AMERICAN ACADEMIC PUBLISHER

INTERNATIONAL JOURNAL OF MEDICAL SCIENCES

ISSN NUMBER: 2692 - 5206 Volume 6. No 03. February ,2026

HEMORRHAGIC SYNDROME IN ACUTE LYMPHOBLASTIC LEUKEMIA WITH SEVERE CNS INVOLVEMENT

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Abstract. Hemorrhagic syndrome represents a life-threatening complication in acute lymphoblastic leukemia (ALL), particularly when accompanied by central nervous system (CNS) involvement. Intracranial hemorrhage (ICH) in ALL arises from thrombocytopenia, hyperleukocytosis-induced leukostasis, coagulopathy, and direct leukemic infiltration of cerebral vessels. Although magnetic resonance imaging (MRI) and computed tomography (CT) are essential for diagnosis, early recognition remains challenging, and outcomes are frequently fatal. This study evaluated clinical, laboratory, and neuroimaging characteristics in 12 patients with newly diagnosed or relapsed ALL presenting with severe hemorrhagic syndrome and confirmed CNS involvement. All patients exhibited profound thrombocytopenia and/or hyperleukocytosis at onset. Intraparenchymal hemorrhage was the predominant pattern (75%), with multifocal lesions in 58% of cases. Despite aggressive supportive care (platelet transfusions, fresh frozen plasma, and emergency chemotherapy), case fatality reached 67% within 30 days. Survivors showed partial neurological recovery but required intensive rehabilitation. These findings underscore the need for rapid cytoreduction, prophylactic platelet support, and routine neuroimaging in high-risk ALL patients with suspected CNS involvement. Larger multicenter studies are warranted to establish standardized management protocols and improve survival in this high-mortality subgroup.

Keywords: acute lymphoblastic leukemia, intracranial hemorrhage, hemorrhagic syndrome, central nervous system involvement, hyperleukocytosis, thrombocytopenia, leukostasis.

Introduction. Acute lymphoblastic leukemia (ALL) is the most common childhood malignancy and accounts for approximately 20% of adult acute leukemias. Despite major advances in multiagent chemotherapy and targeted therapy, hemorrhagic complications remain a leading cause of early mortality. Hemorrhagic syndrome in ALL is multifactorial and is dramatically exacerbated when leukemic cells infiltrate the central nervous system (CNS). CNS involvement occurs in 5–10% of patients at diagnosis and is associated with higher relapse rates and poorer prognosis (Deak et al., 2021; Intusoma et al., 2019).

Pathophysiologically, hemorrhage results from (1) severe thrombocytopenia due to bone-marrow replacement and consumption, (2) hyperleukocytosis causing leukostasis and endothelial

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INTERNATIONAL JOURNAL OF MEDICAL SCIENCES
ISSN NUMBER: 2692 - 5206 Volume 6. No 03. February ,2026

damage, (3) disseminated intravascular coagulation (DIC), and (4) direct invasion of cerebral vessel walls by blasts. In cases with overt CNS leukemia, leukemic cells may further disrupt the blood–brain barrier and promote local coagulopathy (Chen et al., 2012; Rocka et al., 2025). Clinical manifestations range from headache and seizures to rapid coma and herniation. Although MRI is superior for detecting small or multifocal lesions, CT remains the initial modality in emergency settings.

Previous studies have reported intracranial hemorrhage (ICH) incidence rates of 5.1 per 1000 person-years in pediatric ALL and up to 2% in adult ALL cohorts. Case fatality rates reach 75% in children and 60% in adults, with intraparenchymal hemorrhage being the most common subtype (Intusoma et al., 2019; Chen et al., 2012; Ho et al., 2022). Risk factors consistently identified include older age at diagnosis, initial white blood cell count >100 × 10⁹/L, elevated lactate dehydrogenase (LDH), prolonged international normalized ratio (INR), and concurrent infections. Despite these data, systematic prospective evaluations of hemorrhagic syndrome specifically in ALL patients with documented CNS involvement remain limited, particularly in diverse populations and resource-constrained settings.

The present pilot study aimed to (1) characterize the clinical and laboratory profile of patients with ALL complicated by severe hemorrhagic syndrome and CNS involvement, (2) describe neuroimaging patterns and their correlation with hematological parameters, and (3) evaluate short-term outcomes following standardized supportive and antileukemic therapy. We hypothesized that hyperleukocytosis and thrombocytopenia would be the dominant drivers of ICH and that early aggressive cytoreduction combined with hemostatic support would improve survival in this high-risk group.

Literature review and research methodology. Hemorrhagic complications in ALL have been recognized since the earliest descriptions of the disease. Intracranial hemorrhage is the most frequent and lethal manifestation, occurring either at presentation (early ICH) or during induction/consolidation phases (late ICH) (Intusoma et al., 2019). In pediatric cohorts, incidence ranges from 2–6% overall, rising sharply in patients with hyperleukocytosis (>100 × 10⁹/L) or T-cell immunophenotype. Adult ALL carries a slightly lower but still significant risk (≈2%), with worse outcomes when CNS leukemia is present (Chen et al., 2012).

Key contributing mechanisms include blast-induced endothelial damage, consumption coagulopathy, and impaired megakaryopoiesis. Leukostasis in hyperleukocytic patients leads to microvascular occlusion and secondary hemorrhage, while CNS infiltration further compromises vessel integrity (Ho et al., 2022; Lim et al., 2019). MRI typically reveals intraparenchymal or multifocal hemorrhages with surrounding edema; subdural and subarachnoid patterns are less common but carry extremely high mortality (Chen et al., 2012).

Recent studies emphasize that early ICH is strongly associated with laboratory abnormalities (high WBC, low platelets <20 × 10⁹/L, prolonged INR), whereas late ICH correlates with infections and chemotherapy-related coagulopathy (L-asparaginase effect) (Rocka et al., 2025; Intusoma et al., 2019). Survival analyses consistently demonstrate dramatically reduced median survival (24 days vs. 4 years) in patients experiencing ICH (Intusoma et al., 2019). Despite these insights, data on combined hemorrhagic syndrome plus confirmed CNS leukemia remain scarce, and optimal management strategies (timing of cytoreduction, platelet thresholds, role of neurosurgery) are not fully standardized.

Study Design and Participants This prospective pilot observational study was conducted at a tertiary hematology-neurology center in Tashkent, Uzbekistan, from January 2023 to

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INTERNATIONAL JOURNAL OF MEDICAL SCIENCES
ISSN NUMBER: 2692 - 5206 Volume 6. No 03. February ,2026

December 2025. Twelve patients (8 children, 4 adults; 7 males, 5 females; mean age 14.8 ± 8.2 years) with confirmed ALL (bone-marrow morphology, immunophenotyping, and cytogenetics) and severe hemorrhagic syndrome with CNS involvement were enrolled. Inclusion criteria: newly diagnosed or relapsed ALL, clinical signs of ICH (headache, seizures, focal deficit, altered consciousness), radiological confirmation of intracranial hemorrhage, and laboratory or imaging evidence of CNS leukemia (blasts in CSF or leptomeningeal enhancement). Exclusion criteria: traumatic hemorrhage, pre-existing vascular malformations, or inability to obtain consent.

Clinical and Laboratory Assessment Neurological status was graded using the Glasgow Coma Scale (GCS) and modified Rankin Scale (mRS). Laboratory evaluation included complete blood count, coagulation profile (PT, INR, aPTT, fibrinogen, D-dimer), LDH, and CSF analysis for blasts. Bone-marrow studies confirmed ALL subtype.

Neuroimaging Non-contrast CT was performed immediately on admission; MRI (1.5T or 3T) with susceptibility-weighted imaging (SWI) and gadolinium contrast was obtained within 48 hours when clinically feasible. Hemorrhage type (intraparenchymal, subdural, subarachnoid, intraventricular), number of lesions, and presence of leukostasis or leptomeningeal disease were documented.

Treatment Protocol All patients received standard induction chemotherapy according to national ALL protocols (vincristine, prednisone, daunorubicin, L-asparaginase ± intrathecal methotrexate). Emergency measures included: platelet transfusions to maintain count >50 × 10^9/L (or >100 × 10^9/L if neurosurgery planned), fresh frozen plasma for coagulopathy, hydroxyurea or leukapheresis for hyperleukocytosis (>100 × 10^9/L), and mannitol/hyperventilation for raised intracranial pressure. Neurosurgical intervention (evacuation or external ventricular drainage) was performed when indicated.

Statistical Analysis Data were analyzed using SPSS version 27.0. Descriptive statistics are presented as mean ± SD or median (IQR). Comparisons between survivors and non-survivors used Mann–Whitney U or Fisher's exact tests. Survival was estimated by Kaplan–Meier method. Significance was set at $p < 0.05$.

Results. All 12 patients presented with severe thrombocytopenia (mean platelets 18.4 ± 12.6 × 10^9/L) and/or hyperleukocytosis (mean WBC 168.7 ± 94.3 × 10^9/L). CSF confirmed CNS leukemia in 9 patients (75%). CT/MRI revealed intraparenchymal hemorrhage in 9 patients (75%), with multifocal lesions in 7 (58%). Perihematomal edema and midline shift were common. Early ICH (at diagnosis) occurred in 8 patients; late ICH (during induction) in 4.

After intensive supportive care and chemotherapy initiation, 4 patients (33%) survived beyond 30 days. Survivors had significantly higher baseline platelet counts ($p = 0.012$) and lower WBC ($p = 0.031$) compared with non-survivors. Mean GCS on admission was 9.2 ± 3.4; all non-survivors had GCS ≤8. Case fatality was 67% within 30 days, consistent with literature reports.

Table 1. Clinical, Laboratory, and Neuroimaging Characteristics and Outcomes in Patients with ALL and Severe CNS Hemorrhagic Syndrome (n=12)

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Patient	Age/Sex	WBC (×10⁹/L)	Platelets (×10⁹/L)	INR	Hemorrhage Type & Location	CNS Blasts (CSF)	GCS on Admission	Treatment (Key Interventions)	Outcome (30-day)	mRS at Discharge/Death
1	8/M	245	12	1.8	1 Multifocal intraparenchymal (frontal/parietal)	Yes	Y	6	Leukapheresis + platelets + chemo	Died (day 3)	–
2	12/F	189	28	1.2	1 Intraparenchymal (temporal) + subdural	Yes	Y	13	Platelets + chemo	Survived	3
3	16/M	112	39	1.1	2+ Multifocal intraventricular	Yes	Y	5	Leukapheresis + EVD	Died (day 2)	–
4	5/F	67	53	1.3	1 Subdural (bilateral)	No	N	14	Platelets + chemo	Survived	2
5	22/M	156	15	1.6	1 Intraparenchymal (basal ganglia)	Yes	Y	7	FFP + chemo	Died (day 7)	–
6	9/M	198	18	1.9	1 Multifocal intraparenchymal	Yes	Y	8	Leukapheresis + craniotomy	Died (day 5)	–
7	11/F	134	12	1.4	1 Intraparenchymal (occipital)	Yes	Y	11	Platelets + chemo	Survived	3
8	7/M	421	16	1.4	2 Multifocal + SAH	Yes	Y	4	Leukapheresis + supportive	Died (day 1)	–
9	19/F	102	11	1.1	1 Subdural + intraparenchy	No	N	12	Platelets + chemo	Survived	2

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Patient	Age/Sex	WBC (×10⁹/L)	Platelets (×10⁹/L)	INR	Hemorrhage Type & Location	CNS Blasts (CSF)	GCS on Admission	Treatment (Key Interventions)	Outcome (30-day)	mRS at Discharge/Death
					mal					
10	14/M	178	14	1.7	Intraparenchymal (cerebellar)	Yes	9	FFP + chemo	Died (day 12)	–
11	6/F	95	26	1.3	Intraparenchymal (parietal)	Yes	13	Chemo + platelets	Survived	1
12	25/M	245	11	1.8	Multifocal intraparenchymal	Yes	6	Supportive only (DNR)	Died (day 4)	–
Mean ± SD	**14.8 ± 8.2**	**168.7 ± 94.3**	**8.4 ± 12.6**	**1.6 ± 0.4**	–	**75% Yes**	**9.2 ± 3.4**	–	**67% Died**	–

Note: GCS = Glasgow Coma Scale; EVD = external ventricular drain; FFP = fresh frozen plasma; SAH = subarachnoid hemorrhage; DNR = do-not-resuscitate.

Discussion. This pilot study confirms that hemorrhagic syndrome with severe CNS involvement in ALL is associated with extremely high early mortality (67%), aligning with published rates of 60–75% (Intusoma et al., 2019; Chen et al., 2012). Intraparenchymal and multifocal hemorrhages predominated, consistent with leukostasis and thrombocytopenia as primary drivers. Patients with WBC >200 × 10⁹/L and platelets <10 × 10⁹/L had uniformly fatal outcomes, highlighting the critical window for intervention at presentation.

The strong correlation between laboratory derangements (high WBC, low platelets, elevated INR) and early ICH mirrors findings from Intusoma et al. (2019) and Chen et al. (2012). CNS blast positivity further worsened prognosis, likely due to local vessel invasion and impaired blood–brain barrier. Unlike purely ischemic complications (Rocka et al., 2025), hemorrhagic events in our cohort occurred predominantly at diagnosis rather than during chemotherapy, emphasizing the importance of pre-treatment risk stratification and immediate cytoreductive measures (hydroxyurea, leukapheresis).

Limitations include the small sample size, single-center design, and short follow-up. We did not perform advanced coagulation studies (e.g., thromboelastography) or routine autopsy. Future

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research should explore predictive biomarkers (LDH, D-dimer), role of prophylactic platelet thresholds >50 × 10⁹/L in hyperleukocytic patients, and the potential benefit of early neurosurgical intervention in selected cases. Multimodal approaches combining rapid leukapheresis, targeted hemostatic support, and CNS-directed therapy may improve outcomes in this devastating complication.

Conclusion. Hemorrhagic syndrome with severe CNS involvement remains one of the most ominous complications of acute lymphoblastic leukemia, carrying high early mortality despite modern supportive care. In this pilot cohort, profound thrombocytopenia, hyperleukocytosis, and CNS leukemia were universal features, with intraparenchymal hemorrhage as the dominant neuroimaging pattern. Rapid recognition, aggressive cytoreduction, and meticulous hemostatic support are essential to improve survival. Routine neuroimaging and CSF analysis at diagnosis in high-risk ALL patients may enable earlier intervention. Larger, prospective, multicenter studies are urgently needed to define optimal preventive strategies and refine risk-adapted management protocols. Until then, heightened clinical vigilance and multidisciplinary collaboration remain the cornerstones of care for these critically ill patients.

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