survivors (*n*=14)	Deceased in ICU (*n*=21)	*P*-value
Demographic characteristics			
Age (years)	37.00 (26.25–61.50)	61.00 (54.00–67.50)	0.073
Male	6 (42.8)	16 (76.2)	0.442
AML	9 (64.3)	20 (95.2)	0.676
SOFA score	3.0 (2.8–5.5)	8.0 (3.0–10.0)	0.080
Neurological component of SOFA score	0 (0–0.5)	2.0 (0–3.0)	0.031
Supportive care in ICU			
Invasive mechanical ventilation	4 (28.6)	20 (95.2)	0.004
RRT	2 (14.3)	3 (14.3)	1.000
Biological parameters at diagnosis			
Leukocytes ($\times10^9$/L)	106 (44–220)	98(17–259)	0.647
Platelets ($\times10^9$/L)	33 (16–45)	59 (24–89)	0.175
Abnormalities of hemostasis	12 (85.7)	20 (95.2)	0.754
Fibrinogen (g/L)	1.33 (0.92–1.88)	1.49 (1.04–3.10)	0.311
DIC	6 (42.8)	0 (0)	1.000
Nadir values of hemostasis parameters			
Platelets ($\times10^9$/L)	34 (17.0–46.5)	19.5 (12.0–56.0)	0.603
PR (%)	46 (41–55)	42 (34–46)	0.230
Fibrinogen (g/L)	1.23 (0.86–1.40)	1.21 (0.07–1.77)	0.681
Mucocutaneous bleeding	8 (57.1)	11 (52.4)	0.809
Clinical signs of hemorrhage			
Focal deficiency	4 (28.6)	15 (71.4)	0.150
Mydriasis	0 (0)	5 (23.8)	0.217
Seizure	1 (7.1)	0 (0)	0.737
Confusion	4 (28.6)	5 (23.8)	0.736
Stupor or coma	2 (14.3)	21 (100.0)	<0.001
Cerebral location of hemorrhage			
Subtentorial	2 (14.3)	10 (47.6)	0.226
Supratentorial	10 (71.4)	16 (76.2)	1.000
Ventricular hemorrhage	0 (0.0)	4 (19.0)	0.329
Subdural hematoma	3 (21.4)	2 (9.5)	0.424
Cerebral venous thrombosis	2 (14.3)	0 (0)	0.212
Neurological disability			
Modified Rankin scale at 3 months	1.0 (1.0–2.0)	NA	<0.001
Modified Rankin scale at 6 months	0 (0–1.0)	NA	<0.001
Modified Rankin scale at 12 months	0 (0–3.5)	NA	<0.001

Data were expressed as *n* (%) or median (interquartile range).
AL: Acute leukemia; AML: Acute myeloid leukemia; DIC: Disseminated intravascular coagulation; ICU: Intensive care unit; NA: Not applicable; PR: Prothrombin rate; RRT: Renal replacement therapy; SOFA: Sequential Organ Failure Assessment.

at diagnosis had no impact on mortality (Figure 1 and Supplementary Figure S2).

Leukemia patients with IH had a poor outcome. The ICU mortality rate and hospital mortality rate were 60.0% (21/35) and 65.7% (23/35), respectively. End-of-life decisions were implemented in 17 patients (48.6%) because of poor prognosis of the underlying hematological malignancy and the severity of IH without therapeutic options; all of these patients died in the ICU. Only 20.0% (7/35) of patients were alive 1 year after ICU discharge (Table 1). Interestingly, 12 (85.7%) patients were discharged alive from the ICU and received the standard chemotherapy protocol for leukemia after the bleeding event. Of the 12 patients discharged alive from the hospital, 9 (75.0%) were in complete remission.

In the univariate analysis, the assessment of neurological disability by the modified Rankin scale at 3 months, 6 months, and 12 months after ICU discharge was well correlated with long-term mortality (P <0.001) (Table 3). ICU mortality was 60.0% (21/35); 10 patients (28.6%) were still alive 6 months later with a median Rankin score of 0 (IQR: 0–1.0), and 7 (20.0%) patients were still alive 12 months later with a median Rankin score of 0 (IQR: 0–3.5). Among the patients who required mechanical ventilation, 79.2% (19/24) died (modified Rankin score: 6) at 1 year, and only 12.5% (3/24) were asymptomatic and disability-free (modified Rankin score: 0 and 1) at 1 year. In contrast, more than 50% (6/11) of patients who did not require mechanical ventilation were asymptomatic or disability-free (modified Rankin score: 0 and 1) at 1 year. The majority of patients who presented a stupor or coma during ICU stay died (95.8%, 23/24) (modified Rankin score: 6) at 1 year. However, among patients who did not experience stupor or coma, 54.5% (6/11) were asymptomatic or disability-free (modified Rankin score: 0 and 1) at 1 year (Figure 2).

Discussion

The occurrence of IH requiring ICU admission in newly diagnosed leukemia patients is a rare event (about 0.02%) and hence poorly reported in the literature. With therapeutic advances and improvements in critical care protocols, the prognosis of hematological patients in the ICU has improved, with a mortality rate of 30%–40%.[23,24] This encouraging picture contrasts sharply with our data. Herein, we described 35 critically ill patients who experienced cerebral bleeding, with a high mortality of 60.0% in the ICU, and only 7 (20.0%) patients were alive 1 year after the event. These data are comparable to those previously published in the literature. Indeed, Chen et al.[25] reported that 67% of AL patients with IH died within 30 days.

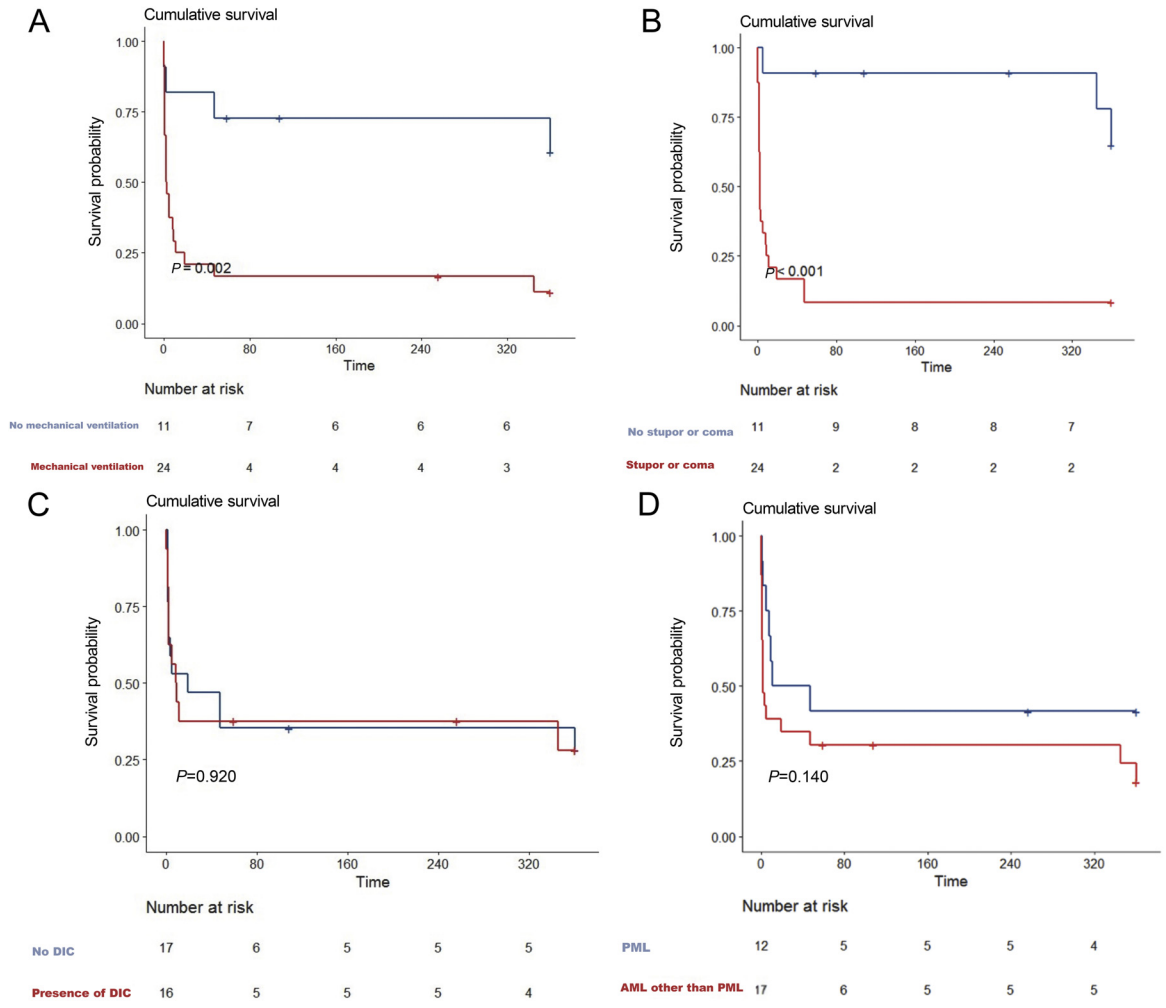

Figure 1. Kaplan–Meier curve estimates of overall survival at 1 year after intensive care unit admission. A: Use of mechanical ventilation. B: Presence of stupor or coma. C: Presence of DIC. D: Type of AML.
AML: Acute myeloid leukemia; DIC: Disseminated intravascular coagulation; PML: Promyelocytic leukemia.

In our study, stupor or coma upon ICU admission is the only factor independently associated with poor neurological prognosis and mortality. Indeed, it increases the risk of death by up to 8.56 times. While the benefit of early ICU admission on mortality has been widely demonstrated in patients with mixed hematological neoplasms,[26,27] this may also be true for AL patients with IH. Lengliné et al.[26] demonstrated that late-ICU admission in newly diagnosed high-risk AML patients was associated with increased use of mechanical ventilation and decreased ICU survival. It could therefore be hypothesized that patients with AL and asymptomatic or paucisymptomatic IH should be referred to the ICU before the onset of severe neurological symptoms, including stupor or coma. Focal neurological signs or headaches are warning signs that should alert physicians and lead to urgent brain imaging.[28,29] Early detection of neurological troubles, even very mild, and prompt initiation of neurocritical care may prevent poor outcomes in these patients. Furthermore, 95.8% of patients referred to the ICU with stupor or confusion, and 79.2% of patients who required mechanical ventilation died at 1 year. However, more than half of the patients who did not present a stupor or coma had no symptoms or disability of IH at 1 year, supporting an aggressive initial ICU management strategy in these patients (Figure 2).

Hemostasis disorders with the presence of DIC are frequent in newly diagnosed AL, occurring in up to 32% of patients.[8] DIC is particularly seen in APL where it is present in more than 75% of cases.[30,31] Although these patients have a high long-term remission rate, severe bleeding is still the leading cause of early death, with an incidence of 3.7% during the first month.[32] Elevated white blood cell count over 20×10^9/L and a low fibrinogen level have been associated with fatal hemorrhages.[33] In our study, patients with APL had a similar risk of early death when compared with other AL patients with IH. Moreover, we did not find any association between the different hemostasis parameters and mortality, either at ICU admission or at the worst values during ICU stay. This likely indicates that guidelines and recommendations for aggressive transfusion management should be followed,[34] while the severity of thrombocytopenia or coagulation test anomalies should not be considered as arguments for non-ICU admission or end-of-life decisions in these patients, as they do not seem to impact short-term prognosis.

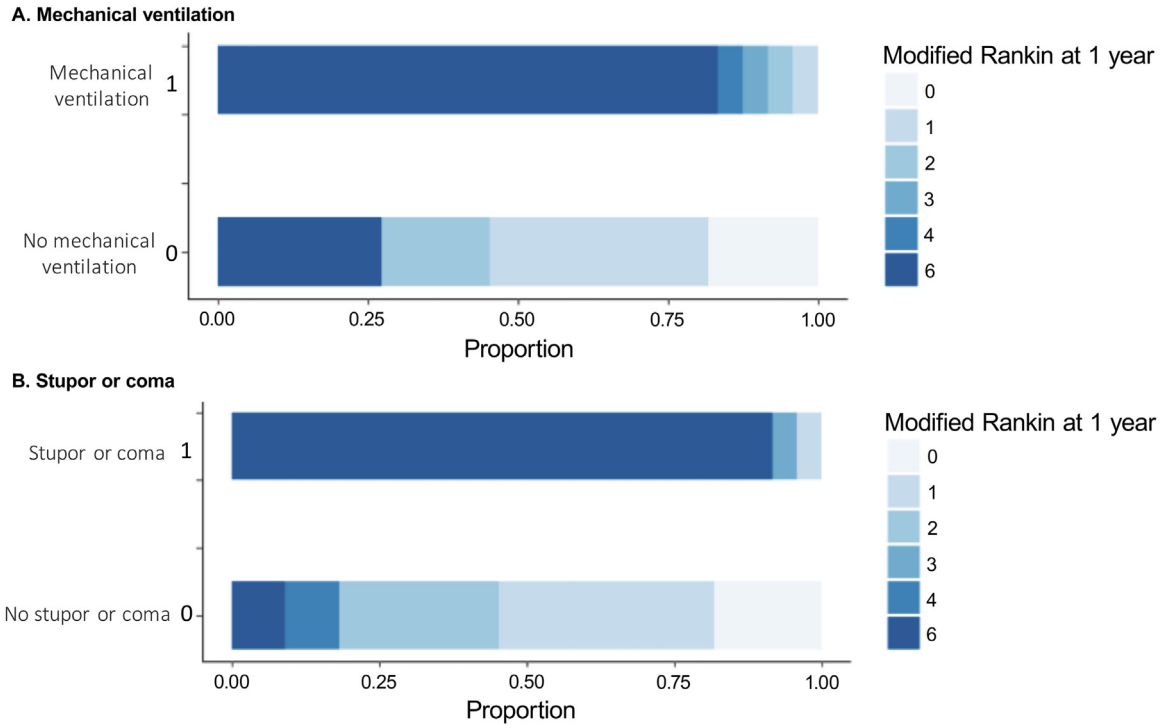

Figure 2. Neurological outcome at 1 year after intensive care unit stay, evaluated with the modified Rankin score. A: Mechanical ventilation requirement. B: Presence of stupor or coma at intracranial hemorrhage diagnosis.

Finally, the occurrence of an IH seemed to have no impact on long-term hematological prognosis. First, 91.4% (32/35) of patients were able to receive appropriate chemotherapy during their ICU stay. Almost all patients discharged alive from the ICU (85.7%, 12/14) had received standard chemotherapy. In some cases, treatment was delayed, but all chemotherapy drugs present in the optimal therapeutic protocols were administered. Moreover, the recommendations for doses and intensities of treatment were also fulfilled. It is therefore necessary to highlight that the occurrence of IH in AL patients should not systematically contraindicate the initiation of potentially curative hematological treatments.[20] This supports aggressive ICU management including prompt chemotherapy administration in patients deemed fit (aside from the hemorrhagic event), as the subsequent hematological prognosis was not impacted in our study.

This study has several limitations. Owing to its single-center design, the management of these patients may not be generalizable to other expert and non-expert centers. Nevertheless, the up-to-date therapeutic guidelines were followed. Furthermore, even if the occurrence of IH at the time of diagnosis of AL remains a relatively rare event, the small size of this study may induce a lack of power; hence, negative findings need to be interpreted cautiously. Last, all patients with AL and IH were probably not deemed eligible for ICU admission, and our results are most certainly derived from a selected population.

Conclusions

IH is associated with a high mortality rate in patients with AL. Although early death was frequent, more than half of the patients without severe neurological symptoms had a favorable neurological outcome, supporting an aggressive initial management including intensive chemotherapy. Early ICU admission should be considered in these patients, while the presence of coma and the need for mechanical ventilation are predictive of a poor outcome.

Author Contributions

Antoine Herault: Writing – review & editing, Writing – original draft, Conceptualization. **Yannick Hourmant:** Writing – review & editing, Data curation, Conceptualization. **Etienne Lengliné:** Writing – review & editing, Conceptualization. **Antoine Lafarge:** Writing – review & editing, Conceptualization. **Eric Mariotte:** Writing – review & editing, Conceptualization. **Michael Darmon:** Writing – review & editing, Methodology, Formal analysis, Conceptualization. **Sandrine Valade:** Writing – review & editing, Validation, Supervision, Project administration, Methodology, Formal analysis, Conceptualization.

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Ethics Statement

The Société de Réanimation de Langue Française ethical committee (N° 19–08) approved this retrospective study.

Conflict of Interest

The authors declare that there are no conflicts of interest regarding the publication of this manuscript. SV reports personal fees from Gilead-Kite, personal fees from Sanofi, outside the submitted work. MD reports grants from MSD, personal fees from Astelas, personal fees and non-financial support from Gilead-Kite, personal fees from Sanofi, outside the submitted work. EM reports personal fees from Sanofi, outside the submitted work. Other authors declare that they have no competing interests.

Data Availability

The data sets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Supplementary Materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jointm.2023.12.008.

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