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Intracranial hemorrhage in newly diagnosed non-promyelocytic acute myeloid leukemia patients admitted for intensive induction chemotherapy

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Abstract

Objectives and Methods: Intracranial hemorrhage (ICH) in acute myeloid leukemia (AML) patients is a major concern due to the increased risk of mortality. Few studies have examined ICH specifically in newly diagnosed AML patients receiving intensive induction chemotherapy (IC) and prophylactic platelet transfusions during thrombocytopenia <10/nL. This retrospective cohort study included 423 newly diagnosed AML patients without acute promyelocytic leukemia who underwent IC between 2007 and 2019. We assessed risk factors, clinical features, and outcomes of ICH.

Results: 17 of 423 patients (4%) suffered ICH during hospital stay, and 4 patients (24%) died directly because of ICH despite routine prophylactic platelet transfusions. Patients with ICH had a negatively impacted overall survival (median OS, 20.1 vs. 104.8 months) and were more likely not to continue with curative treatment. Main risk factors were female gender, severe thrombocytopenia, and decreased fibrinogen. Patients with subsequent ICH also had laboratory signs of liver dysfunction.

Conclusions: Intracranial hemorrhage remains a potentially deadly complication with notable incidence despite prophylactic platelet substitution, suggesting that additional prophylactic interventions may be required to further reduce the frequency of ICH in high-risk patients. Unrecognized genetic factors may simultaneously predispose to AML and platelet dysfunction with ICH.

KEYWORDS
AML, bleeding, induction chemotherapy, intracranial hemorrhage, platelet substitution

Novelty statement: 1. In the real-life setting, ICH occurred in 4% of AML patients admitted for induction chemotherapy despite routine prophylactic platelet transfusions. 2. Female AML patients presenting with low platelets and decreased fibrinogen at time of diagnosis were at increased risk for subsequent ICH, independent of hyperleukocytosis. 3. Intensified surveillance and individualized prophylactic measures may be required to further lower the incidence of ICH and thus improve overall survival.

1 | INTRODUCTION

Acute myeloid leukemia (AML) is an aggressive malignancy of the hematopoietic system and the most frequent form of acute leukemias in adults.[1] The main curative treatment approach for patients without acute promyelocytic leukemia (APL) consists of high-intensity induction chemotherapy, followed by consolidation chemotherapy or allogeneic stem cell transplantation.[1] Bone marrow dysfunction due to disease- and therapy-related factor predisposes AML patients to hemorrhage events and contributes to morbidity and mortality. Although serious bleeding events are common in patients with APL due to severe plasma coagulation factors deficiencies,[2] hemorrhagic events also occur in non-APL AML patients. Among these, intracranial hemorrhage (ICH) constitutes a life-threatening complication. Known acute risk factors for the occurrence of ICH in leukemia patients in general are severe thrombocytopenia and leukocytosis.[3–8] Additionally, platelet dysfunction has been suggested to contribute to bleeding diathesis in the absence of severe thrombocytopenia.[9] Several prospective studies have independently concluded that a threshold of 10 thrombocytes/nL in the absence of fever, sepsis, active bleeding, or invasive procedures is not inferior to transfusion at a threshold of 20 thrombocytes/nL with regard to bleeding complications.[10–13]

The majority of serious bleeding episodes are known to occur during induction chemotherapy,[12] and intracranial bleeding events are the most common serious bleeding complication in AML patients.[4] ICH was reported to occur in up to 6% of acute leukemia patients.[8,14] Early (28/30 days) mortality rates from all causes in AML patients undergoing induction chemotherapy after 2000 range between 3 and 12%.[15,16] ICH events specifically in newly diagnosed AML patients without APL undergoing intensive induction chemotherapy with prophylactic platelet transfusion at a threshold of 10 thrombocytes/nL have not yet been described retrospectively for a large cohort. We conducted a retrospective single-center analysis and examined risk factors at admission, features, and outcomes of ICH in 423 patients with newly diagnosed AML (excluding APL) admitted for intensive induction chemotherapy.

2 | METHODS

2.1 | Patients

All patients newly diagnosed with AML (excluding APL) according to WHO criteria[17] who underwent intensive induction chemotherapy between 2007 and 2019 at our institution were retrospectively included. The screening period for ICH consisted of the inpatient hospital stay during which induction chemotherapy was administered. Study group and screening period were predefined. Standard induction chemotherapy consisted of cytarabine 100 mg/m^2 given continuously for 7 days combined with daunorubicin 60 mg/m^2 given for 3 days (7+3). Patients under the age of 60 received either a second induction therapy cycle of 7 + 3 if they achieved bone marrow blast clearance on day 15 after start of induction therapy, or they received a salvage induction therapy cycle consisting of cytarabine 3000 mg/m^2 every 12 h for 3 days and mitoxantrone 10 mg/m^2 for 3 days (HAM) if blast clearance was not achieved on day 15.[18] Patients above the age of 60 only received a second induction therapy cycle with HAM (with reduced cytarabine dose of 1000 mg/m^2) if they did not achieve bone marrow blast clearance on day 15. Standard antimicrobial prophylaxis consisted of levofloxacin and posaconazole.[19,20]

Laboratory values including C-reactive protein, hemoglobin (Hb), platelet count, activated partial thromboplastin time, and international normalized ratio were routinely monitored. Transfusion thresholds were Hb <8.0 g/dL (2007–08/2014)/Hb ≤7.0 g/dL (after 08/2014) and/or platelet count <10/nL, except for febrile patients (Hb ≤8.0 g/dL and/or platelet count <20/nL). The red blood cell transfusion threshold was lowered in 2014, in accordance with updated recommendations by the German Medical Association. The platelet transfusion threshold remained consistent throughout the entire time period. Pooled random donor platelet concentrates were routinely administered. Patients with overt clinical signs of bleeding or planned invasive procedures were managed on an individual basis.

Patient data and consent to anonymized publication were provided after approval by the local ethics committee (ref. nr. UCT-71–2020) according to the 2013 Declaration of Helsinki. Patients were identified from the clinical cancer registry of the university cancer center and annotated based on manual chart review and archived medical records. For assessment of ICH, results from all inhouse cranial imaging studies for this patient cohort were retrieved from the medical records and manually annotated. The clinical threshold for cranial computed tomography scan (CT) in thrombocytopenic patients was not formally defined. Generally, a high degree of suspicion for ICH was maintained, and thrombocytopenic patients with accidental falls, headaches, reduced vigilance, altered mental state, or focal neurological findings received prompt cranial imaging at a low threshold to rule out ICH. Inhouse CT and magnetic resonance imaging (MRI) modalities were available 24/7 during the entire study period. Patients without any cranial imaging during the hospital stay were defined to not have ICH.

2.2 | Statistical analysis

R 4.0.3[21] and ggplot2 3.3.2[22] were used for statistical analyses, data reporting, and plotting. The Kaplan-Meier method was used for estimation of the percentage of surviving patients. Survival between patient groups was compared with the log-rank test. Cox proportional hazard regression analysis was used for multivariate survival analyses. The reverse-KM method was used to estimate median follow-up time. Multivariate logistic regression was used for risk factor assessment; continuous variables were not dichotomized unless explicitly indicated. Comparative analyses for differences in proportion and other numerical variables between groups were performed using Chi^2 test and Mann-Whitney U test. A p value <.05 was considered statistically significant.

3 | RESULTS

3.1 | Baseline characteristics of AML patients with and without ICH

We identified 423 patients with newly diagnosed non-promyelocytic AML who underwent intensive induction chemotherapy between 2007 and 2019. 17 patients (4.0%) exhibited ICH during their in-house hospital stay. Comparative descriptive statistics of the study group are shown in Table 1. Median age was 64 years (range, 42–73 years) in patients with ICH and 59 years (range, 18–85 years) in patients without ICH ($p = .18$). Female patients accounted for 76% (n = 13) of patients with ICH and 45% (n = 182) of patients without ICH ($p = .02$). The two groups did not differ with respect to WHO classification[23] or AML risk groups according to the European Leukemia Net (ELN) recommendations from 2010.[24]

3.2 | Clinical characteristics of AML patients with and without ICH

The median duration of the hospital stay for patients who survived induction chemotherapy was 52 days (inter-quartile range (IQR), 49–66 days) for AML patients with ICH and 50 days (IQR, 38–59 days) for AML patients without ICH (Table 1).

Per the definition of our study group, all AML patients had received at least one cycle of induction chemotherapy. 18% (n = 3) of patients with ICH and 49% (n = 199) of patients without ICH received a 2nd cycle of induction chemotherapy ($p = .001$). 47% (n = 8) of patients with ICH and 26% (n = 104) of patients without ICH showed no response to induction chemotherapy ($p = .05$). 29% (n = 5) of patients with ICH and 57% (n = 230) of patients without ICH later underwent allogeneic hematopoietic stem cell transplantation ($p = .05$).

3.3 | Laboratory findings at hospital admission in AML patients with and without ICH

Laboratory findings of newly diagnosed AML patients at admission for intensive induction chemotherapy are shown in Table 1. At admission, patients with and without ICH during their hospital stay had a similar percentage of bone marrow blasts (61% vs. 54%, $p = .95$). However, blast percentages in peripheral blood were significantly higher in patients with ICH (median 60%, IQR 35–67%) compared to patients without ICH (median 24%, IQR 4–56%). Similarly, leukocyte counts at admission were significantly higher in patients with ICH (median 44/nL, IQR 10–184/nL) vs. without ICH (median 11/nL, IQR 3–54/nL). Patients with ICH further had significantly lower platelet counts at admission (median 30/nL, IQR 21–53/nL) compared to patients without ICH (median 60/nL, IQR 31–106/nL; $p = .01$). Fibrinogen and albumin levels were also found to be significantly lower in patients with ICH compared to patients without ICH (289, IQR 245–359 vs 372, 295–461, $p = .01$ and 3.5, IQR 3.1–3.7 vs. 4.0, IQR 3.5–4.3, $p = .01$ respectively), and glutamic oxaloacetic transaminase (GOT) was higher in patients with ICH.

3.4 | Characteristics of AML patients with ICH

Individual AML patients with ICH are detailed in Table S1. The median number of days from day 1 of induction chemotherapy to diagnosis of ICH was 18 days (IQR, 4–26 days) (Table 2). Out of 17 patients with ICH, five patients (29%) had <10 thrombocytes/nL on the day prior to ICH and had received prophylactic platelet transfusions per our platelet transfusion policy. Four ICH patients (24%) had intracerebral bleeding (ICB), one patient (6%) suffered a subarachnoid bleeding (SAB), four patients (24%) exhibited subdural hematoma (SDH), and the remaining eight patients (47%) presented with multiple bleeding types (Table 2).

Notably, all patients were symptomatic or showed bleeding signs, thus eliciting clinical suspicion of intracranial abnormalities and triggering cranial imaging (Table S1). Six patients (35%) had a prior history of arterial hypertension. Only seven patients (41%) showed thrombocytopenia ≤10/nL immediately prior to bleeding. One patient was diagnosed with intracranial bleeding after an in-hospital fall. Five patients (29%) had known prior intracranial abnormalities; one of these suffered a subacute ischemic stroke diagnosed shortly after diagnosis and developed secondary intracerebral bleeding two days later. Two patients (12%) had extended stays due to persisting bone marrow suppression after induction chemotherapy and showed late onset of ICH (days 53 and 82 after the start of induction chemotherapy). One patient (6%) presented with an acute epidural hematoma at initial diagnosis of AML, two days prior to start of induction chemotherapy. No patient had a known coagulopathy prior to diagnosis of AML (not listed).

Patients were treated on an individual basis in consultation with our inhouse neurosurgery department. All patients received therapeutic platelet transfusions. Patients were monitored by repeated neurological examinations and cranial CT imaging. Five patients underwent burr hole trepanation to relieve intracranial pressure or evacuate the bleeding, two of whom died. Two additional patients died directly due to intracranial hemorrhage without receiving surgical intervention: patient #4 suffered massive intracranial hemorrhage with rapid brain herniation and patient #5 showed subdural hematoma and intracerebral bleeding and decided against continued therapy. No autopsies were performed. Of the surviving patients, three patients were switched from a curative approach to a non-curative chemotherapy protocol due to ICH (Table S1).

3.5 | Risk factors for ICH in AML patients undergoing induction chemotherapy

To analyze risk factors for ICH in AML patients receiving induction chemotherapy, we conducted a multivariate logistic regression analysis. We aimed to identify risk factors assessable at initial

TABLE 1 Baseline and clinical characteristics

	All patients (n = 423)	With ICH (n = 17)	No ICH (n = 406)	*p* value[a]
Baseline characteristics				
Gender				
Female	195 (46%)	13 (76%)	182 (45%)	.02
Male	228 (54%)	4 (24%)	224 (55%)	
Age at diagnosis, median (IQR), years	59 (18–85)	64 (42–73)	59 (18–85)	.18
WHO classification				
AML with recurrent genetic abnormalities	179 (42%)	8 (47%)	171 (42%)	.88
AML with dysplasia-related changes	59 (14%)	2 (12%)	57 (14%)	1
Therapy-related AML	5 (1%)	1 (6%)	4 (1%)	.49
AML, not otherwise specified	178 (42%)	6 (35%)	172 (42%)	.74
Myeloid sarcoma	1 (0%)	0	1 (0%)	1
Acute leukemias of ambiguous lineage	1 (0%)	0	1 (0%)	1
ELN2010				
Favorable	84 (20%)	5 (29%)	79 (19%)	.49
Intermediate-I/II	252 (60%)	9 (53%)	243 (60%)	.75
Adverse	78 (18%)	2 (12%)	76 (19%)	.69
Not classified	9 (2%)	1 (6%)	8 (2%)	.81
Clinical characteristics				
Hospital days, median (IQR)				
Alive at discharge	50 (38–59)	52 (49–66)	50 (38–59)	.18
Died during stay	30 (18–44)	26 (13–43)	30 (20–42)	.70
Induction chemotherapy				
1st induction cycle	423 (100%)	17 (100%)	406 (100%)	1
2nd induction cycle	202 (48%)	3 (18%)	199 (49%)	.001
Response to induction chemotherapy				
CR/CRi	302 (71%)	9 (53%)	293 (72%)	.15
No response	112 (26%)	8 (47%)	104 (26%)	.05
Missing data	9 (2%)	0 (0%)	9 (2%)	1
Allo-HSCT	235 (56%)	5 (29%)	230 (57%)	.05
Laboratory findings at admission				
Bone marrow blasts, %	54 (35–71)	61 (35–69)	54 (35–71)	.95
Peripheral blood blasts, %	24 (4–56)	60 (35–67)	23 (4–56)	.01
Leukocytes, /nL	11 (3–56)	44 (10–184)	11 (3–54)	.02
Lymphocytes, /nL	1.7 (0.9–3.5)	3.0 (0.82–4.8)	1.7 (0.92–3.3)	.41
Hemoglobin, g/dL	9.1 (7.9–10.5)	8.1 (6.7–9.8)	9.1 (7.9–10.5)	.10
Thrombocytes, /nL	57 (30–105)	30 (21–53)	60 (31–106)	.01
LDH, U/L	427 (256–718)	523 (340–1075)	421 (254–715)	.09
CRP, mg/dL	2.7 (0.5–6.7)	6.9 (1.7–12.9)	2.7 (0.5–6.5)	.08
Creatinine, mg/dL	0.91 (0.75–1.11)	0.90 (0.68–1.29)	0.91 (0.75–1.10)	.93
eGFR (MDRD), mL/min/1.73 m^2	77 (61–94)	62 (48–97)	77 (62–94)	.22
Blood urea nitrogen, mg/dL	30 (24–39)	26 (20–30)	31 (24–39)	.18
Albumin, g/dL	3.9 (3.5–4.3)	3.5 (3.1–3.7)	4.0 (3.5–4.3)	.01
Total protein, g/dL	6.8 (6.3–7.3)	6.4 (6.1–7.0)	6.8 (6.3–7.3)	.15
Total bilirubin, mg/dL	0.5 (0.4–0.8)	0.5 (0.4–0.8)	0.5 (0.4–0.7)	.92
GOT (AST), U/L	29 (21–41)	36 (30–75)	29 (21–41)	.03
GPT (ALT), U/L	25 (16–41)	29 (24–47)	24 (16–41)	.09

(Continues)

TABLE 1 (Continued)

	All patients (n = 423)	With ICH (n = 17)	No ICH (n = 406)	*p* value[a]
TPZ (Quick), %	80 (68–90)	72 (63–82)	80 (69–90)	.08
INR	1.16 (1.07–1.31)	1.26 (1.14–1.38)	1.16 (1.07–1.29)	.07
aPTT, sec	31 (28–35)	32 (28–41)	31 (28–35)	.50
Fibrinogen, mg/dL	368 (293–460)	289 (245–359)	372 (295–461)	.01

Count data are shown unless indicated otherwise. For laboratory values, continuous data are shown with median and inter-quartile range (IQR), unless indicated otherwise.

Abbreviations: allo-HSCT, allogeneic hematopoietic stem cell transplantation; CR, complete response; CRi, incomplete response; ICH, intracranial hemorrhage; ICU, intensive care unit.

[a]Differences between patients with ICH and without ICH were tested. ELN2010, AML risk classification according to the European LeukemiaNet 2010 score.[24]

TABLE 2 Characteristics of intracranial hemorrhage events

		Survival
All	17 (100%)	76%
Type		
ICB	4 (24%)	75%
SAB	1 (6%)	100%
SDH	4 (24%)	100%
Multiple	8 (47%)	63%
ICB locations (all: n=10)		
Supratentorium	6 (60%)	67%
Multiple	4 (40%)	50%
Prior intracranial pathology		
Yes	5 (29%)	60%
No	12 (71%)	83%
Days to ICH, median (IQR)		
From induction	18 (4–26)	
From admission	21 (12–30)	

Count data are shown unless indicated otherwise. Survival indicates absence of death directly attributable to ICH within each subgroup.

Abbreviations: ICB, intracerebral bleeding; ICH, intracranial hemorrhage; IQR, inter-quartile range; SAB, subarachnoid bleeding; SDH, subdural hematoma.

TABLE 3 Multivariate analysis of risk factors determinable at admission for intracranial hemorrhage

Risk factor	Comparator	OR	95% CI	*p* value
Gender: female	Gender: male	3.79	(1.14–12.53)	.03
Age (years)		1.02	(0.98–1.06)	.42
Peripheral blasts (%)		1.01	(0.99–1.03)	.27
Leukocytes, per nL		1.00	(0.99–1.01)	.99
Thrombocytes, 10/nL decrease		1.2	(1.02–1.41)	.03
Fibrinogen, 100 mg/dL decrease		1.62	(1.04–2.53)	.03
INR		1.11	(0.34–3.64)	.86
Albumin, g/dL decrease		2.09	(0.76–5.71)	.15

Logistical regression analysis. Age (years), thrombocytes (per 10/nL thrombocyte decrease), leukocytes, peripheral blasts, fibrinogen (per 100 mg/dL decrease in fibrinogen), INR, and albumin (per 1 g/dL decrease in serum albumin) were used as continuous predictors.

Abbreviations: CI, confidence interval; OR, odds ratio.

Risk factor	Comparator	OR	95% CI	P value
Gender: female	Gender: male	4.62	(1.38–15.47)	.01
Thrombocytes <50/nL	Thrombocytes ≥50/nL	3.19	(1.1–9.31)	.03
Fibrinogen <300 mg/dL	Fibrinogen ≥300 mg/dL	3.1	(1.12–8.59)	.03
INR ≥1.5	INR <1.5	2.2	(0.76–6.4)	.15
Albumin <3.5 mg/dL	Albumin ≥3.5 mg/dL	2.08	(0.49–8.78)	.32

TABLE 4 Multivariate analysis of *dichotomized* risk factors for intracranial hemorrhage

Logistical regression analysis of discriminatory variables. The dichotomized variables were thrombocytes, fibrinogen, INR, and albumin (in addition to gender).
Abbreviations: CI, confidence interval; OR, odds ratio.

diagnosis to predict the occurrence of ICH. Variables included in the model were gender, age at diagnosis, thrombocyte and leukocyte counts, peripheral blast percentage, fibrinogen, INR, and albumin (all at admission). Of these, female gender (OR 3.79), lower thrombocyte counts, and decreased fibrinogen levels were significantly associated with the occurrence of ICH (Table 3). When dichotomized, thrombocytes <50/nL (OR 3.19) and fibrinogen <300 mg/dL (OR 3.1) were significantly associated with ICH (Table 4).

3.6 | ICH impact on survival

AML patients who developed ICH had a significantly poorer overall survival (OS) (median OS, 20.1 months) compared to AML patients without ICH (median OS, 104.8 months) (Figure 1). A multivariate Cox regression analysis with ELN2010 risk score[24] and age as additional covariates confirmed the occurrence of ICH as a risk factor for death in AML patients admitted for induction chemotherapy (Table 5). Of the 17 patients with ICH, four patients (24%) died directly because of ICH (Figure 1). The median follow-up time of the entire cohort was 52.0 months. AML patients with ICH also had significantly poorer 30-day and 60-day survival (Figure S1A,B).

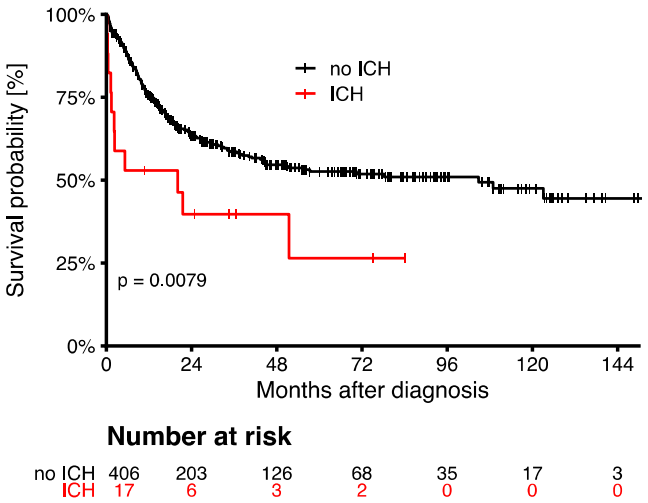


FIGURE 1 Kaplan-Meier estimates of overall survival in AML patients with and without intracranial hemorrhage (ICH). P value was obtained by testing the difference between the two groups by log-rank test

4 | DISCUSSION

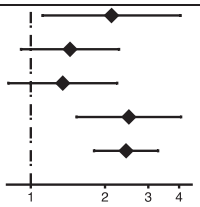
This single-center retrospective study describes incidence, risk factors, features, and outcomes of intracranial hemorrhage in newly diagnosed AML patients without APL that were admitted for intensive induction chemotherapy with routine platelet transfusions at <10 thrombocytes/nL. Four % of patients had ICH. Female gender, severe thrombocytopenia, and decreased fibrinogen at admission were risk factors for ICH. Patients with subsequent ICH also had laboratory signs of liver dysfunction. Earlier work identified hyperleukocytosis and thrombocytopenia immediately prior to bleeding onset as risk factors for ICH in patients with acute leukemias.[5] Our data suggest that severe thrombocytopenia at initial diagnosis of AML is a risk factor for later ICH independent of initial hyperleukocytosis, at least in patients undergoing induction chemotherapy. Corroborating our results, female gender was previously identified as a risk factor for fatal ICH in a broadly defined cohort of acute leukemia patients.[7]

We report an incidence of 4% for ICH, with prophylactic platelet transfusions at a platelet count <10/nL (< 20/nL for patients with fever or infection). This is a lower incidence than reported in the literature. Chen et al.[8] examined intracranial hemorrhages in 841 AML patients (including APL) admitted for various treatments and identified ICH in 6.1% of patients, with fatal ICH in 67% of cases. However, they do not describe their entire study cohort and thus do not allow the determination of risk factors for ICH. Further, the admission/inclusion criteria and screening period are not clearly defined and the platelet transfusion policy is not stated. Zhang et al.[14] also report an incidence of 6.1% for ICH in patients with acute leukemias hospitalized for similarly unspecified reasons and screening time, but did not conduct a risk factor analysis for the occurrence of ICH and did not state the platelet transfusion policy. They show a disproportionate high number of female leukemia patients among those with ICH, as well as hyperleukocytosis, thrombocytopenia, and decreased fibrinogen at unspecified time points related to onset of bleeding. Our observed ICH incidence of 4% appears plausible within this context.

Kim et al.[6] reported a majority of fatal bleeding events to occur within seven days of diagnosis. This study differed from ours since it included patients with acute lymphoblastic leukemia, patients with APL, and AML patients that did not receive induction chemotherapy.

TABLE 5 Multivariate analysis of risk factors for death

Risk Factor	Comparator	HR	95% CI	P value
ICH	No ICH	2.13	(1.12–4.06)	.02
ELN2010: 2	ELN2010: 1	1.44	(0.91–2.28)	.12
ELN2010: 3	ELN2010: 1	1.35	(0.81–2.24)	.25
ELN2010: 4	ELN2010: 1	2.50	(1.53–4.08)	<.001
Age ≥ 65 years	Age < 65 years	2.44	(1.81–3.29)	<.001



Cox proportional hazard regression analysis (number of events=178). ELN2010, AML risk classification according to the European LeukemiaNet 2010 score.[24]

Abbreviations: ICH, intracranial hemorrhage; CI, confidence interval; HR, hazard ratio.

Further, the platelet transfusion policy followed for these patients is unknown. In our cohort, the median time to ICH was 19 days from start of induction chemotherapy and 22 days from admission. Only four patients suffered ICH within the first seven days of diagnosis. This difference may partially be attributable to our focus on patients that were fit enough to receive induction chemotherapy; however, we lack the necessary data to conclude this.

It is intriguing to speculate that common underlying factors may affect both leukemia development and platelet function. Germline loss-of-function mutations in *RUNX1* cause familial platelet disorder with variable penetrance and predispose to adult myeloid malignancy with a life-time risk of myeloid disease of over 40%.[25–27] Alterations in *ANKRD26* or *ETV6* lead to related phenotypes.[28] AML patients have dysfunctional platelets in the absence of severe thrombocytopenia.[9] It seems plausible that a range of possibly cooperating mutations in progenitor cells are capable of predisposing to AML in conjunction with platelet dysfunction. This might explain why AML patients with a proliferative leukemia phenotype and thrombocytopenia at initial diagnosis may continue to persist in their increased risk of bleeding at later time points. Unfortunately, we do not have the required molecular sequencing data and platelet function test results available to investigate this further.

Our study screening procedure has limitations. We used radiologic confirmation to diagnose ICH. It is possible that some patients with subclinical ICH went undetected because no imaging was done. However, the consequences of such manifestations are unknown and may be benign. Further, we cannot exclude the possibility that the diagnosis of ICH was missed in some rapidly deteriorating patients with multiorgan failure where—in the absence of obduction—cause of death was instead ascribed to other factors. Nevertheless, both the low threshold for cranial imaging in our clinic and the established adverse survival impact of diagnosed ICH argue against a misdiagnosis bias in our cohort. Additionally, we have not systematically analyzed performance status or comorbidities, and this could confound the results. However, all patients were considered fit enough to receive intensive induction chemotherapy, and at least the prevalence of arterial hypertension in patients with ICH (35%, Table S1) was similar to the prevalence in the general adult German population (around 34%).[29]

We acknowledge the limitations of a single-center retrospective explorative analysis. Induction chemotherapy protocols and supportive treatment regimens at our institution closely follow national and international guidelines. We therefore believe that our data can be representative of AML patients treated at similar medical centers. However, we would caution against overinterpreting our results. More studies will be required to draw general conclusions. Careful monitoring and clinical judgment continue to remain cornerstones of platelet transfusion practice.

In summary, this study shows that ICH events continue to be an important clinical problem in the treatment of non-APL AML patients. All patients with ICH and platelet counts <10/nL had received prophylactic platelet transfusions on the day prior to ICH. Our data, in conjunction with several randomized studies on the safety of prophylactic platelet transfusions at a threshold of 10 thrombocytes/nL, indicate that additional factors need to be addressed to further lower the risk of ICH in AML patients undergoing intensive induction chemotherapy. Risk factors determinable at admission for ICH were female gender, severe thrombocytopenia, and decreased fibrinogen. Underlying genetic alterations may simultaneously predispose a subset of patients to aggressive AML and platelet dysfunction with bleeding events. Patients at high risk for hemorrhage may benefit from additional individualized prophylactic measures and intensified surveillance.

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CONFLICTS OF INTEREST

The authors have no relevant financial or non-financial interests to disclose.

AUTHORS CONTRIBUTIONS

SEK and OB designed the study. SEK collected and annotated imaging studies and detailed data on patients with intracranial hemorrhage. OB collected and annotated clinical data of the AML patient cohort. SEK analyzed the data, created the figures and tables, and wrote the manuscript. SEK and FF conceived the study. JAS, WM, BS, HS CHB, and FF assisted in conceptualization and discussed the results. HS and CHB provided administrative support. CHB supervised the study. All authors edited and approved the manuscript.

DATA AVAILABILITY STATEMENT

Anonymized data generated and analyzed during this study are available from the corresponding author on reasonable request.

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SUPPORTING INFORMATION

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