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Endothelial Activation and Stress Index Predicts Survival in Acute Myeloid Leukemia Independent of FLT3 Mutation Status

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Abstract

Background

Endothelial dysfunction and inflammatory biomarkers may provide prognostic information beyond conventional molecular risk factors in acute myeloid leukemia. This study evaluated the prognostic significance of hematological, biochemical, and cytogenetic parameters, with particular emphasis on the endothelial activation and stress index, in adult patients with acute myeloid leukemia.

Methods

This retrospective single-center study included 126 AML patients at İzmir City Hospital (2024–2025), analyzing overall and relapse-free survival in remission-achieving patients. Baseline hematologic, biochemical, cytogenetic, and molecular variables were evaluated. EASIX was calculated as creatinine × lactate dehydrogenase / platelet count and analyzed after natural logarithmic transformation. Survival distributions were estimated using the Kaplan–Meier method and compared with the log-rank test. Cox proportional hazards regression was used for univariable and multivariable analyses.HR 1.66 (95% CI 1.22–2.27; p = 0.001)

Results

Higher log(EASIX) independently predicted worse overall survival in multivariable Cox analysis adjusted for age, FLT3 status, and ELN risk. Log(EASIX) was also independently associated with relapse-free survival (hazard ratio 1.66, 95% confidence interval 1.22–2.27; p = 0.001) after adjustment for age and FLT3 mutation status. FLT3 mutation status alone was not significantly associated with overall or relapse-free survival. Patients with log(EASIX) values corresponding to EASIX ≥ 4.4 showed significantly inferior survival by Kaplan–Meier analysis. In exploratory landmark analysis, baseline EASIX demonstrated moderate discrimination for 24-month mortality, with an optimal cohort-specific threshold of 11.7.

Conclusions

Baseline EASIX independently predicts overall and relapse-free survival in AML and may complement molecular risk systems for early prognostic assessment in practice.

1. Introduction

Acute myeloid leukemia (AML) is a group of hematological malignancies characterized by poor clinical outcomes and marked underlying clinical and biological heterogeneity. The median age at diagnosis is

68 years, and the disease shows significant heterogeneity across age groups, with patients under 60 years of age accounting for less than 10% of all AML cases [1–2].

One of the most important factors determining prognosis in AML is the genetic and molecular characteristics of the disease. In this context, FLT3(FMS-benzeri tirozin kinaz 3) mutations, particularly FLT3-ITD(internal tandem duplication) and FLT3-TKD(tyrosine kinase domain), are observed in approximately 20–25% of AML cases. The FLT3 gene, located on chromosome 13q12 and belonging to the class III receptor tyrosine kinase family, plays an important role in the regulation of hematopoiesis. The FLT3-ITD mutation is associated with leukocytosis, an increased bone marrow blast percentage, and poor prognosis [3–6].

Although currently available FLT3 inhibitors and newly developed agents have contributed to improving the efficacy of standard treatments, no significant improvement in overall survival has been achieved. One of the main reasons for this is the development of resistance to FLT3 inhibitors. While several FLT3 inhibitors are available for clinical use, novel molecules are still under investigation in clinical trials. However, the limited efficacy of these agents against certain FLT3 mutants complicates the treatment process [7–8].

Although the prognostic significance of low platelet counts and high white blood cell levels has been demonstrated in patients with APL, the prognostic value of these hematological parameters in other AML subtypes remains unclear [9]. While the importance of FLT3 mutations is increasingly recognized, there is still a need for more accessible and easily assessable biomarkers in patients without these mutations or in clinical settings where molecular testing is limited. In this context, simple hematological parameters such as platelet and white blood cell counts, as well as derived ratios including Neutrophil-to-Lymphocyte Ratio(NLR), Platelet-to-White Blood Cell Ratio (PWR), and Lymphocyte-to-Monocyte Ratio (LMR) have recently attracted growing interest for their potential role in AML prognosis.

Accumulating evidence from the literature indicates that hematological biomarkers such as the platelet-to–white blood cell ratio (PWR), neutrophil-to-lymphocyte ratio (NLR), absolute neutrophil count (ANC), absolute lymphocyte count (ALC), and lymphocyte-to-monocyte ratio (LMR), together with cytogenetic factors, play a significant and potentially complementary role in predicting prognosis and survival outcomes in patients with acute myeloid leukemia [10–16].

In various studies, a higher pre-transplant EASIX score has been shown to be associated with increased mortality and reduced overall survival; furthermore, it has been demonstrated to serve as an important prognostic marker for predicting early mortality and for the assessment of overall survival in patients with acute myeloid leukemia [17–18].

At present, the factors influencing prognosis between FLT3-positive and FLT3-negative patients have not been clearly established, and further studies are needed. In our study, the clinical characteristics of FLT3-positive and FLT3-negative patients, as well as the factors affecting overall survival, were investigated. However, the EASIX score was found to independently affect both overall survival and relapse-free

survival in patients with acute myeloid leukemia, regardless of FLT3 status. Although the EASIX score has been shown to influence mortality in diseases such as multiple myeloma and myelodysplastic syndrome, studies evaluating its role in acute myeloid leukemia are still limited in the literature [19–21].

2. Methods

2.1 Study design and setting

This retrospective cohort study was conducted at the Hematology Clinic of İzmir City Hospital. Adult patients diagnosed with AML and followed between 01.01.2024 and 01.06.2025 were evaluated. Demographic, clinical, hematological, biochemical, and molecular/genetic data were extracted from electronic medical records and laboratory databases.

2.2 Study population and eligibility criteria

All adult AML patients with available diagnostic and follow-up data were eligible for overall survival (OS) analysis. A second cohort was defined for relapse-free survival (RFS) analysis, restricted to patients who achieved complete remission (CR) or complete remission with incomplete hematologic recovery (CRi).

Patients were included in the OS analysis if the diagnosis date was available and at least one of death date or last follow-up date was recorded. Patients were included in the RFS analysis if remission date was available and relapse/death and/or follow-up information was recorded.

2.3 Data collection and variable definitions

Baseline characteristics included age and sex. Hematological parameters included white blood cell count (WBC), hemoglobin (HGB), platelet count (PLT), neutrophil count, lymphocyte count, monocyte count, and red blood cell distribution width indices (RDW-CV, RDW-SD). Biochemical parameters included albumin, C-reactive protein (CRP), lactate dehydrogenase (LDH), creatinine, and estimated glomerular filtration rate (GFR).

Derived inflammation-related indices including neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and platelet-to-white blood cell ratio (PWR) were analyzed when available. The endothelial activation and stress index (EASIX) was calculated at diagnosis. Laboratory parameters used for EASIX calculation were obtained from routine blood samples collected at the time of diagnosis prior to initiation of treatment. All analytical measurements were performed in the hospital's central laboratory according to standard clinical protocols.

FLT3 mutation status was determined from molecular diagnostic reports obtained by next-generation sequencing (NGS) and/or PCR-based assays and recorded as binary. ELN risk classification was assigned according to the European LeukemiaNet (ELN) 2022 recommendations based on cytogenetic and molecular findings at diagnosis. Patients were categorized into favorable, intermediate, or adverse risk groups.

For multivariable survival modeling, ELN risk was additionally simplified into a binary grouping to address complete separation and limited event numbers. Favorable-risk patients were classified as ELN-low, whereas intermediate- and adverse-risk patients were grouped as ELN-high.This dichotomization was performed to improve model stability under event-per-variable constraints.

2.4 Data Preprocessing and Survival Time Construction

All clinical and laboratory data were reviewed for internal consistency prior to analysis. Date variables, including diagnosis date, remission date, relapse date, death date, and last follow-up date, were harmonized and validated to ensure chronological accuracy. Inconsistent or implausible date sequences were manually reviewed and corrected when necessary.

Survival time variables were constructed using predefined rules. Overall survival and relapse-free survival times were calculated in months.Censoring status was verified against follow-up documentation.Only patients with complete time-to-event and event status information were included in survival analyses.

2.5 Survival outcomes

Overall survival was defined as the time from the date of AML diagnosis to death from any cause. Patients alive at last follow-up were censored at the last documented follow-up date. OS was evaluated in the entire AML cohort.

Relapse-free survival was evaluated in patients achieving complete remission (CR) or complete remission with incomplete hematologic recovery (CRi). RFS was defined as the time from the date of remission to the earliest occurrence of relapse or death. Patients without relapse who were alive at last follow-up were censored at the last follow-up date. Patients with primary refractory disease were excluded from RFS analysis.

2.6 Statistical analysis

Statistical analyses were performed using Python (pandas, scipy, lifelines) and Jamovi/GemOV. Continuous variables were summarized as mean ± standard deviation (SD) or median (IQR), as appropriate, and categorical variables were reported as counts and percentages.

EASIX was calculated as: creatinine (mg/dL) × lactate dehydrogenase (LDH, U/L) / platelets (10^9/L), using routinely obtained laboratory measurements. Because EASIX exhibited a right-skewed distribution, a natural logarithmic transformation was applied (log[EASIX]) and used as the primary exposure variable in regression models.

Kaplan–Meier curves were generated and compared using the log-rank test. For graphical stratification, patients were dichotomized according to the commonly cited EASIX threshold of 4.4; because modeling was performed on the log scale, the corresponding log(EASIX) cutoff (ln[4.4] ≈ 1.48) was used to define low versus high log(EASIX) groups in Kaplan–Meier analyses.

Cox proportional hazards regression was used to evaluate prognostic factors for overall survival and relapse-free survival. Univariable Cox models were applied to all candidate baseline variables available in the dataset to screen for potential associations with survival outcomes. Based on clinical relevance and model parsimony considerations, key variables including log(EASIX), age, FLT3 mutation status, and ELN risk group were selected for inclusion in multivariable models. Multivariable models were then constructed including log(EASIX), age, FLT3 mutation status, and dichotomized ELN risk. ELN risk was simplified as ELN-high (intermediate or adverse) versus ELN-low (favorable) to improve model stability given limited event counts.A two-sided p-value < 0.05 was considered statistically significant.Multivariable Cox regression models were constructed by including clinically relevant covariates selected a priori based on established prognostic importance in acute myeloid leukemia, rather than solely on univariable statistical significance. Specifically, age, FLT3 mutation status, and ELN risk group were included in the multivariable models regardless of their univariable p values to account for potential confounding and to ensure clinically meaningful adjustment. This approach is consistent with recommended modeling strategies, as reliance on univariable screening alone may exclude important prognostic variables and lead to biased effect estimates.

3. Results

3.1 Study Population

A total of 126 adult patients with AML were included in the overall survival analysis. Among these patients, 109 achieved complete remission (CR) or complete remission with incomplete hematologic recovery (CRi) and were therefore eligible for relapse-free survival analysis. During follow-up, 30 deaths occurred in the OS cohort. In the RFS cohort, 30 relapse or death events were observed.

Baseline characteristics are summarized in Table 1. The median age was 55.5 years (IQR 42–69), and 64 patients (50.8%) were male. Thirty-eight patients (30.2%) were FLT3-positive. ELN risk classification was favorable in 20 (15.9%), intermediate in 54 (42.9%), and adverse in 52 (41.3%) patients. CR or CRi was achieved in 109 patients (86.5%), while 13 (10.3%) had refractory disease, and 43 (34.1%) underwent allogeneic stem cell transplantation. Compared with FLT3-negative patients, FLT3-positive patients had significantly higher WBC counts, LDH levels, and EASIX scores, whereas platelet- and albumin-derived inflammatory ratios were significantly lower, likely reflecting leukocytosis-driven dilutional effects. No significant between-group differences were observed in age, sex, hemoglobin, albumin, CRP, NLR, ELN distribution, response rate, or transplant rate.

Table 1
Baseline Characteristics Of AML Patients According To Flt3 Mutation Status

Variable	Total (n = 126)	FLT3+ (n = 38)	FLT3− (n = 88)	p-value
Age, Median (IQR)	55.5 (42–69)	51.0 (42–65)	56.5 (43–69)	0.321
Male Sex, n (%)	64 (50.8%)	17 (44.7%)	47 (53.4%)	0.484
Ldh, U/L	355 (235–590)	499 (277–741)	317 (225–545)	**0.018**
Easix Score	7.24 (2.75–14.2)	11.13 (4.92–17.1)	5.74 (2.42–12.2)	**0.020**
Hb, g/dL	8.65 (8.0–10.0)	8.55 (7.7–9.9)	8.80 (8.1–10.0)	0.557
Plt, ×10⁹/L	46.5 (26–85)	46.5 (26–77)	46.5 (28–111)	0.263
Wbc, ×10⁹/L	6.35 (2.5–31.4)	20.99 (5.1–61.5)	4.74 (2.3–12.9)	**< 0.001**
Albumin, g/L	390 (350–430)	400 (360–420)	390 (340–430)	0.634
Crp, mg/L	22 (7.2–70.8)	18.5 (8.3–64.3)	25.0 (6.5–73.5)	0.970
NLR	0.61 (0.25–1.77)	0.68 (0.26–2.09)	0.57 (0.23–1.60)	0.425
PLR	19.9 (6.6–56.5)	11.5 (3.7–24.5)	32.4 (10.8–73.7)	**< 0.001**
PWR	8.16 (1.4–22.5)	2.19 (0.68–7.4)	11.6 (2.5–33.9)	**< 0.001**
ALB/WBC	5.83 (1.2–14.8)	1.94 (0.55–7.7)	8.62 (2.9–19.1)	**0.001**
Alb/Lym	17.5 (7.5–36.4)	9.61 (2.4–24.4)	21.3 (9.2–38.8)	**0.003**
CRP/WBC	2.57 (0.55–10.7)	1.42 (0.35–4.3)	2.81 (0.87–15.0)	**0.014**
CRP/LYM	7.77 (2.3–35.0)	5.72 (1.2–9.9)	12.5 (3.0–40.9)	**0.022**
ELN Favorable	20 (15.9%)	8 (21.1%)	12 (13.6%)	0.299
ELN Intermediate	54 (42.9%)	18 (47.4%)	36 (40.9%)	—
ELN Adverse	52 (41.3%)	12 (31.6%)	40 (45.5%)	—
Transplant, n (%)	43 (34.1%)	16 (42.1%)	27 (30.7%)	0.300

Data are presented as median (interquartile range) for continuous variables and number (percentage) for categorical variables. Between-group comparisons were performed using the mann–whitney u test for continuous variables and the chi-square test for categorical variables. Bold p-values indicate statistical significance ($p < 0.05$). Flt3 mutation status was determined by next-generation sequencing and/or pcr-based assays.

Abbreviations: AML, acute myeloid leukemia; FLT3, FMS-like tyrosine kinase 3; LDH, lactate dehydrogenase; EASIX, endothelial activation and stress index (calculated as creatinine [mg/dL] × LDH [U/L] / platelet count [×10⁹/L]); Hb, hemoglobin; PLT, platelet count; WBC, white blood cell count; CRP, C-

reactive protein; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; PWR, platelet-to-white blood cell ratio; Alb/WBC, albumin-to-white blood cell ratio; Alb/Lym, albumin-to-lymphocyte ratio; CRP/WBC, C-reactive protein-to-white blood cell ratio; CRP/Lym, C-reactive protein-to-lymphocyte ratio; ELN, European LeukemiaNet; IQR, interquartile range.

3.2 Kaplan–Meier Survival Analysis

For graphical visualization, patients were stratified according to the commonly cited EASIX threshold of 4.4, corresponding to ln(EASIX) = 1.48 on the logarithmic scale.

Patients with high log(EASIX) (≥ 1.48) demonstrated significantly inferior overall survival compared with those with low log(EASIX) (< 1.48) (log-rank p = 0.022) (Fig. 1).

During follow-up, 24 deaths occurred in the high log(EASIX) group compared with 6 deaths in the low log(EASIX) group. Separation of the survival curves was observed early during follow-up and remained evident throughout the 48-month observation period.

Among patients achieving CR or CRi (n = 109), high log(EASIX) was also associated with significantly shorter relapse-free survival (log-rank p = 0.037) (Fig. 2).

A total of 23 relapse or death events occurred in the high log(EASIX) group compared with 7 events in the low log(EASIX) group. A similar pattern was observed for relapse-free survival, with early and sustained separation of the curves.

These Kaplan–Meier analyses were performed primarily for graphical comparison, whereas continuous log(EASIX) modeling was used for the primary inferential analyses.

3.3 Cox Proportional Hazards Regression Analysis

Overall survival

In univariable Cox regression analysis, log(EASIX) was significantly associated with inferior overall survival (HR 1.41, 95% CI 1.05–1.88, p = 0.022) (Table 2). Age, FLT3 mutation status, and ELN risk group were not significantly associated with overall survival in univariable analysis.

Table 2
Univariable and multivariable Cox proportional hazards regression analysis for overall survival (n = 126).

Variable	N (%)	Univariable HR (95% CI)	p value	Multivariable HR (95% CI)	p value
log(EASIX)	–	1.41 (1.05–1.88)	**0.022**	1.48 (1.11–1.98)	**0.008**
Age	–	1.01 (0.99–1.03)	0.467	1.01 (0.99–1.03)	0.513
FLT3 mutation (Positive vs negative)	38 (30.2) vs 88 (69.8)	0.78 (0.35–1.75)	0.544	0.61 (0.26–1.44)	0.259
ELN risk group Low vs high)	20 (15.9) vs 106 (84.1)	0.45 (0.13–1.55)	0.209	0.52 (0.15–1.84)	0.307

N (%) denotes the number and proportion of patients in the positive category for binary variables; dashes indicate continuous variables. Hazard ratios (HR) greater than 1.0 indicate increased risk of death; HR less than 1.0 indicate reduced risk relative to the reference category. The multivariable model included all four variables simultaneously. ELN risk was dichotomized as low (favorable risk) versus high (intermediate or adverse risk) to improve model stability under limited event-per-variable conditions. Bold p-values indicate statistical significance ($p < 0.05$).
Abbreviations: HR, hazard ratio; CI, confidence interval; EASIX, endothelial activation and stress index; FLT3, FMS-like tyrosine kinase 3; ELN, European LeukemiaNet; AIC, Akaike Information Criterion

In multivariable Cox regression analysis including log(EASIX), age, FLT3 mutation status, and ELN risk, log(EASIX) remained independently associated with overall survival (HR 1.48, 95% CI 1.11–1.98, p = 0.008). Age (HR 1.01, 95% CI 0.99–1.03, p = 0.513), FLT3 mutation status (HR 0.61, 95% CI 0.26–1.44, p = 0.259), and ELN risk group (HR 0.52, 95% CI 0.15–1.84, p = 0.307) were not independently associated with OS (Fig. 3).Although age, FLT3 mutation status, and ELN risk group were not statistically significant in univariable analyses, these variables were included in multivariable models based on their established clinical relevance in AML and to ensure appropriate adjustment for potential confounding.

Relapse-free survival

In univariable Cox regression analysis, log(EASIX) was significantly associated with shorter relapse-free survival (HR 1.57, 95% CI 1.15–2.15, p = 0.004) (Table 3). FLT3 mutation status was not significantly associated with RFS (HR 0.49, 95% CI 0.20–1.21, p = 0.124).Age was not significantly associated with relapse-free survival.
Table 3. Univariable and multivariable Cox proportional hazards regression analysis for relapse-free survival (n = 109).

Variable	N (%)	Univariable HR (95% CI)	p value	Multivariable HR (95% CI)	p value
log(EASIX)	–	1.57 (1.15–2.15)	**0.004**	1.66 (1.22–2.27)	**0.001**
Age	–	1.02 (1.00–1.04)	0.075	1.02 (1.00–1.04)	0.064
FLT3 mutation (Positive vs negative)	32 (29.4) vs 77 (70.6)	0.49 (0.20–1.21)	0.124	0.44 (0.18–1.10)	0.078

Analysis was restricted to patients achieving complete remission (CR) or complete remission with incomplete hematologic recovery (CRi). N (%) denotes the number and proportion of patients in the positive category for binary variables; dashes indicate continuous variables. Hazard ratios (HR) greater than 1.0 indicate increased risk of relapse or death; HR less than 1.0 indicate reduced risk relative to the reference category. ELN risk was not included in the RFS multivariable model due to limited estimability under event-per-variable constraints. Bold p-values indicate statistical significance ($p < 0.05$).

Abbreviations: HR, hazard ratio; CI, confidence interval; EASIX, endothelial activation and stress index; FLT3, FMS-like tyrosine kinase 3; CR, complete remission; CRi, complete remission with incomplete hematologic recovery; AIC, Akaike Information Criterion
In multivariable Cox regression analysis including log(EASIX), age, and FLT3 mutation status, log(EASIX) remained independently associated with RFS (HR 1.66, 95% CI 1.22–2.27, p = 0.001). Age (HR 1.02, 95% CI 1.00–1.04, p = 0.064) and FLT3 mutation status (HR 0.44, 95% CI 0.18–1.10, p = 0.138) were not independently associated with RFS (Fig. 4).

Consistent with Cox regression findings, additional exploratory Kaplan–Meier analyses stratified by FLT3 mutation status did not demonstrate a statistically significant difference between FLT3-positive and FLT3-negative patients for either overall survival or relapse-free survival (log-rank $p > 0.05$ for both comparisons). Survival curves showed substantial overlap throughout the follow-up period, suggesting limited discriminatory ability of FLT3 mutation status alone in this cohort (Supplementary Figure S1).

3.4 Exploratory Landmark Analysis

An exploratory time-dependent receiver operating characteristic (ROC) analysis was performed to evaluate the ability of baseline EASIX to discriminate 24-month mortality. Because this analysis was cohort-specific and intended to generate a hypothesis-driven, time-dependent threshold rather than to define a universal clinical cutoff, the detailed results are provided in the Supplementary Appendix (Supplementary Figure S2).

In an exploratory analysis, baseline EASIX demonstrated moderate discrimination for 24-month mortality (mean AUC 0.67). The optimal threshold identified using the Youden index was EASIX = 11.7. When

applied to the full cohort, this cutoff was associated with inferior overall survival in Kaplan–Meier analysis (Supplementary Figure S3; log-rank p = 0.023).

Bootstrap resampling (1000 iterations) yielded a median cutoff of 11.7, consistent with the original estimate; however, variability was observed (interquartile range 3.14–11.7), indicating limited stability. Therefore, this threshold should be considered hypothesis-generating and cohort-specific, and requires validation in independent datasets.

Discussion

In this retrospective cohort study of adult patients with acute myeloid leukemia, we evaluated the prognostic significance of the endothelial activation and stress index for overall survival and relapse-free survival. Our findings demonstrate that higher log-transformed EASIX values at diagnosis were independently associated with inferior survival outcomes. Specifically, log(EASIX) remained a significant predictor of both OS and RFS after adjustment for established prognostic factors, including age, FLT3 mutation status, and ELN risk classification. These findings suggest that biomarkers reflecting endothelial dysfunction provide additional prognostic information beyond conventional genetic and clinical risk stratification in AML.

Kaplan–Meier analyses further supported these observations. Patients with higher log(EASIX) values demonstrated significantly inferior overall survival and relapse-free survival compared with those with lower values. Notably, separation of the survival curves occurred early during follow-up, suggesting that baseline endothelial stress reflects biological mechanisms influencing early disease progression or treatment response. Although the dichotomized EASIX threshold was used primarily for graphical visualization, the primary inferential analyses were conducted using continuous log(EASIX), which improves statistical robustness and reduces information loss associated with arbitrary categorization.

FLT3 mutations play a central role in AML biology and are associated with enhanced proliferative signaling and aggressive disease phenotypes. In line with this, FLT3-ITD mutations have been consistently linked to leukocytosis and increased blast burden [22, 24, 25]. In our cohort, leukocyte counts were significantly higher in FLT3-positive patients, supporting the presence of a proliferative disease phenotype. This observation is consistent with the known biological effects of FLT3 activation and suggests that FLT3-mutated AML may be characterized by a distinct inflammatory and hematologic profile.

Despite these biological associations, FLT3 mutation status was not significantly associated with overall or relapse-free survival in our cohort. Both Kaplan–Meier analyses and Cox regression models demonstrated limited prognostic discrimination for FLT3 alone. This apparent discrepancy between biological activity and survival impact may reflect several factors, including limited sample size, heterogeneity in co-mutation patterns, and the influence of contemporary treatment strategies. In particular, the use of FLT3 inhibitors such as midostaurin may have attenuated the adverse prognostic effect traditionally attributed to FLT3 mutations [22]. Importantly, the lack of independent prognostic

significance for FLT3 in this analysis highlights the potential value of alternative biomarkers, such as EASIX, which capture complementary aspects of disease biology related to endothelial dysfunction and systemic stress.

The presence of FLT3-ITD mutations is associated with increased blast counts and leukocytosis [21]. In our study, the leukocyte count was found to be significantly higher in FLT3-positive patients ($p < 0.001$).This observation is consistent with the known association between FLT3-ITD mutations and leukocytosis-driven disease biology, and may explain the significantly lower platelet- and albumin-derived inflammatory ratios observed in FLT3-positive patients in our cohort.

Interestingly, the prognostic impact of log(EASIX) appeared to be more pronounced for relapse-free survival than for overall survival. The multivariable RFS model demonstrated stronger discrimination (C-index 0.76) compared with the OS model (C-index 0.60). This observation suggests that endothelial activation and microvascular injury are more closely related to relapse biology and disease persistence rather than mortality alone. Endothelial dysfunction has been implicated in leukemic cell–microenvironment interactions, inflammatory signaling, and treatment-related vascular injury, mechanisms that may contribute to disease recurrence and therapy resistance. Further mechanistic studies are required to clarify the biological pathways linking endothelial stress markers to AML relapse risk.

The stronger association observed between EASIX and relapse-free survival provides additional insight into the potential biological relevance of endothelial dysfunction in AML. While overall survival reflects a combination of disease biology, treatment response, and competing risks, relapse-free survival more directly captures mechanisms related to disease persistence and recurrence.

In this context, elevated EASIX may not only reflect a patient's physiological response to treatment but also broader alterations in the leukemic microenvironment, including endothelial activation, inflammatory signaling, and vascular niche interactions that may facilitate leukemic cell survival and relapse [26–28]. Although this interpretation remains speculative, it suggests that endothelial stress markers such as EASIX may capture aspects of disease biology beyond treatment tolerance alone.

Notably, FLT3 mutation status was not significantly associated with either overall survival or relapse-free survival in our cohort. Both Kaplan–Meier analyses and Cox regression models demonstrated limited prognostic discrimination for FLT3 alone, with hazard ratios not reaching statistical significance. This finding may reflect the relatively small cohort size, potential heterogeneity in co-mutation patterns, or the influence of contemporary treatment strategies. Importantly, the lack of independent prognostic impact of FLT3 in this analysis further underscores the potential value of endothelial dysfunction–based biomarkers such as EASIX, which remained consistently associated with both survival outcomes.Our subgroup analysis demonstrated that high EASIX remained a potent predictor of poor OS even within the FLT3-negative cohort, suggesting that endothelial dysfunction contributes to mortality through pathways distinct from classical molecular mutations. Additionally, the use of FLT3 inhibitors such as midostaurin in combination with standard induction chemotherapy may have partially mitigated the adverse

prognostic impact of FLT3 mutations in this cohort, as these agents have been shown to improve survival outcomes in FLT3-mutated AML [22].

These findings are consistent with prior evidence highlighting the prognostic relevance of endothelial dysfunction markers in hematologic conditions. Pedraza et al. reported that elevated EASIX scores were associated with endothelial injury and significantly increased risk of acute graft-versus-host disease following allogeneic hematopoietic stem cell transplantation [25]. In that study, higher log-transformed EASIX values were strongly associated with adverse outcomes and demonstrated substantial discriminatory performance for predicting severe complications after transplantation. These observations support the concept that EASIX reflects systemic endothelial damage and may serve as a surrogate marker of vascular stress in hematologic diseases. Our results extend this concept to newly diagnosed AML by demonstrating that endothelial stress measured at baseline is associated with inferior survival outcomes.Together, these findings suggest that endothelial stress represents a complementary biological dimension of disease risk not fully captured by established molecular markers.

Kasaeian et al. evaluated EASIX in 195 pediatric acute leukemia patients undergoing allogeneic HSCT, demonstrating that a pre-transplant EASIX score above 0.836 was independently associated with inferior OS (HR 1.83, p = 0.039) [17]. Our findings are directionally consistent — higher EASIX values predicted worse survival — but extend this association to adult AML patients at the time of initial diagnosis, independent of transplantation. The considerably higher EASIX threshold identified in our cohort (11.7) likely reflects the different clinical context of diagnosis-stage endothelial stress versus pre-transplant conditioning, reinforcing that EASIX cutoffs are context-specific and require independent validation.An important observation in our study is the substantially higher EASIX threshold identified at diagnosis compared with previously reported cutoffs in transplant settings. While EASIX thresholds around 4.4 have been widely used in allogeneic hematopoietic stem cell transplantation studies, our analysis identified a higher optimal cutoff (11.7) for predicting mortality in newly diagnosed AML.

This difference likely reflects the distinct biological context of these clinical settings. In transplant cohorts, patients are typically in remission or have controlled disease burden, with relatively lower systemic inflammation and endothelial stress. In contrast, newly diagnosed AML is characterized by high leukemic burden, elevated lactate dehydrogenase levels, and pronounced inflammatory activation, all of which may contribute to higher baseline EASIX values.

These findings suggest that EASIX should not be interpreted using a universal threshold across different clinical scenarios, but rather that context-specific cutoffs may be required. However, given the exploratory nature of this analysis and the limited sample size, the proposed threshold should be considered hypothesis-generating and requires validation in independent cohorts.

In addition to endothelial-related biomarkers, several studies have investigated the prognostic significance of laboratory-derived inflammatory and hematologic indices in acute myeloid leukemia. Zhao et al. reported that the platelet-to-white blood cell ratio (PWR) independently predicted overall

survival and event-free survival in patients with cytogenetically normal AML [10]. Stefaniuk et al. further demonstrated that complete blood count–derived parameters, including neutrophil-to-lymphocyte ratio, lymphocyte-to-monocyte ratio, and red blood cell distribution width, were associated with treatment response and survival outcomes in newly diagnosed AML [12] .

In the present study, the prognostic value of baseline laboratory variables was systematically evaluated using Cox proportional hazards models applied to all candidate variables available in the primary dataset. None of the individual hematologic ratios or conventional laboratory parameters demonstrated statistically significant associations with overall survival or relapse-free survival. FLT3 mutation status was not significantly associated with survival outcomes in this cohort, which may reflect limited statistical power, biological heterogeneity of FLT3 alterations, and the impact of contemporary targeted therapies.Although molecular markers such as NPM1, DNMT3A, and IDH1/2 are known to influence prognosis in AML, these variables were not included separately in the multivariable models. NPM1 and FLT3 mutation status are already incorporated within the ELN risk classification, which represents an integrated genetic risk framework [24]. Including these variables separately could introduce collinearity and overfitting. Moreover, additional mutations such as DNMT3A and IDH1/2 are not formally included in ELN risk stratification due to insufficient evidence for standardized prognostic categorization and were not available for all patients in our cohort.In contrast, the log-transformed EASIX index remained significantly associated with both outcomes in multivariable analyses. These findings suggest that composite indices reflecting endothelial dysfunction capture biologically relevant prognostic information beyond conventional hematologic parameters.

Several limitations should be acknowledged. First, this was a single-center retrospective study, which may introduce selection bias and limit generalizability. Second, the number of observed events was relatively limited, which constrained the complexity of multivariable modeling and required simplification of certain variables such as ELN risk grouping. Although internal validation procedures were performed, independent AML cohorts will be required to confirm the reproducibility and generalizability of these findings.Third,treatment data including induction regimen, use of FLT3 inhibitors, and consolidation strategy were not systematically included in the multivariable models due to data heterogeneity, which represents an important confounding factor that could not be fully accounted for in the present analysis.

Despite these limitations, the present study suggests that baseline endothelial stress measured by EASIX may serve as a simple and readily available prognostic biomarker in AML. Because EASIX is derived from routinely measured laboratory parameters, it has the potential to be easily integrated into clinical risk assessment frameworks. From a clinical perspective, EASIX may serve as a rapid and cost-effective tool for early risk stratification at diagnosis, particularly in settings where comprehensive molecular profiling is not immediately available.Future studies incorporating larger multicenter cohorts and prospective validation are warranted to determine whether EASIX could complement existing molecular risk stratification systems and improve prediction of relapse and survival outcomes in AML.

In conclusion, this study demonstrates that baseline endothelial activation, as quantified by the EASIX score, is independently associated with both overall survival and relapse-free survival in patients with acute myeloid leukemia. The stronger association observed for relapse-free survival suggests that endothelial dysfunction may contribute not only to treatment tolerance but also to mechanisms of disease persistence and relapse.

Importantly, the prognostic value of EASIX appears to extend beyond established molecular risk factors such as FLT3 mutation status, indicating that it captures a complementary dimension of disease biology related to endothelial stress and systemic inflammation. These findings support the concept that EASIX reflects dynamic disease-related processes rather than a fixed risk category defined solely by genetic alterations.

Conclusion

Given its simplicity, reproducibility, and reliance on routinely available laboratory parameters, EASIX represents a practical and cost-effective tool for early risk stratification at diagnosis. However, the optimal threshold may vary according to clinical context, and the cutoff identified in this study should be considered hypothesis-generating. Future prospective, multicenter studies are warranted to validate these findings and to determine whether incorporation of EASIX into clinical decision-making frameworks can improve individualized risk assessment and guide therapeutic strategies in acute myeloid leukemia.

Abbreviations

AML
acute myeloid leukemia
FLT3
FMS-like tyrosine kinase 3
LDH
lactate dehydrogenase
EASIX
endothelial activation and stress index (calculated as creatinine [mg/dL] × LDH [U/L] / platelet count [×10^9/L])
Hb
hemoglobin
PLT
platelet count
WBC
white blood cell count
CRP
C-reactive protein

NLR
neutrophil-to-lymphocyte ratio
PLR
platelet-to-lymphocyte ratio
PWR
platelet-to-white blood cell ratio
Alb/WBC
albumin-to-white blood cell ratio
Alb/Lym
albumin-to-lymphocyte ratio
CRP/WBC
C-reactive protein-to-white blood cell ratio
CRP/Lym
C-reactive protein-to-lymphocyte ratio
ELN
European LeukemiaNet
IQR
interquartile range.

Declarations

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Data availability

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request, within ethical boundaries.

Author contributions

All authors have contributed to the study, discussed the results, and approved the final version of the manuscript.YCO contributed to the conceptualization of the study, methodology development, supervision of the research process, software implementation, and preparation of the original draft of

the manuscript.EI contributed to the conceptualization and supervision of the study, methodology development, software-related work, and critical review and editing of the manuscript.DÜE and EÖY were responsible for data curation and contributed to critical review and editing of the manuscript.ÖÖK contributed to software support, data validation, and data curation.CC, OB, and ZNÖ contributed to data collection, data visualization, and critical review and editing of the manuscript.

Ethical Approval

This study was approved by the Institutional Review Board of Izmir City Hospital (09.07.2025 – Decision No: 2025/312). All procedures were conducted in accordance with the Declaration of Helsinki. Informed consent was waived due to the retrospective nature of the study.

Competing İnterests

The authors declare no competing interests.

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Figures

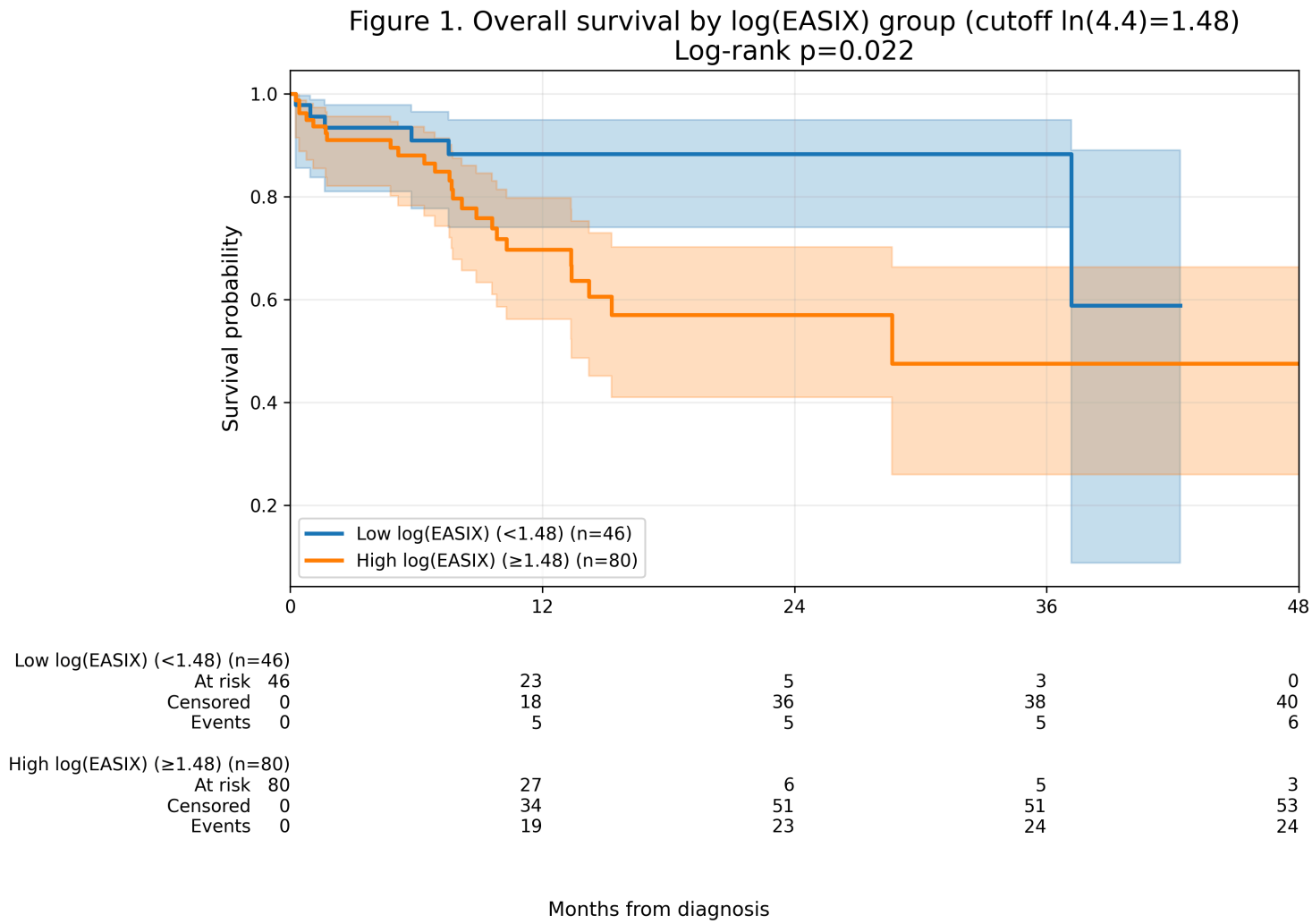


Figure 1

Kaplan–Meier curves for overall survival stratified by log(EASIX) group (n = 126).

Patients were dichotomized according to a log(EASIX) cutoff of 1.48, corresponding to the commonly cited EASIX threshold of 4.4 [ln(4.4) ≈ 1.48]. Blue line: low log(EASIX) group (<1.48, n = 46); orange line: high log(EASIX) group (≥1.48, n = 80). Shaded areas represent 95% confidence intervals. Numbers at risk, censored patients, and cumulative events are shown below the x-axis at 0, 12, 24, 36, and 48 months. Six deaths occurred in the low log(EASIX) group compared with 24 deaths in the high log(EASIX) group. Between-group difference was assessed using the log-rank test (p = 0.022). Overall survival was measured from the date of AML diagnosis to death from any cause; patients alive at last follow-up were censored. The number of patients at risk decreased substantially at later time points, and therefore survival estimates beyond 36 months should be interpreted with caution.

Abbreviations: EASIX, endothelial activation and stress index; AML, acute myeloid leukemia.

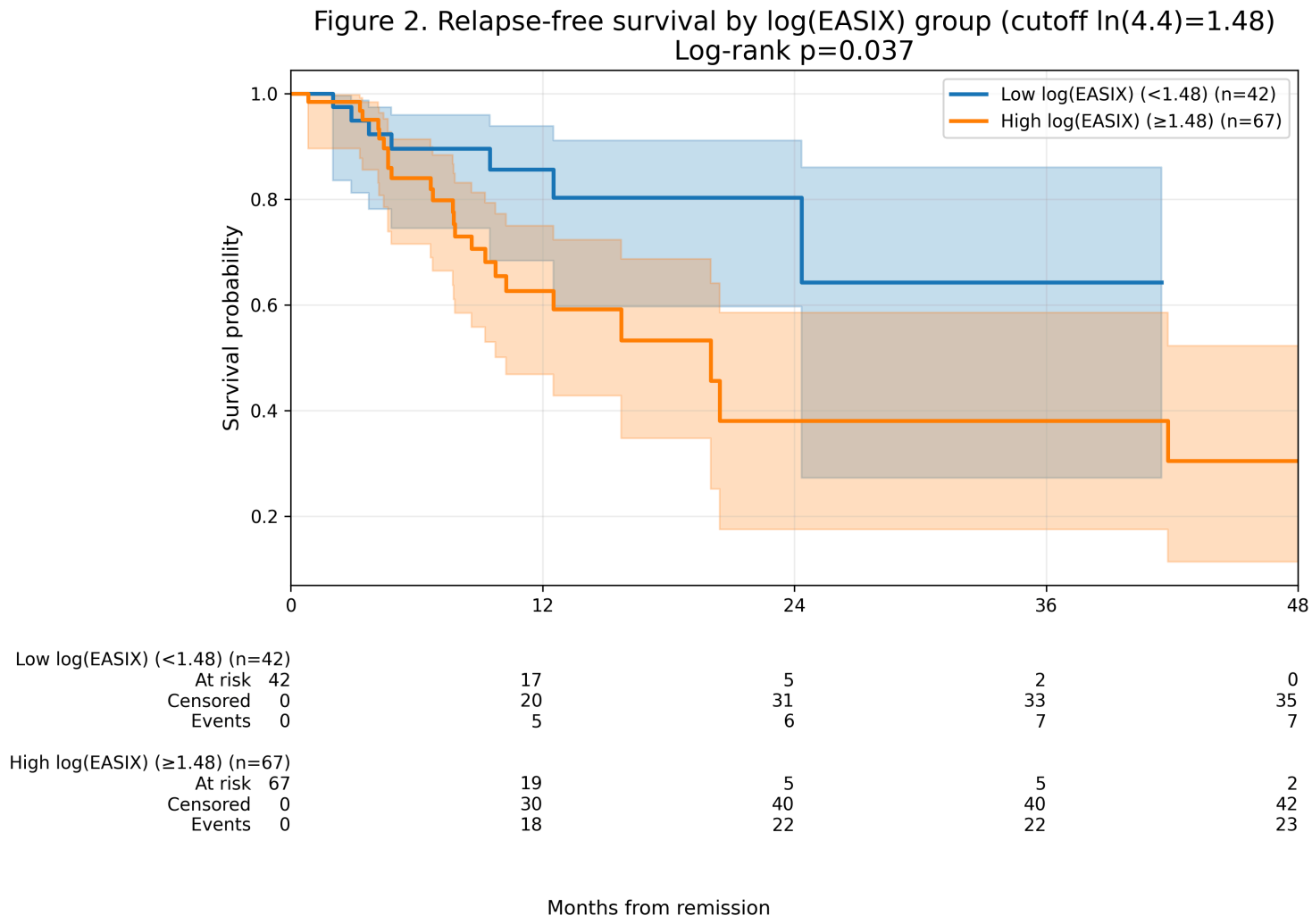


Figure 2

Kaplan–Meier curves for relapse-free survival stratified by log(EASIX) group (n = 109).

Analysis was restricted to patients achieving complete remission (CR) or complete remission with incomplete hematologic recovery (CRi). Patients were dichotomized according to a log(EASIX) cutoff of 1.48, corresponding to the commonly cited EASIX threshold of 4.4 [ln(4.4) ≈ 1.48]. Blue line: low log(EASIX) group (<1.48, n = 42); orange line: high log(EASIX) group (≥1.48, n = 67). Shaded areas represent 95% confidence intervals. Numbers at risk, censored patients, and cumulative events are shown below the x-axis at 0, 12, 24, 36, and 48 months. Seven relapse or death events occurred in the low log(EASIX) group compared with 23 events in the high log(EASIX) group. Between-group difference was assessed using the log-rank test (p = 0.037). Relapse-free survival was measured from the date of remission to the earliest occurrence of relapse or death; patients without events were censored at last follow-up. The number of patients at risk decreased substantially at later time points, and therefore survival estimates beyond 36 months should be interpreted with caution.

Abbreviations: EASIX, endothelial activation and stress index; CR, complete remission; CRi, complete remission with incomplete hematologic recovery.

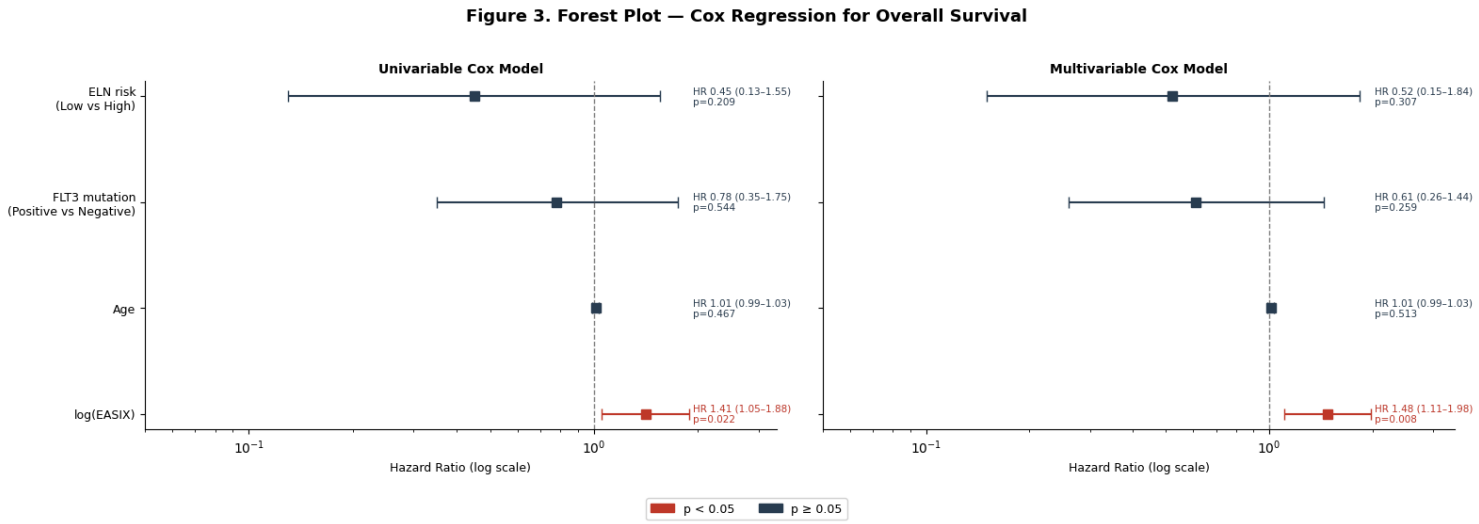


Figure 3

Forest plot of univariable and multivariable Cox proportional hazards regression analysis for overall survival.

Hazard ratios (squares) with 95% confidence intervals (horizontal lines) are displayed on a logarithmic scale. The dashed vertical line indicates HR = 1.0 (no effect). Red indicates statistically significant associations ($p < 0.05$); navy indicates non-significant associations ($p \geq 0.05$). The multivariable model included log(EASIX), age, FLT3 mutation status, and dichotomized ELN risk group. ELN risk was classified as low (favorable) versus high (intermediate/adverse).

Abbreviations: HR, hazard ratio; CI, confidence interval; ELN, European LeukemiaNet; FLT3, FMS-like tyrosine kinase 3; EASIX, endothelial activation and stress index.

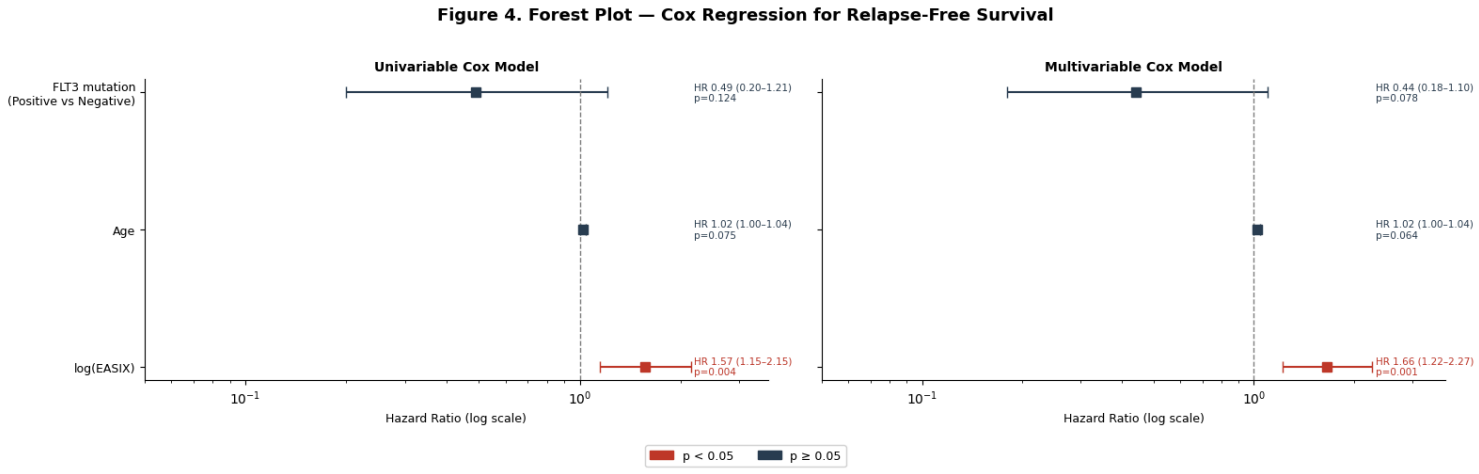


Figure 4

Forest plot of univariable and multivariable Cox proportional hazards regression analysis for relapse-free survival.

Hazard ratios (squares) with 95% confidence intervals (horizontal lines) are displayed on a logarithmic scale. The dashed vertical line indicates HR = 1.0 (no effect). Red indicates statistically significant associations ($p < 0.05$); navy indicates non-significant associations ($p \geq 0.05$). The RFS analysis was restricted to patients achieving complete remission (CR) or complete remission with incomplete hematologic recovery (CRi) (n = 109). The multivariable model included log(EASIX), age, and FLT3 mutation status.

Abbreviations: HR, hazard ratio; CI, confidence interval; FLT3, FMS-like tyrosine kinase 3; EASIX, endothelial activation and stress index; CR, complete remission; CRi, complete remission with incomplete hematologic recovery.

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