Clinical Outcomes and Prognostic Factors in AML with Hyperleukocytosis: A Multicenter Real-World Study

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ABSTRACT

Hyperleukocytosis, defined as a white blood cell (WBC) count exceeding 100x10^9/L, is a life-threatening complication in acute myeloid leukemia (AML) and is associated with early mortality (EM) and poor outcomes. This multicenter retrospective study included 58 newly diagnosed adult AML patients with hyperleukocytosis. Clinical features and survival outcomes were analyzed. The median age at diagnosis was 55 years, with 24.1% of patients aged above 65. Clinical leukostasis (CL) was observed in 48.3%. FLT3 and NPM1 mutations were present in 56.8% and 44.8% of patients, respectively. Overall, 22% experienced EM, and the median overall survival (OS) was 15.0 months. Intensive induction chemotherapy was administered in 77.3% of cases, with a composite complete remission (CR + CRi) rate of 80.5% compared to 45.5% in patients receiving low-intensity therapy (p= 0.020). In multivariate analysis, age > 65 years was the only independent predictor of EM (OR: 10.05; p= 0.035), while both advanced age and poor ECOG performance status (2-3) were independently associated with inferior OS (HR: 2.59 and 3.26, respectively). Leukapheresis, performed in all patients with CL, was not associated with improved survival outcomes. The interval between cytoreduction and induction therapy initiation did not significantly affect EM or OS. Hyperleukocytic AML continues to pose a high risk of early death, particularly among elderly patients. Advanced age remains the most powerful predictor of adverse outcomes. Given the acute clinical complexity and poor outcomes in this high-risk group, prospective trials are urgently needed to guide evidence-based, standardized management approaches.

Keywords: Acute myeloid leukemia, Hyperleukocytosis, Early mortality, Overall survival, Clinical leukostasis

INTRODUCTION

Acute myeloid leukemia (AML) is a rare hematologic malignancy characterized by the uncontrolled proliferation of clonal hematopoietic cells.[1] It accounts for approximately 1% of all cancers in the United States, with a median age at diagnosis of 68 years.[2] Advancements in diagnostics and prognostic evaluation, as well as molecular monitoring and the use of targeted therapies, have contributed to better survival in AML.[3-5]

Hyperleukocytosis, defined as a white blood cell (WBC) count greater than 100×10^9/L due to the rapid proliferation of leukemic cells, is observed in approximately 10-18% of newly diagnosed AML cases.[6,7] The accumulation of blasts within the microvasculature may lead to clinical leukostasis (CL), typically presenting with complications such as cerebrovascular events or respiratory failure. This condition is also considered a medical emergency, as it can result in significant morbidity and early mortality due to complications such as tumor lysis syndrome (TLS), acute kidney injury (AKI), and disseminated intravascular coagulation (DIC), thereby requiring prompt cytoreductive therapy.[6,8,9] As a consequence of these severe complications, early mortality (EM) rates may reach 8% within the first 24 hours and up to 29% within the first week.[10,11] Additionally, 20-25% of patients with hyperleukocytosis fail to achieve complete remission due to EM.[9]

Monocytic AML subtypes, along with MLL rearrangements and FLT3-ITD mutations, are more commonly associated with hyperleukocytosis.[12,13] Furthermore, this patient population also demonstrates a higher prevalence of mutations in NPM1, DNMT3A, CEBPA, and TET2, along with alterations in the RAS signaling pathway such as N-RAS, K-RAS, CBL, SETBP1, and NF1.[7]

Hydroxyurea, leukapheresis, and chemotherapy are commonly utilized prior to induction therapy to control leukemic burden, mitigate TLS risk, and manage symptoms of leukostasis.[6,7,14] Hydroxyurea is recommended for cytoreduction in current guidelines by both the National Comprehensive Cancer Network (NCCN) and the European LeukemiaNet (ELN), owing to its rapid onset of action and favorable safety profile.[5,15,16] There is ongoing debate regarding the prognostic value of leukapheresis in the management of hyperleukocytosis. The procedure requires venous catheterization and the use of anticoagulation, both of which have been associated with increased complication rates in certain patient subgroups.[10,17] Moreover, leukapheresis entails practical limitations, including the need for specialized personnel and equipment, making it essential to carefully weigh its risks and benefits.[17] Consequently, due to the lack of randomized controlled trials, the optimal cytoreductive approach for this patient population remains uncertain.

In this multicenter study, we aimed to evaluate the clinical characteristics and outcomes of newly diagnosed AML patients presenting with hyperleukocytosis (WBC >100×10^9/L), and to identify factors associated with EM and overall survival (OS) in this high-risk population.

PATIENTS AND METHODS

Study Design and Patient Population

This multicenter, retrospective study was conducted at two institutions: Hematology Departments of Ankara Gülhane Training and Research Hospital and Etlik City Hospital. A total of 58 adult patients diagnosed with AML and presenting with hyperleukocytosis were included between November 2016 and July 2024. Patient selection was based on the following inclusion criteria: newly diagnosed AML, age ≥ 18 years, a white blood cell (WBC) count of ≥ 100×10^9/L at the time of diagnosis, and availability of complete clinical and treatment data. Exclusion criteria included a diagnosis of acute promyelocytic leukemia, missing diagnostic or follow-up information, or loss to follow-up.

Diagnosis, Risk Stratification, and Response Assessment

AML diagnosis was established based on World Health Organization (WHO) criteria.[3,18] Risk groups were defined according to the European LeukemiaNet (ELN) 2022 guidelines. Treatment responses were assessed according to ELN criteria, with complete remission (CR) defined as < 5% bone marrow blasts, no extramedullary disease, absence of circulating blasts and Auer rods, and recovery of neutrophils (≥ 1×10^9/L) and platelets (≥100×10^9/L), Complete Remission with Incomplete Count Recovery (CRi) was defined as meeting all CR criteria except for neutrophil and/or platelet recovery.[5,15]

Clinical, Laboratory, and Genetic Assessment

Clinical, laboratory, and molecular data were collected at the time of diagnosis. Baseline laboratory parameters included WBC count, hemoglobin (Hb), platelet count, lactate dehydrogenase (LDH), uric acid, and creatinine levels. Clinical complications evaluated during disease included acute kidney injury (AKI), clinical leukostasis (CL), and tumor lysis syndrome (TLS). CL was defined as the presence of newly developed hypoxia, chest pain, visual disturbances, headache, focal neurological deficits without radiological evidence of central nervous system hemorrhage or thrombosis, priapism, bowel ischemia attributable to hyperleukocytosis.[7] TLS was diagnosed according to the modified Cairo-Bishop criteria.[19] At the time of diagnosis, genetic analyses were performed on bone marrow samples using reverse transcription quantitative polymerase chain reaction (RT-qPCR), fluorescence in situ hybridization (FISH), and conventional cytogenetics.

Treatment Approaches

Cytoreductive therapies administered prior to induction were documented, including hydroxyurea, leukapheresis, and chemotherapy. The interval

between cytoreduction and induction therapy initiation was recorded. Induction treatment regimens were selected by the treating physician based on patient age, performance status, and comorbidities. Patients received either intensive induction chemotherapy (7+3 regimen: anthracycline + cytarabine) or low-intensity therapy (azacitidine ± venetoclax). For patients with FLT3 mutations receiving intensive chemotherapy, midostaurin was administered at 50 mg twice daily for 14 days, starting between days 8 and 21.

Outcome Definitions

Overall survival (OS) was defined as the time interval from the date of diagnosis to the date of death from any cause or last follow-up. Early mortality (EM) was defined as death occurring within the first 30 days after diagnosis.

Ethical Approval: Written informed consent was obtained from all patients. The study adhered to the Declaration of Helsinki and Good Clinical Practice guidelines. Ethical approval was granted by the Ethics Committee of the University of Health Sciences, Gülhane Faculty of Medicine (Approval No: 2024-446, dated 08.10.2024).

Statistical Analysis

All statistical analyses were conducted using SPSS software version 24 (IBM Corp., Armonk, NY, USA). Descriptive statistics were reported as medians and ranges for continuous variables and as frequencies and percentages for categorical variables. Comparisons between categorical variables were performed using the chi-square or Fisher's exact test, as appropriate. Continuous variables were compared using the Mann-Whitney U test due to non-normal distribution. A p-value < 0.05 was considered statistically significant. Survival probabilities were estimated using the Kaplan-Meier method, and differences between groups were assessed using the log-rank test. Median OS and 95% confidence intervals (CI) were reported. Univariate and multivariate Cox proportional hazards regression models were used to identify independent predictors of OS. Variables with a p-value < 0.10 in univariate analysis were included in the multivariate model. Hazard ratios (HRs) and corresponding 95% CIs were calculated. Factors associated with EM were analyzed using univariate and multivariate logistic regression models. Odds ratios (ORs) with 95% CIs were calculated, and variables with $p< 0.10$ in univariate analysis were included in the multivariate model. Statistical significance was set at $p< 0.05$ (two-sided) for all analyses.

RESULTS

Baseline Characteristics and Treatment Approaches

A total of 58 patients with AML presenting with hyperleukocytosis were included in this analysis. The median age at diagnosis was 55 years (range, 22-88), with 24.1% of patients aged > 65 years. The majority of patients were male (58.6%). ECOG performance status (PS) was 0-1 in 53.4% and 2–3 in 46.6% of patients. The median WBC count at presentation was 119×10^9/L (range, 106-373), with 31% of patients having WBC $>150\times10^9$/L and 12.1% > 200×10^9/L. Clinical leukostasis (CL) was observed in 48.3% of patients, acute renal failure in 24.1%, and spontaneous TLS in 24.1% of cases. The median hemoglobin and platelet counts were 8.6 g/dL (range, 4.2–11.2) and 40×10^9/L (range, 8-82), respectively. LDH levels were elevated in the majority of patients, with a median value of 887 U/L. Notably, 12.1% of patients had LDH levels exceeding 2000 U/L. According to the ELN 2022 risk classification, 22.4% of patients were categorized as favorable risk, 48.3% as intermediate risk, and 29.3% as adverse risk. FLT3 mutations were detected in 56.8%, NPM1 mutations in 44.8%, and KMT2A rearrangements in 8.6%. Baseline demographic and clinical characteristics are summarized in Table 1.

All patients received hydroxyurea as initial cytoreductive therapy. In 7 patients (12.0%), subcutaneous cytarabine (Ara-C) was combined with hydroxyurea for cytoreduction. Leukapheresis was performed on all patients presenting with clinical leukostasis (n= 28, 48.3%), while none of the patients without CL (51.7%) underwent leukapheresis. The rate of combination therapy with cytarabine did not differ significantly between patients who underwent leukapheresis and those who did not (13.9% vs. 9.1%, p= 0.698).

Table 1. Clinical, hematologic, and cytogenetic profile of patients with AML and hyperleukocytosis

		Total Patients (n= 58)
Age	Median - years	55 (22-88)
Age Groups	≤ 65 years	44 (75.9%)
	>65 years	14 (24.1%)
Gender	Male	34 (58.6%)
	Female	24 (41.4%)
ECOG PS	0-1	31 (53.4%)
	2-3	27 (46.4%)
WBC Count	Median - $x10^9$/L	119 (106-373)
WBC Count	>150 x 10^9/L	18 (31%)
WBC Count	>200 x 10^9/L	7 (12.1%)
Hemoglobin	Median – g/dl	8.6 (4.2-11.2)
Platelets	$x10^9$/L	40 (8-82)
LDH	Median U/L	887 (261-7839)
LDH	>2000 U/L	7 (12.1%)
Creatinine	Median – mg/dl	1.07 (0.5-9)
Acute Renal Failure	Yes	14 (24.1%)
Clinical Leukostasis (CL)	Yes	28 (48.3%)
Uric Acid Levels	Median- mg/dl	6.65 (0.55-24.5)
Spontaneous Tumor) Lysis Syndrome (TLS	Yes	14 (24.1%)
Bone Marrow Blast Percentage	Median	90% (55-100)
ELN-2022		
Risk Group	Favorable	13 (22.4%)
	Intermediate	28 (48.3%)
	Adverse	17 (29.3%)
ELN Adverse Risk	Yes	17 (29.3%)
FLT-3	Yes	33 (56.8%)
NPM-1	Yes	26 (44.8%)
KMT2A Rearrangements	Yes	5 (8.6%)

When baseline demographic and clinical features were compared between patients with and without CL, spontaneous TLS was the only variable significantly associated with CL. TLS occurred in 42.9% of patients with CL versus 6.7% without CL (p= 0.002). No other clinical or demographic characteristics were significantly associated with the presence of CL.

Induction chemotherapy was administered to 52 of the 58 (89.7%) patients, while 6 patients (10.3%) died before induction treatment could be initiated. Of these, 3 were aged > 65 years and 3 were ≤ 65 years. Among those who received induction therapy, 41 patients (77.3%) were treated with a 7+3-based intensive chemotherapy regimen, whereas 11 (22.7%) patients received a hypomethylating agent (HMA±Venetoclax)-based low-intensity induction regimen. Among the 41 patients who received intensive induction chemotherapy, the median age was 47 years (range, 22-66), and 40 of them belonged to the ≤65 age group. In contrast, patients treated with low-intensity induction regimens had a median age of 75 years (range, 61-88), with only one patient in this group aged ≤ 65 years.

Among the 41 patients treated with intensive induction, the composite complete remission (CR + CRi) rate was 80.5% (n= 33). In comparison, 5 of 11 patients (45.5%) receiving low-intensity induction achieved composite CR. The difference in remission rates between the two groups was statistically significant (80.5% vs. 45.5%, p= 0.020).

The median interval from initiation of cytoreductive therapy to the start of induction chemotherapy was 5 days (range, 1-15). In 27 of 52 patients (51.9%), induction therapy commenced ≥ 5 days after cytoreduction. In 34 patients (65.4%), induction was started ≥ 3 days after cytoreductive treatment.

Survival Outcomes

After a median follow-up of 24 months, the median overall survival (OS) for the entire cohort was 15.0 months (95% CI: 8.8-21.2), as illustrated in the Kaplan-Meier survival plot (Figure 1). The estimated 1-year and 2-year OS rates were 57% and 40%, respectively. Early mortality (EM) was defined as death occurring within the first 30 days following diagnosis and was observed in 13 patients (22%). Notably, 6 of these early deaths occurred prior to the initiation of induction chemotherapy, during the cytoreductive phase.

In subgroup analysis, patients aged ≤ 65 years demonstrated a markedly superior median OS of 37.0 months, whereas those aged > 65 years had a median OS of 6.0 months (95% CI: 0.0-17.5 months, p< 0.001) as shown in Figure 2.

Table 2. Univariate and multivariate logistic regression analyses of factors associated with early mortality (EM)

		Total Patients	Univariate analysis – Early mortality (EM)		Multivariate analysis – Early mortality (EM)	
			EM -OR	p	EM -OR	p
Age >65 years	Yes	14 (24.1%)	**10.4 (2.54-42.58)**	**0.001**	**10.05 (1.18-44.67)**	**0.035**
Gender	Male	34 (58.6%)	0.77 (0.22-2.69)	0.692		
	Female	24 (41.4%)				
ECOG PS	0-1	31 (53.4%)	**9.96 (1.96-50.65)**	**0.006**	4.66 (0.54-39.76)	0.159
	2-3	27 (46.4%)				
WBC Count	Median - x10^9/L	119 (106-373)	1.00 (1.00-1.00)	0.409		
WBC Count	>150 x 10^9/L	18 (31%)	1.53 (0.42-5.58)	0.513		
WBC Count	>200 x 10^9/L	7 (12.1%)	**6.22 (1.18-32.76)**	**0.031**	4.63 (0.54-22.9)	0.079
Hemoglobin	Median – g/dl	8.6 (4.2-11.2)	0.83 (0.59-1.15)	0.279		
Platelets	x10^9/L	40 (8-82)	1.00 (1.00-1.00)	0.611		
LDH	Median U/L	887 (261-7839)	0.99 (0.99-1.01)	0.989		
LDH	>2000 U/L	7 (12.1%)	1.45 (0.24-8.54)	0.678		
Creatinine	Median – mg/dl	1.07 (0.5-9)	1.64 (0.99-2.73)	0.054		
Acute Renal Failure	Yes	14 (24.1%)	**10.40 (2.54-42.58)**	**0.001**	2.99 (0.57-35.57)	0.929
Clinical Leukostasis (CL)	Yes	28 (48.3%)	**9.05 (1.78-45.89)**	**0.008**	3.53 (0.38-29.3)	0.275
Uric Acid	Median- mg/dl	6.65 (0.55-24.5)	**1.19 (1.02-1.39)**	**0.027**	0.92 (0.72-1.16)	0.500
Spontaneous Tumor Lysis Syndrome (TLS)	Yes	14 (24.1%)	**7.44 (2.13-32.58)**	**0.021**	3.13 (0.28-27.68)	0.461
Bone Marrow Blast Percentage		Median	90% (55-100)	0.97 (0.92-1.02)	0.330	

The 12-month survival rate was 62% in the patients aged ≤ 65 years and 16% in those aged >65 years. By 22 months, survival in the elderly group had declined to 0%, while estimated survival in the younger group remained approximately 46% at 37 months.

The time interval between cytoreductive therapy and the initiation of induction chemotherapy—whether ≥ 3 days or ≥ 5 days—had no statistically significant impact on overall survival.

Factors Associated with Overall Survival

In univariate Cox regression analysis, the following variables were significantly associated with inferior overall survival (OS): Age > 65 years (HR: 3.70; 95% CI: 1.74-7.84; p= 0.001), ECOG performance status (PS) 2–3 (HR: 4.05; 95% CI: 1.77-9.26; p= 0.001), acute kidney injury (HR: 4.16; 95% CI: 1.89-9.15; p< 0.001), clinical leukostasis (CL) (HR: 2.64; 95% CI: 1.23–5.65; p= 0.012), spontaneous TLS (HR: 3.74; 95% CI: 1.67-8.37; p< 0.001), and elevated serum uric acid levels (per mg/dL increase; HR: 1.12; 95% CI: 1.02-1.22; p= 0.011).

In the multivariate Cox regression model, age > 65 years (HR: 2.59; 95% CI: 1.43-12.6; p= 0.031) and ECOG PS 2–3 (HR: 3.26; 95% CI: 1.06–10.04; p= 0.039) remained independent predictors of worse OS. Univariate and multivariate analyses of factors associated with overall survival are summarized in Table 2.

Factors Associated with Early Mortality

Univariate logistic regression analysis identified several significant predictors of early mortality: Age > 65 years (OR: 10.4; 95% CI: 2.54-42.58; p= 0.001), ECOG PS 2-3 (OR: 9.96; 95% CI: 1.96-50.65; p= 0.006), WBC > 200×10^9/L (OR: 6.22; 95% CI: 1.18–32.76; p= 0.031), acute kidney injury (OR: 10.40; 95% CI: 2.54-42.58; p= 0.001), CL (OR: 9.05; 95% CI: 1.78-45.89; p= 0.008), spontaneous TLS (OR: 7.44; 95% CI: 2.13-32.58; p= 0.021), and elevated uric acid levels (per mg/dL increase; OR: 1.19; 95% CI: 1.02-1.39; p= 0.027).

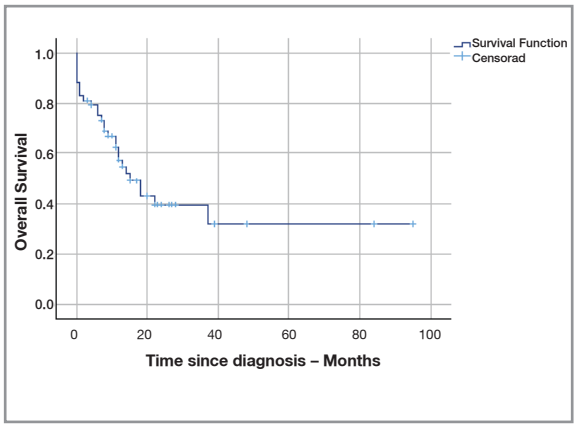

Figure 1. Overall survival in patients with AML and hyperleukocytosis

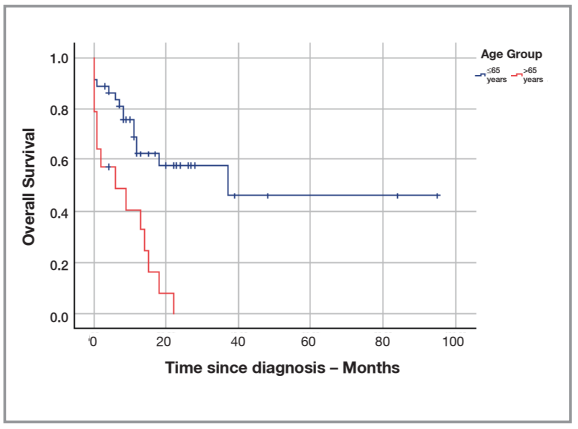

Figure 2. Overall survival stratified by age in AML patients with hyperleukocytosis

In the multivariate logistic regression model, only age > 65 years remained a statistically independent predictor of early mortality (OR: 10.05; 95% CI: 1.18-44.67; p= 0.035). Factors associated with early mortality, based on both univariate and multivariate analyses, are presented in Table 3.

DISCUSSION

The management of patients with AML presenting with hyperleukocytosis remains a clinical challenge due to the lack of randomized controlled trials, variability in treatment approaches, and the increased risk of early mortality (EM).[6,9] There is considerable heterogeneity in the literature, institutional practices, and guideline recommendations regarding the indications, efficacy, and risks of leukapheresis, as well as the timing of cytoreduction or induction chemotherapy initiation in this patient population.[8,20] While some clinicians advocate for prompt cytoreductive therapy prior to remission induction, others support the immediate initiation of definitive AML treatment without any delay.[21,22]

Similarly, the role of leukapheresis in reducing EM remains controversial. Some studies have demonstrated a survival benefit with early leukapheresis[23,24], whereas others—including meta-analyses—have shown no significant effect on EM.[25,26] Beyond leukapheresis, the prognostic impact of CL on early mortality also remains inconsistent across published studies.

In our study, several factors were found to be significantly associated with EM in univariate analysis, including age > 65 years, poor ECOG performance status, clinical leukostasis, acute kidney injury, and spontaneous TLS. However, in multivariate analysis, only age > 65 years remained an independent predictor of early mortality.

In a study by Stahl et al., which included 779 AML patients with hyperleukocytosis defined as WBC > 50×10^9/L at diagnosis, 57% of patients had WBC counts exceeding 100×10^9/L, similar to our cohort. CL was observed in 27% of patients, and the EM rate was 16.7%. The median OS for the entire cohort was 12.6 months, while it was 4.5 months among patients aged > 65 years. Among those with WBC > 100×10^9/L, median OS was 11.3 months[8] Compared to Stahl et al., our cohort showed a higher incidence of CL (48.3%) and EM (22%), which may reflect the inclusion of patients with more severe leukocytosis, defined by a higher WBC threshold (≥ 100×10^9/L). While both studies identified older age as an independent predictor of early mortality, clinical leukostasis was additionally associated with inferior EM and OS only in the Stahl cohort, whereas ECOG performance status emerged as an independent prognostic factor for OS in our study. In line with our findings, FLT3 mutations were present in over half of the patients in the Stahl cohort, reinforcing prior evidence that FLT3 alterations—particularly FLT3-ITD—are significantly enriched in AML cases with hyperleukocytosis compared to other AML subsets.[9,27,28]

Table 3. Univariate and multivariate Cox regression analyses of factors associated with overall survival (OS)

		Total patients	Univariate analysis – Overall survival		Multivariate analysis- Overall survival	
			OS- HR	p	OS - HR	p
Age >65 years	Yes	14 (24.1%)	**3.70 (1.74-7.84)**	**0.001**	**2.59 (1.43-12.6)**	**0.031**
Gender	Male	34 (58.6%)	1.50 (0.69-3.27)	0.298		
	Female	24 (41.4%)				
ECOG PS	0-1	31 (53.4%)	**4.05 (1.77-9.26)**	**0.001**	**3.26 (1.06-10.04)**	**0.039**
	2-3	27 (46.4%)				
WBC Count	Median - x10^9/L	119 (106-373)	1.00 (1.00-1.00)	0.409		
WBC Count	>150 x 10^9/L	18 (31%)	0.74 (0.33-1.69)	0.489		
WBC Count	>200 x 10^9/L	7 (12.1%)	2.51 (0.93-6.74)	0.068		
Hemoglobin	Median – g/dl	8.6 (4.2-11.2)	0.92 (0.75-1.12)	0.416		
Platelets	x10^9/L	40 (8-82)	1.00 (1.00-1.00)	0.945		
LDH Level	Median U/L	887 (261-7839)	1.00 (1.00-1.00)	0.942		
LDH	>2000 U/L	7 (12.1%)	0.93 (0.32-2.70)	0.904		
Creatinine	Median – mg/dl	1.07 (0.5-9)	**1.25 (1.07-1.45)**	**0.004**	1.20 (0.94-1.52)	0.137
Acute Renal Failure	Yes	14 (24.1%)	**4.16 (1.89-9.15)**	**<0.001**	2.34 (0.20-26.4)	0.491
Clinical Leukostasis (CL)	Yes	28 (48.3%)	**2.64 (1.23-5.65)**	**0.012**	1.43 (0.49-4.13)	0.511
Uric Acid Level	Median- mg/dl	6.65 (0.55-24.5)	**1.12 (1.02-1.22)**	**0.011**	0.97 (0.87-1.09)	0.702
Spontaneous Tumor Lysis Syndrome (TLS)	Yes	14 (24.1%)	**3.74 (1.67-8.37)**	**<0.001**	0.99 (0.09-10.3)	0.998
Bone Marrow Blast Percentage	Median	90% (55-100)	0.97 (0.94-1.12)	0.169		
ELN High Risk	Yes	17 (29.3%)	2.37 (0.71-7.8)	0.157		
NPM-1	Yes	26 (44.8%)	0.47 (0.13-1.63)	0.239		
FLT-3	Yes	33 (56.8%)	0.61 (0.28-1.18)	0.139		
KMT2A Rearrangements	Yes	5 (8.6%)	2.28 (0.58-9.83)	0.234		

Several studies have investigated the prognostic implications of the time interval between cytoreductive therapy and induction chemotherapy. In line with our findings, the study by Stahl et al. did not demonstrate any significant impact of this interval on EM or OS. In contrast, earlier work by Sekeres et al. suggested that treatment delays may adversely affect prognosis in younger patients[21]; however, more recent studies have not substantiated this concern. For instance, a large analysis by Röllig et al. using data from the German Study Alliance Leukemia–Acute Myeloid Leukemia (SAL-AML) registry, which included 2263 AML patients (21% with hyperleukocytosis), revealed no detrimental effect of delayed induction therapy on OS.[29] Consistent results were reported by Bertoli et al., who found no adverse prognostic impact of treatment delay in a cohort of 599 newly diagnosed AML patients[22]

In the study by Haddad et al., which evaluated 129 newly diagnosed AML patients with hyperleukocytosis (WBC > 100×10^9/L), the incidence of CL was reported as 58%, and FLT3 mutations were identified in 63% of patients.[7] The 4-week and 8-week EM rates were 9% and 13%, respectively, and the median OS for the entire cohort was 14.3 months. Age-stratified OS was 42 months for patients < 65 years and 8 months for those ≥ 65 years. Independent predictors of EM included older age, CL, and platelet count < 40×10^9/L, while predictors of inferior OS were older age, CL, and LDH > 2000 U/L. These findings are consistent with our results, particularly regarding the adverse impact of advanced age. Rates of CL, TLS, and mutation profiles

(FLT3, NPM1) were comparable between the two cohorts. Notably, leukapheresis was performed in all CL patients in our study (48.3%), while only 24% received leukapheresis in the Haddad cohort despite a higher CL frequency.

Although overall survival (OS) outcomes in our study were comparable to those reported by Haddad et al.,[7] the 4-week early mortality (EM) rate was relatively lower in our cohort. Notably, EM rates among patients with hyperleukocytic AML remain highly variable across studies. For instance, a multicenter retrospective study reported an EM rate of 42% in hyperleukocytic AML[30], while another study focusing exclusively on older patients (≥ 65 years) who were unfit for intensive chemotherapy (IC) found an EM rate as high as 57.1%, with a median OS of only 25 days.[10] In that cohort, leukapheresis did not appear to affect EM or OS. In our study, 24.1% of patients were aged >65 years, and multivariate analysis confirmed advanced age as an independent predictor of both EM and OS. These findings underscore the persistently poor prognosis of hyperleukocytic AML, particularly in elderly or IC-ineligible patients.

The impact of leukapheresis on early mortality (EM) in patients with CL remains uncertain. A 2020 meta-analysis by Bewersdorf et al., which included 1.743 patients (486 who underwent leukapheresis and 1,257 who did not), found no significant reduction in EM associated with leukapheresis.[17] Notably, patients who underwent leukapheresis were twice as likely to have CL. In line with these findings, our study also failed to demonstrate a survival benefit from leukapheresis regarding EM, and all patients who received leukapheresis presented with CL.

This study has several limitations. It is a retrospective analysis with a relatively small sample size and limited follow-up duration, which may affect the generalizability of the findings. The study also possesses important strengths. It reflects real-world clinical practice data and includes patients treated with contemporary targeted therapies (e.g., venetoclax, midostaurin), which have become more widely adopted in recent years.

Conclusion

Our findings demonstrate that early mortality remains substantial in patients with hyperleukocytic AML, particularly in those aged >65 years. Advanced age emerged as the sole independent predictor of EM, while both age and ECOG performance status were independently associated with inferior OS. Given the acute clinical complexity and poor outcomes in this high-risk group, prospective trials are urgently needed to guide evidence-based, standardized management approaches.

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