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Original Articles

Association of Baseline Platelet Count with Complete Remission, Severe Bleeding, and 24-Month Overall Survival in Patients with Newly Diagnosed Acute Myeloid Leukemia: A Multi-Center Retrospective Cohort Study

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Abstract. ***Objective*: To investigate the association between baseline platelet count at diagnosis and complete remission (CR) rate, severe bleeding during induction, and overall survival (OS) in newly diagnosed acute myeloid leukemia (AML).**
***Methods*: This multi-center retrospective cohort study enrolled 356 non-acute promyelocytic leukemia (non-APL) AML patients treated with first-line therapy between January 2020 and December 2025. Patients were classified as having a low baseline platelet count (<50 × 10⁹/L, n=218) or a normal/high count (≥50 × 10⁹/L, n=138). The primary outcomes were severe bleeding (CTCAE grade ≥3) occurring during induction and OS administratively censored at 24 months. The primary severe-bleeding analysis excluded patients with bleeding already present at diagnosis (n=125) to avoid endpoint–covariate overlap; the full-cohort analysis served as a sensitivity check. Parsimonious Firth logistic and Cox models, Kaplan–Meier analysis, 1:1 propensity score matching (PSM), continuous platelet modeling, restricted cubic splines (RCS), common-outcome censoring scenario analyses, an intensive-induction subgroup analysis, and center- and calendar-period sensitivity analyses were used.**
***Results*: CR (53.7% vs. 50.7%, P=0.665) and CR/CRi rates (63.3% vs. 68.8%, P=0.339) did not differ significantly between groups. After excluding patients with bleeding at diagnosis, low baseline platelet count was not independently associated with severe bleeding in the primary Firth logistic analysis (OR=1.761, 95% CI 0.631–5.583, P=0.287; 20 events in 231 patients), although the association remained in the full-cohort sensitivity analysis (adjusted OR=2.753, 95% CI 1.318–5.749, P=0.007). Kaplan–Meier analysis showed lower 24-month OS in the low-platelet group (58.2% vs. 77.8%; log-rank P<0.001), and the adjusted 24-month Cox model yielded an HR of 1.811 (95% CI 1.145–2.864, P=0.011). The association persisted after additional adjustment for participating center (HR=1.896, 95% CI 1.192–3.017, P=0.007). Per 10 × 10⁹/L higher baseline platelet count, the adjusted 24-month death hazard was 11.3% lower. The OS association was also directionally consistent in the intensive-induction subgroup (HR=2.402, P=0.007). Both common-outcome scenarios produced hazard ratios in the same direction as the primary analysis; however, these scenarios do not address differential informative censoring between platelet groups. Restricted cubic spline analyses showed a significant, approximately linear association between platelet count and 24-month OS and no significant overall association with severe bleeding in the primary analysis. In the PSM sensitivity analysis, which retained residual covariate imbalance, the 24-month OS estimate remained significant (HR=1.981, 95% CI 1.228–3.193, P=0.005). The**

matched severe-bleeding analysis was not informative because of insufficient events after excluding patients with bleeding at diagnosis. Per 10 × 10⁹/L higher baseline platelet count, the adjusted odds of severe bleeding decreased by 16.8% (OR=0.832, 95% CI 0.701–0.988, P=0.036), but this continuous association was not confirmed by categorical or spline analyses.
***Conclusion*: A baseline platelet count <50 × 10⁹/L was not independently associated with induction severe bleeding after excluding patients with bleeding at diagnosis but was associated with lower 24-month OS in this retrospective AML cohort. The bleeding finding was sensitive to endpoint definition and should be interpreted cautiously. This study did not assess incremental predictive value beyond established AML risk systems; the findings should therefore be considered hypothesis-generating and require prospective external validation.**

Keywords: Acute myeloid leukemia; Platelet count; Bleeding; Propensity score matching; Retrospective cohort study.

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Introduction. Acute myeloid leukemia (AML) is a group of malignant clonal disorders originating from hematopoietic stem/progenitor cells, characterized by abnormal proliferation of blasts in the bone marrow and suppression of normal hematopoiesis. The 2022 European LeukemiaNet (ELN) recommendations for the diagnosis and management of AML[1] systematically describe the disease heterogeneity of AML and the risk stratification system based on genetic and molecular features. In the same year, the International Consensus Classification (ICC) also updated the integrated classification system for myeloid neoplasms and acute leukemias,[2] further refining the understanding of the biological heterogeneity of AML. El-Khazragy et al.[4] demonstrated that specific chromosomal abnormalities, such as 12p aberrations, interact with long noncoding RNA-mediated pathways (HOTAIR/miR-193a/c-Kit) to influence AML prognosis, further underscoring the molecular complexity of this disease. Thrombocytopenia at initial diagnosis is relatively common and represents an important clinical manifestation in assessing bone marrow suppression and bleeding risk in AML. The underlying mechanisms include impaired megakaryopoiesis caused by leukemic bone marrow infiltration, as well as consumptive reduction secondary to disseminated intravascular coagulation (DIC) in some patients. Ten Cate and Leader[3] noted that leukemia-associated DIC involves multiple mechanisms, including platelet consumption, coagulation activation, and fibrinolytic dysregulation, and that procoagulant substances released by leukemic cells, inflammatory responses, and endothelial injury may also contribute to the bleeding tendency. Clinically, thrombocytopenia at diagnosis is closely associated with increased bleeding risk and may influence the selection of initial treatment strategies and supportive care, thereby indirectly affecting disease outcomes. Therefore, thrombocytopenia at AML diagnosis is not merely a passive reflection of bone marrow failure but may also indicate increased disease burden, compromised bone marrow hematopoietic reserve, and underlying coagulation abnormalities. Emerging molecular markers such as long non-coding RNAs (e.g., HOTAIR) and their interacting microRNA networks have been shown to carry independent prognostic significance in AML, further underscoring the biological complexity of clinical outcomes.[4]

Thrombocytopenia is a recognized correlate of bleeding risk in hematologic malignancies. Versluis et al.[5] developed and validated a prediction model for life-threatening bleeding during AML induction therapy based on two independent cohorts and found that baseline platelet count and prothrombin time–international normalized ratio (PT-INR) contributed to risk stratification, with a platelet count ≤40 × 10⁹/L identified as a high-risk factor. That study also revealed marked heterogeneity in bleeding risk. Some patients with extremely low platelet counts did not experience significant bleeding, whereas others developed life-threatening bleeding at higher platelet levels. This discrepancy suggests that bleeding risk depends not only on platelet quantity but also on coagulation function, vascular integrity, infection/inflammation, and leukemia biology. Platelet transfusion is the primary approach to bleeding prevention and treatment in AML. Rebulla et al.[6] supported a prophylactic transfusion threshold of 10 × 10⁹/L, and ASCO guidelines emphasize integrating platelet count, bleeding manifestations, and clinical risk.[7]

The TOPPS trial[8] further showed that a no-prophylaxis strategy did not meet the non-inferiority criterion and that bleeding remained common despite prophylaxis. These transfusion thresholds concern real-time counts during treatment; the present study instead evaluates the association of the diagnostic platelet count with subsequent clinical outcomes.

The associations of thrombocytopenia with bleeding and adverse outcomes in AML are clinically plausible and are not new concepts. Previous studies, however, have often focused on life-threatening bleeding, intracranial hemorrhage, or transfusion strategies during treatment.[6,9] Fewer studies have quantified the associations of the platelet count measured at diagnosis with remission, severe bleeding, and survival within the same contemporary treatment cohort. Zhang et al.[10] evaluated 330 patients with non-APL AML and found that a high diagnostic platelet count (>65 × 10^9/L) was associated with a lower CR rate and poorer relapse-free survival, but did not focus on low platelet levels or concurrently examine severe bleeding. The present study was therefore designed as a hypothesis-generating effect-estimation analysis, not as the development of a new prognostic classification system or a replacement for ELN risk stratification.

Against this background, the present multi-center retrospective cohort study examined whether baseline platelet count was associated with three clinically distinct outcomes: (1) remission after induction therapy; (2) severe bleeding (CTCAE grade ≥3); and (3) OS through 24 months. A threshold of 50 × 10^9/L was selected as a pragmatic, clinically familiar boundary for enhanced bleeding vigilance rather than as a uniquely optimal biological cutoff. Because previous AML work identified 40 × 10^9/L as a high-risk threshold,[5] the revised analysis also treated platelet count continuously, evaluated non-linearity using RCS, and repeated the primary models at 40, 30, and 20 × 10^9/L. PSM was used only as a secondary sensitivity analysis.

Materials and Methods.

Study Design and Participants. Patients with non-APL AML who were newly diagnosed at the Departments of Hematology of the participating hospitals between January 2020 and December 2025 (follow-up cutoff date: June 1, 2026) and received first-line induction therapy or initial antileukemic therapy were consecutively enrolled. This study is a multi-center retrospective cohort study, and the report was prepared in accordance with the STROBE statement.[11] The study protocol was approved by the Medical Ethics Committee of each participating hospital, and the requirement for informed consent was waived owing to the retrospective nature of the study. All procedures followed the ethical principles of the Declaration of Helsinki. The study was conducted at three participating hospitals and pooled all consecutively enrolled patients under a single uniform protocol.

Inclusion and Exclusion Criteria. Inclusion criteria: (1) age ≥18 years; (2) newly diagnosed AML (non-acute promyelocytic leukemia, non-APL) confirmed by bone marrow aspiration morphology, immunophenotyping, cytogenetics, and molecular genetics (MICM classification), meeting the World Health Organization (WHO) 2016 classification criteria for myeloid neoplasms.[12] Because the 5th edition of the WHO Classification of Hematolymphoid Tumors (WHO-HAEM5)[13] was published in 2022 and the participating centers did not uniformly transition to the new criteria until 2023, the WHO 2016 classification was uniformly applied throughout the study to ensure consistency of diagnostic inclusion criteria over the entire enrollment period; (3) no prior antileukemic treatment before diagnosis; (4) initial treatment regimen consisting of daunorubicin plus cytarabine (DA regimen), idarubicin plus cytarabine (IA regimen), hypomethylating agent plus venetoclax (HMA+VEN regimen), or other cytarabine-containing regimens. Exclusion criteria: (1) acute promyelocytic leukemia (APL, M3 subtype) was excluded because of its unique coagulation abnormality profile (DIC and hyperfibrinolysis) and treatment paradigm (all-trans retinoic acid plus arsenic trioxide), with bleeding risk assessment and management strategies that are fundamentally different from those for non-APL AML;[1] (2) a prior history of myelodysplastic syndrome (MDS) or myeloproliferative neoplasm (MPN) without transformation to AML (i.e., therapy-related AML and AML transformed from MDS were included, but untransformed MDS/MPN were excluded); (3) concurrent other active malignancies; (4) pregnant or lactating women; (5) failure to receive initial treatment at the participating hospitals after diagnosis or severe missing key baseline data (missing >30% of key variables). Although WHO-HAEM5 and the International Consensus Classification (ICC) were published in 2022, the participating centers did not uniformly transition until 2023, and the molecular testing required for contemporary classification (myelodysplasia-related gene mutations) was not systematically available during the earlier years. Retrospective reclassification would therefore have produced incomplete and calendar-period-dependent results. We elected to retain the WHO 2016 and ELN 2017 systems uniformly and acknowledge the resulting risk of genetic-risk misclassification.

Cohort Size and Model Adequacy. Because this was a retrospective cohort study, the cohort size was determined by all consecutive patients who met the eligibility criteria during the study period; no post hoc hypothesis-testing power calculation was used to claim

adequacy. Model complexity was instead evaluated against the observed number of outcome events. The primary severe-bleeding model (Firth logistic regression, restricted to patients without bleeding at diagnosis) contained approximately 5 degrees of freedom for 20 events (EPV=4.0); the full-cohort sensitivity analysis contained approximately 7 degrees of freedom for 61 events (EPV=8.7). The primary 24-month Cox model contained approximately 10 degrees of freedom for 106 deaths (EPV=10.6). The low EPV for the bleeding endpoint was acknowledged, and Firth penalization was used; all estimates with wide confidence intervals were interpreted cautiously.

Clinical Data Collection. The following data were retrospectively collected from the electronic medical record system. (1) Demographics and baseline/design characteristics: age, sex, Eastern Cooperative Oncology Group (ECOG) performance status score,[14] participating center (Center 1, Center 2, or Center 3), and calendar period of data collection (2020–2022 or 2023–2025). (2) Hematologic indices at diagnosis: white blood cell count (WBC), hemoglobin (Hb), baseline platelet count (PLT), bone marrow blast percentage (BM Blast), lactate dehydrogenase (LDH), albumin (ALB), creatinine (Cr), alanine aminotransferase (ALT). (3) Coagulation parameters: prothrombin time (PT), activated partial thromboplastin time (APTT), fibrinogen (FIB), D-dimer. DIC was diagnosed according to the International Society on Thrombosis and Haemostasis (ISTH) overt DIC scoring criteria,[15] with a score ≥5 defined as overt DIC. (4) Disease characteristics: AML type (de novo/secondary or therapy-related), French American-British (FAB) classification[16]—a traditional morphologic classification used in this study solely for baseline characteristic description—, cytogenetic risk category (favorable, intermediate, adverse, classified according to the European LeukemiaNet [ELN] 2017 criteria).[17] (5) Molecular genetics: Fms-like tyrosine kinase 3–internal tandem duplication (FLT3-ITD) mutation, nucleophosmin 1 (NPM1) mutation, CCAAT/enhancer-binding protein alpha (CEBPA) biallelic mutation, tumor protein p53 (TP53) mutation, complex karyotype. (6) Initial treatment regimen: DA, IA, HMA+VEN, and other regimens. (7) Bleeding events: graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE v5.0); because data extraction and retrospective grading in this study were primarily based on v5.0, this version was uniformly applied (grade 0: no bleeding; grade 1: mild; grade 2: moderate; grade 3: severe bleeding requiring transfusion or intervention; grade 4: life-threatening; grade 5: bleeding-related death), and bleeding sites (skin/mucosa, gastrointestinal, urinary, respiratory, intracranial, multiple sites) were recorded. (8) Platelet transfusion and recovery: platelet transfusion rate during induction therapy, total transfusion volume (units), number of transfusions, platelet nadir (× 10^9/L), duration of PLT <10 × 10^9/L, days to platelet recovery >20 × 10^9/L and >50 × 10^9/L, and whether bleeding led to treatment interruption or delay.

Measurement Methods and Instruments. (1) Complete blood count: Sysmex XN-9000 automated hematology analyzer (Sysmex Corporation, Japan) with proprietary reagents was used for the measurement of WBC, Hb, PLT, and other parameters. (2) Coagulation function: Sysmex CS-5100 automated coagulation analyzer (Sysmex Corporation, Japan) was used for PT, APTT, FIB (Clauss clotting method), and D-dimer (immunoturbidimetric method), all with instrument-matched proprietary reagents. (3) Biochemical indices: Roche Cobas c702 automated biochemistry analyzer (Roche Diagnostics, Switzerland) with proprietary reagents was used for LDH, ALB, Cr, ALT, and other indices. (4) Bone marrow morphology: Bone marrow aspirate smears were stained with Wright–Giemsa stain, and the bone marrow blast percentage was independently counted by two experienced hematopathologists, with the average value taken. (5) Immunophenotyping: BD FACSCanto II flow cytometer (BD Biosciences, USA) was used for leukemic cell immunophenotyping with a routine eight-color antibody panel. (6) Cytogenetics: Bone marrow cells were cultured for 24 hours followed by R-banding karyotype analysis; at least 20 metaphase spreads were analyzed per case, and karyotypic abnormalities were described according to the International System for Human Cytogenetic Nomenclature (ISCN). (7) Molecular genetics: FLT3-ITD mutation was detected by PCR amplification combined with capillary electrophoresis; NPM1, CEBPA, and TP53 mutations were detected by PCR amplification combined with Sanger sequencing or next-generation sequencing (NGS). All tests were performed at the Department of Laboratory Medicine or the central laboratory of the participating hospitals according to standardized operating procedures. The molecular testing panel was limited to FLT3-ITD (PCR amplification with capillary electrophoresis), NPM1, CEBPA, and TP53 (PCR amplification with Sanger sequencing) throughout the study period. Myelodysplasia-related gene mutations required by ELN 2022 (ASXL1, BCOR, EZH2, RUNX1, SF3B1, SRSF2, STAG2, U2AF1, ZRSR2) were not uniformly tested. A subset of 77 patients (21.6%) enrolled after 2023 underwent expanded next-generation sequencing panels. Because of this heterogeneity, the ELN 2017 classification was uniformly applied to ensure consistent application of a single validated risk schema across the entire cohort, and the WHO 2016 classification was used for diagnostic inclusion for the same reason.

Outcome Measures. (1) Primary outcomes were severe bleeding (CTCAE grade ≥3) and OS through 24 months. The bleeding observation window was defined from the date of AML diagnosis to the end of the first induction chemotherapy or initial antileukemic treatment cycle. Bleeding events were independently abstracted from the electronic medical record (physician progress notes, nursing records, and transfusion records) by two investigators (T.Z. and Z.N.); discrepancies were resolved by consensus. CTCAE grading was applied retrospectively, and assessors were not blinded to baseline platelet count because platelet values are recorded in the same medical record. Because the recorded CTCAE grade represents the maximum severity and could not distinguish baseline from treatment-emergent events, patients with bleeding already present at diagnosis (n=125) were excluded from the primary severe-bleeding analysis; the full-cohort analysis (n=356, 61 events) was retained as a sensitivity analysis. OS was measured from AML diagnosis to death from any cause or last follow-up; for the primary survival estimand, follow-up was administratively censored at 24 months, so only deaths occurring on or before 24 months were events. Patients alive beyond 24 months were censored at 24 months, whereas patients lost to follow-up before 24 months were censored at their last known follow-up and were not classified as 24-month survivors in a binary analysis. (2) Secondary outcomes were CR and CRi after induction therapy, any-grade and grade ≥2 bleeding, 30- and 60-day mortality, platelet transfusion measures, platelet recovery, and bleeding-related treatment interruption or delay. Bleeding events already present at diagnosis (baseline bleeding) were excluded from the primary severe-bleeding endpoint to avoid overlap between the baseline covariate and the outcome; the original inclusive definition was retained as a sensitivity analysis. Bleeding events were independently abstracted from the electronic medical record (including physician progress notes, nursing records, and transfusion records) by two investigators (T.Z. and Z.N.). Discrepancies were resolved by consensus. CTCAE grading was applied retrospectively; because assessors were not blinded to baseline platelet count, potential measurement bias cannot be excluded.

Statistical Analysis. All analyses were performed using R version 4.5.1 and SPSS version 27.0. Continuous variables are presented as mean ± standard deviation and were compared using an independent-samples t-test or Mann–Whitney U test, as appropriate. Categorical variables are presented as number (percentage) and were compared using the χ^2 test or Fisher's exact test. SMDs were used to assess covariate balance, with $|SMD|<0.1$ considered acceptable. Covariates in the primary models were selected on prespecified clinical grounds rather than by stepwise selection. Age, ECOG performance status, and AML type (de novo vs. secondary/therapy-related) were included as markers of frailty, fitness, and disease biology that may influence both baseline platelet count (through marrow reserve) and clinical outcomes. WBC and bone marrow blast percentage were included as markers of disease burden. Cytogenetic risk category (ELN 2017) was included as the established AML prognostic factor. Induction treatment class (intensive DA/IA, lower-intensity HMA+VEN, or other) was included to account for treatment intensity; HMA+VEN coefficients were not interpreted as treatment effects because treatment was not randomized. DIC was included in bleeding models as an established bleeding-risk factor. The primary severe-bleeding model was a parsimonious Firth logistic regression including baseline platelet group, WBC, DIC, and induction treatment class (approximately 5 degrees of freedom), restricted to patients without bleeding at diagnosis (n=231, 20 events). The full-cohort sensitivity analysis used all 356 patients (61 events) with the same covariates plus ECOG and AML type in a standard logistic model. The 24-month Cox model included baseline platelet group, age, WBC, bone marrow blast percentage, cytogenetic risk, induction treatment class, ECOG, and AML type (approximately 10 degrees of freedom for 106 deaths; EPV=10.6). Kaplan–Meier curves and the log-rank test were used for unadjusted survival comparisons. The Cox PH assumption was assessed using variable-specific and global Schoenfeld-residual tests, and discrimination was summarized using Harrell's C-index. Full-follow-up Cox analysis was retained only as supplementary because its global PH test indicated a violation. The revised analysis did not use a binary mortality status at 24 months or ordinary ROC analysis for survival. Because 88 of 356 patients (24.7%) were censored at their last known contact before 24 months, median follow-up was estimated by the reverse Kaplan–Meier method, and baseline characteristics were compared between patients censored before 24 months and those with adequate follow-up. Two common-outcome scenarios were evaluated: all patients censored before 24 months were assumed to have died within 24 months, or all were assumed to have survived through 24 months. Sensitivity analyses included: (1) restriction to patients receiving intensive induction (DA or IA regimens); (2) continuous platelet count per 10×10^9/L; (3) repetition of primary models at thresholds of 40, 30, and 20×10^9/L; (4) three-knot restricted cubic splines to assess non-linearity; and (5) a 24-month Cox model that additionally adjusted for participating center. Effect modification by center was explored using a center-by-platelet-group interaction term. Calendar-period analyses stratified the cohort into 2020–2022 and 2023–2025 and repeated the 24-month OS and primary severe-bleeding models within each period. Because the period-specific event counts were small, particularly for severe bleeding, these analyses

were considered exploratory, and estimates were interpreted with emphasis on their confidence intervals. For PSM, 1:1 nearest-neighbor matching with a caliper of 0.2 standard deviations of the logit propensity score included age, sex, WBC, Hb, bone marrow blasts, cytogenetic risk, infection/fever, induction regimen, FLT3-ITD, NPM1, biallelic CEBPA, TP53, and complex karyotype. Conditional logistic regression was used for matched binary outcomes and a 24-month Cox model with cluster-robust standard errors for matched survival. PSM was considered a secondary sensitivity analysis, and residual imbalance was reported rather than interpreted as complete control of confounding. Ordinary ROC curves were limited to CR and severe bleeding. All primary-model variables were complete within their respective analysis populations, so multiple imputation was not required. For supportive-care variables, zero was assigned only when the record indicated no platelet transfusion (for transfusion volume and number) or when the platelet nadir did not cross the relevant threshold (for duration below threshold and time to platelet recovery); genuinely unrecorded values were retained as missing. All tests were two-sided, with $P<0.05$ considered statistically significant. The functional form of WBC in the 24-month Cox model was evaluated using martingale residuals from a model excluding WBC, loess smoothing on the original and log-transformed scales, and DFBETA influence diagnostics. The primary linear-WBC model was compared with log (WBC+0.1) and a natural cubic spline specification with two degrees of freedom (corresponding to a three-knot natural spline). Model fit was compared using AIC and a likelihood-ratio test, and the stability of the platelet-group HR was assessed across WBC specifications. Coagulation abnormality was defined as the presence of at least one of the following: prolonged PT (>3 seconds above the upper limit of normal), prolonged APTT (>10 seconds above the upper limit of normal), or fibrinogen <1.5 g/L, as documented in the clinical record at the time of AML diagnosis.

Results

Baseline Characteristics. A total of 356 patients were included: 218 (61.2%) in the low baseline platelet group and 138 (38.8%) in the normal/high group. All variables in the 24-month OS model had 0 missing values (356/356 patients). The primary severe-bleeding analysis used 231 patients after excluding 125 patients with bleeding at diagnosis, all of whom had complete data for the model covariates. Missingness was confined to descriptive/supportive-care variables: platelet transfusion volume and number of transfusions each had 25 missing values (7.0%), duration of PLT $<10 \times 10^9$/L had 68 (19.1%), and time to PLT recovery $>20 \times 10^9$/L had 44 (12.4%). These missing entries represent genuinely unrecorded data and were retained as missing. Separately, for transfusion volume and number, patients who received no platelet transfusion were coded as 0; for duration below a threshold and time to platelet recovery, patients whose platelet nadir did not cross the relevant threshold were coded as 0. These structural zeros were not counted as missing. Center 1 contributed 180 patients (50.6%), Center 2 contributed 106 (29.8%), and Center 3 contributed 70 (19.7%); 279 patients (78.4%) were enrolled in 2020–2022 and 77 (21.6%) in 2023–2025. Center distribution and collection period did not differ significantly between the platelet groups (P=0.650 and P=0.219, respectively; **Table 1**). Among the 356 patients, molecular testing by PCR and Sanger sequencing for FLT3-ITD, NPM1, CEBPA, and TP53 was complete in all patients. Expanded next-generation sequencing covering additional genes was available for 77 patients (21.6%), predominantly those enrolled after 2023.

Compared with the normal/high platelet group, patients in the low baseline platelet group were older (P=0.002), had higher white blood cell counts at diagnosis (P<0.001) and higher bone marrow blast percentages (P<0.001), and exhibited more pronounced coagulation abnormalities (prolonged PT and APTT, decreased fibrinogen, elevated D-dimer; all P<0.01). In addition, the low baseline platelet group showed a trend toward a higher TP53 mutation rate (P=0.062), a lower CEBPA biallelic mutation rate (P=0.028), and a trend toward a higher proportion of complex karyotype (P=0.052). No statistically significant differences were observed between the two groups in sex, ECOG performance status score, AML type (de novo/secondary), FAB classification, cytogenetic risk category, overall distribution of induction regimens, FLT3-ITD mutation rate, or NPM1 mutation rate (**Table 1**).

Early Response to Induction Therapy. Among the 356 patients in the entire cohort, 187 (52.5%) achieved CR, 46 (12.9%) achieved CRi, 29 (8.1%) achieved partial remission (PR), 72 (20.2%) had no response (NR), 22 (6.2%) died during induction, and 233 (65.4%) achieved the composite endpoint of CR/CRi. No significant differences were observed between the low baseline platelet group and the normal/high platelet group in the CR rate (53.7% vs. 50.7%, P=0.665) or the CR/CRi rate (63.3% vs. 68.8%, P=0.339) (**Table 2**).

Multivariable logistic regression analyses (adjusting for age, WBC, Hb, bone marrow blast percentage, cytogenetic risk category, induction regimen, FLT3-ITD, NPM1, CEBPA biallelic mutation, TP53, and complex karyotype) with CR and CR/CRi as the dependent variables, respectively, showed that low baseline platelet status was not an independent factor associated with CR (OR=1.254, 95% CI 0.783–2.007, P=0.346) or CR/CRi (OR=1.175, 95% CI 0.714–1.932, P=0.526). Of note, the HMA+VEN regimen was associated with higher odds of CR/CRi (multivariable OR=1.939, 95% CI 1.046–3.594,

Table 1. Comparison of baseline characteristics between the low-PLT group and the normal/high-PLT group.

Variable	Total (n=356)	Normal/high-PLT (n=138)	Low-PLT (n=218)	P value	SMD
Age, years	51.7±13.5	48.9±13.7	53.5±13.1	0.002	0.344
WBC, × 10⁹/L	60.7±40.5	51.5±37.5	66.4±41.2	<0.001	0.379
Hb, g/L	78.2±19.0	79.9±20.2	77.1±18.2	0.189	0.145
Baseline PLT, × 10⁹/L	58.8±47.0	108.4±38.4	27.4±11.6	<0.001	2.856
BM Blast, %	59.1±16.9	53.9±16.0	62.4±16.7	<0.001	0.516
LDH, U/L	518.2±226.8	497.7±228.5	531.2±225.2	0.176	0.148
ALB, g/L	35.7±4.9	36.1±5.0	35.4±4.7	0.192	0.143
Cr, μmol/L	76.5±21.2	76.0±20.5	76.8±21.7	0.723	0.038
ALT, U/L	39.3±19.2	39.7±19.6	39.0±19.0	0.734	0.037
PT, s	14.0±2.1	13.5±1.6	14.4±2.2	<0.001	0.469
APTT, s	37.4±7.4	35.5±7.3	38.6±7.3	<0.001	0.425
FIB, g/L	2.6±0.9	2.7±0.8	2.5±0.9	0.003	0.328
D-dimer, mg/L	5.1±3.0	4.1±2.5	5.8±3.2	<0.001	0.599
Sex, n(%)				1.000	
Male	204 (57.3)	79 (57.2)	125 (57.3)		
Female	152 (42.7)	59 (42.8)	93 (42.7)		
ECOG PS, n(%)				0.608	
0–1	259 (72.8)	103 (74.6)	156 (71.6)		
≥2	97 (27.2)	35 (25.4)	62 (28.4)		
Cytogenetic risk, n(%)				0.455	
Favorable	61 (17.1)	25 (18.1)	36 (16.5)		
Intermediate	190 (53.4)	68 (49.3)	122 (56.0)		
Adverse	105 (29.5)	45 (32.6)	60 (27.5)		
Coagulation abnormality, n(%)				1.000	
Yes	90 (25.3)	35 (25.4)	55 (25.2)		
No	266 (74.7)	103 (74.6)	163 (74.8)		
Bleeding at diagnosis, n(%)				0.656	
Yes	125 (35.1)	46 (33.3)	79 (36.2)		
No	231 (64.9)	92 (66.7)	139 (63.8)		
Infection/fever at diagnosis, n(%)				0.981	
Yes	130 (36.5)	51 (37.0)	79 (36.2)		
No	226 (63.5)	87 (63.0)	139 (63.8)		
DIC, n(%)				0.817	
Yes	47 (13.2)	17 (12.3)	30 (13.8)		
No	309 (86.8)	121 (87.7)	188 (86.2)		
AML type, n(%)				0.423	
De novo AML	296 (83.1)	118 (85.5)	178 (81.7)		
Secondary/therapy-related AML	60 (16.9)	20 (14.5)	40 (18.3)		
FAB classification, n(%)				0.181	
M0/M1	52 (14.6)	13 (9.4)	39 (17.9)		
M2	106 (29.8)	44 (31.9)	62 (28.4)		
M4/M5	128 (36.0)	52 (37.7)	76 (34.9)		
M6/M7 & others	70 (19.7)	29 (21.0)	41 (18.8)		
FLT3-ITD, n(%)				0.180	
Positive	79 (22.2)	25 (18.1)	54 (24.8)		
Negative	277 (77.8)	113 (81.9)	164 (75.2)		

NPM1, n(%)				0.768	
Positive	86 (24.2)	35 (25.4)	51 (23.4)		
Negative	270 (75.8)	103 (74.6)	167 (76.6)		
CEBPA biallelic, n(%)				0.028	
Positive	37 (10.4)	21 (15.2)	16 (7.3)		
Negative	319 (89.6)	117 (84.8)	202 (92.7)		
TP53, n(%)				0.062	
Positive	32 (9.0)	7 (5.1)	25 (11.5)		
Negative	324 (91.0)	131 (94.9)	193 (88.5)		
Complex karyotype, n(%)				0.052	
Yes	45 (12.6)	11 (8.0)	34 (15.6)		
No	311 (87.4)	127 (92.0)	184 (84.4)		
Induction regimen, n(%)				0.129	
DA	148 (41.6)	50 (36.2)	98 (45.0)		
IA	116 (32.6)	46 (33.3)	70 (32.1)		
HMA+VEN	64 (18.0)	26 (18.8)	38 (17.4)		
Others	28 (7.9)	16 (11.6)	12 (5.5)		
Participating center, n(%)				0.650	
Center 1	180 (50.6)	66 (47.8)	114 (52.3)		
Center 2	106 (29.8)	42 (30.4)	64 (29.4)		
Center 3	70 (19.7)	30 (21.7)	40 (18.3)		
Collection period, n(%)				0.219	
2020–2022	279 (78.4)	103 (74.6)	176 (80.7)		
2023–2025	77 (21.6)	35 (25.4)	42 (19.3)		

Note: Continuous variables are presented as mean ± standard deviation; categorical variables are presented as number (percentage). P values: independent-samples t-test or Mann–Whitney U test for continuous variables; χ^2 test or Fisher's exact test for categorical variables. SMD, standardized mean difference, used to assess between-group balance. Participating centers are anonymized as Center 1–3.
Abbreviations: PLT, platelet count; WBC, white blood cell count; Hb, hemoglobin; LDH, lactate dehydrogenase; ALB, albumin; Cr, creatinine; ALT, alanine aminotransferase; PT, prothrombin time; APTT, activated partial thromboplastin time; FIB, fibrinogen; DIC, disseminated intravascular coagulation; ECOG, Eastern Cooperative Oncology Group; FAB, French-American-British classification; FLT3-ITD, Fms-like tyrosine kinase 3–internal tandem duplication; NPM1, nucleophosmin 1; CEBPA, CCAAT/enhancer-binding protein alpha; TP53, tumor protein p53; DA, daunorubicin plus cytarabine; IA, idarubicin plus cytarabine; HMA+VEN, hypomethylating agent plus venetoclax; SMD, standardized mean difference.

P=0.035), whereas none of the other included variables reached statistical significance. These estimates describe adjusted associations within this cohort and should not be interpreted as evidence of comparative treatment efficacy or as a validated remission-prediction model.

The 30-day mortality rate was 5.0% in the low-platelet group and 1.4% in the normal/high group (P=0.089); the corresponding 60-day rates were 11.9% and 1.4% (P<0.001). Because there were only 13 deaths by 30 days and 28 by 60 days, these secondary regression analyses were considered exploratory. Firth regression for 30-day mortality produced an imprecise estimate (OR=1.725, 95% CI 0.417–10.160, P=0.470). The adjusted 60-day estimate was also imprecise despite statistical significance (OR=7.162, 95% CI 1.559–32.916, P=0.011) and should not be interpreted as evidence of a causal pathway.

Bleeding Events. The incidence of any-grade bleeding was similar between the two groups (52.8% vs. 52.9%, P=1.000). However, when assessed by CTCAE grade, grade ≥2 bleeding (42.2% vs. 27.5%, P=0.007) and severe bleeding (CTCAE grade ≥3) were more frequent in the low-platelet group in the full-cohort sensitivity analysis (22.5% vs. 8.7%, P=0.001). In the primary analysis excluding patients whose severe bleeding was already present at diagnosis (n=231; 125 patients excluded, among whom 41 had severe bleeding at baseline), severe bleeding occurred in 10.8% of the low-platelet group (15/139) and 5.4% of the normal/high group (5/92) (P=0.164 by Fisher's exact test).

Analysis by bleeding site showed that skin/mucosal bleeding was the most common (approximately 40% in both groups), with no statistically significant differences between the two groups in gastrointestinal, urinary, respiratory, or multi-site bleeding. Notably, intracranial hemorrhage showed an increasing trend in the low baseline platelet group (4.1% vs. 0.7%, P=0.096), and bleeding-related deaths occurred exclusively in the low baseline platelet group (3 cases, 1.4%). However, the

Table 2. Comparison of induction therapy response, bleeding events, and platelet transfusion between the two groups.

Variable	Low-PLT (n=218)	Normal/high-PLT (n=138)	P value
Response distribution, n(%)			0.224*
CR	117(53.7)	70(50.7)	
CRi	21(9.6)	25(18.1)	
PR	20(9.2)	9(6.5)	
NR	39(17.9)	33(23.9)	
Death during induction	17(7.8)	5(3.6)	
Primary efficacy endpoints			
CR rate, n(%)	117(53.7)	70(50.7)	0.665
CR/CRi rate, n(%)	138(63.3)	95(68.8)	0.339
Early mortality, n(%)			
30-day death	11(5.0)	2(1.4)	0.089
60-day death	26(11.9)	2(1.4)	<0.001
Bleeding events, n(%)			
Any-grade bleeding	115(52.8)	73(52.9)	1.000
Grade ≥2 bleeding	92(42.2)	38(27.5)	0.007
Grade ≥3 bleeding	49(22.5)	12(8.7)	0.001
Platelet transfusion			
Transfusion rate, n(%)	166(76.1)	96(69.6)	0.212
Total volume, units	10.2±7.6	5.7±6.2	<0.001
No. of transfusions	5.4±4.2	3.1±3.4	<0.001
Platelet nadir, × 10^9/L	12.1±6.7	13.1±6.2	0.154
Duration of PLT <10 × 10^9/L, days	4.1±5.0	2.9±4.5	0.051
Days to PLT >20 × 10^9/L	19.2±6.9	17.6±6.2	0.033
Days to PLT >50 × 10^9/L	30.6±8.4	28.3±5.6	0.002
Bleeding-induced treatment interruption, n(%)	29(13.3)	6(4.3)	0.010

Note: Continuous variables are presented as mean ± standard deviation; categorical variables are presented as number (percentage). *P value for the overall comparison of induction therapy response distribution (χ^2 test). CR rate and CR/CRi rate are the primary efficacy endpoints, each with a separately reported P value; CR/CRi is the composite endpoint of CR + CRi and is not mutually exclusive with CR or CRi. Transfusion volume/number: recorded as 0 only for patients not receiving transfusion; genuinely unrecorded values were retained as missing. Duration below threshold and days to PLT recovery: recorded as 0 only for patients whose platelet nadir did not cross the relevant threshold; genuinely unrecorded values were retained as missing. Bleeding-event proportions (any-grade, grade ≥2, grade ≥3) are reported for the full cohort and include bleeding already present at diagnosis; the primary severe-bleeding analysis excluded such patients (see Methods).
Abbreviations: CR, complete remission; CRi, complete remission with incomplete hematologic recovery; PR, partial remission; NR, no response; CTCAE, Common Terminology Criteria for Adverse Events; PLT, platelet count.

between-group difference did not reach statistical significance (P=0.286).

Risk Factors for Severe Bleeding. In univariable analysis within the primary risk set (n=231), low baseline platelet count was not significantly associated with severe bleeding (OR=2.105, 95% CI 0.738–6.006, P=0.164). WBC, DIC, and lower-intensity HMA+VEN treatment were associated with severe bleeding in both univariable and multivariable analyses (**Table 3**).

In the primary analysis, which excluded 125 patients with bleeding at diagnosis (n=231, 20 severe-bleeding events; EPV=4.0), low baseline platelet count was not independently associated with severe bleeding in the Firth logistic regression model (adjusted OR=1.761, 95% CI 0.631–5.583, P=0.287). The model included baseline platelet group, WBC, DIC, and induction treatment class (approximately 5 degrees of freedom for 20 events). WBC (adjusted OR=1.016 per 10 × 10^9/L, 95% CI 1.005–1.028, P=0.005), DIC (adjusted OR=0.292, 95% CI 0.097–0.946, P=0.041), and lower-intensity HMA+VEN treatment versus intensive DA/IA (adjusted OR=5.049, 95% CI 1.772–14.481, P=0.003) were independently associated with severe bleeding (**Table 3**).

Platelet Transfusion and Recovery. The platelet transfusion rate in the low baseline platelet group showed an increasing trend, but the difference did not reach statistical significance (76.1% vs. 69.6%, P=0.212). However, both the total transfusion volume and the number of transfusions were significantly higher in the

Table 3. Parsimonious univariable and multivariable Firth logistic regression analyses of severe bleeding (CTCAE grade ≥3) during induction — primary analysis (n=231, excluding patients with bleeding at diagnosis).

Variable	Univariable			Multivariable (Firth)		
Variable	OR	95% CI	P value	OR	95% CI	P value
PLT group (Low vs. Normal/High)	2.105	0.738–6.006	0.164	1.761	0.631–5.583	0.287
WBC, × 10⁹/L	1.018	1.007–1.030	0.001	1.016	1.005–1.028	0.005
DIC: No (vs. Yes)	0.285	0.100–0.816	0.019	0.292	0.097–0.946	0.041
Lower-intensity HMA+VEN (vs. intensive DA/IA)	5.156	1.900–13.995	0.001	5.049	1.772–14.481	0.003
Other regimen (vs. intensive DA/IA)	2.619	0.515–13.319	0.246	3.292	0.557–14.289	0.169

Note: The primary analysis excluded 125 patients with bleeding at diagnosis. The model included 231 patients and 20 severe-bleeding events. Multivariable analysis used Firth logistic regression (approximately 5 degrees of freedom; EPV=4.0). The full-cohort sensitivity analysis (n=356, 61 events) is presented in Supplementary Table 1. Intensive DA/IA was the reference treatment class. "No" is shown relative to "Yes" for DIC. OR >1 indicates higher odds of severe bleeding.
Abbreviations: OR, odds ratio; CI, confidence interval; PLT, platelet count; WBC, white blood cell count; DIC, disseminated intravascular coagulation; HMA+VEN, hypomethylating agent plus venetoclax.

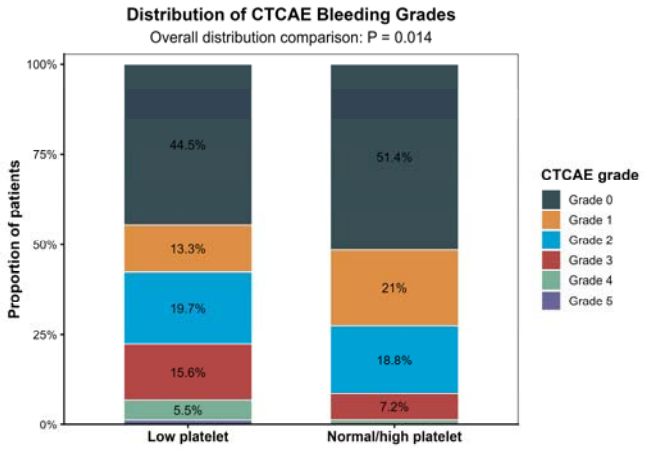

Figure 1. Distribution of CTCAE bleeding grades. Distribution of CTCAE bleeding grades (grades 0–5) in the low baseline platelet group (PLT <50 × 10⁹/L) and the normal/high platelet group (PLT ≥50 × 10⁹/L). The difference in the overall distribution between the two groups was statistically significant (P=0.016), with the low baseline platelet group having a higher proportion of grade ≥3 bleeding than the normal/high platelet group. This figure presents the full cohort (including patients with bleeding at diagnosis) for descriptive purposes; the primary severe-bleeding analysis excluded such patients (see Methods).
Abbreviations: CTCAE, Common Terminology Criteria for Adverse Events; PLT, platelet count.

low baseline platelet group than in the normal/high platelet group (both P<0.001; see **Table 2** for details). The platelet nadir during induction therapy did not differ significantly between the two groups (P=0.154), but the time to platelet recovery >20 × 10⁹/L (P=0.033) and >50 × 10⁹/L (P=0.002) was significantly prolonged in the low baseline platelet group. The proportion of patients with bleeding-induced treatment interruption or delay was significantly higher in the low baseline platelet group (13.3% vs. 4.3%, P=0.010). Because these means include patients whose platelet nadir never fell below the relevant threshold (structural zeros), subgroup means restricted to patients whose nadir actually crossed each threshold were computed. Among those with both nadir <10 × 10⁹/L and a recorded duration (n=61), the mean duration of PLT <10 × 10⁹/L was 9.5 ± 4.0 days in the normal/high group and 9.8 ± 3.7 days in the low-platelet group (P=0.804). Among those with both nadir <20 × 10⁹/L and a recorded recovery time (n=260), mean PLT recovery to >20 × 10⁹/L was 18.2 ± 5.5 versus 19.8 ± 6.3 days, respectively (P=0.035). Among those with nadir <50 × 10⁹/L (entire cohort, n=356), mean recovery to >50 × 10⁹/L was 28.3 ± 5.6 versus 30.6 ± 8.4 days (P=0.002). The subgroup pattern of longer platelet recovery times in the low-platelet group was consistent with the full-cohort analysis.

Survival Analysis. Kaplan–Meier analysis with administrative censoring at 24 months showed poorer OS in the low baseline platelet group (log-rank χ^2=18.68, P<0.001; **Figure 2A**). The estimated 12-month OS was 77.0% (95% CI 71.6%–82.9%) in the low-platelet group and 90.8% (95% CI 86.0%–95.9%) in the normal/high group. The corresponding 24-month estimates were 58.2% (95% CI 51.4%–66.0%) and 77.8% (95% CI 70.7%–85.6%). Because survival remained above 50% in both groups at 24 months, median OS was not reached within the primary 24-month analysis. Of the 356 patients, 106 died within 24 months, 88 were censored at their last known follow-up before 24 months, and 162 were administratively censored at 24 months. The 149 deaths observed over the full available follow-up were therefore not classified as deaths within 24 months.

The primary parsimonious Cox model included 356 patients, 106 deaths within 24 months, and approximately 10 degrees of freedom (EPV=10.6). Univariable results are shown in **Table 4**. In the adjusted model, low baseline platelet count was associated with a higher hazard of death through 24 months (HR=1.811, 95% CI 1.145–2.864, P=0.011). The model C-index was 0.717, and the global Schoenfeld-residual test was P=0.209, indicating no significant violation of the proportional-hazards assumption.

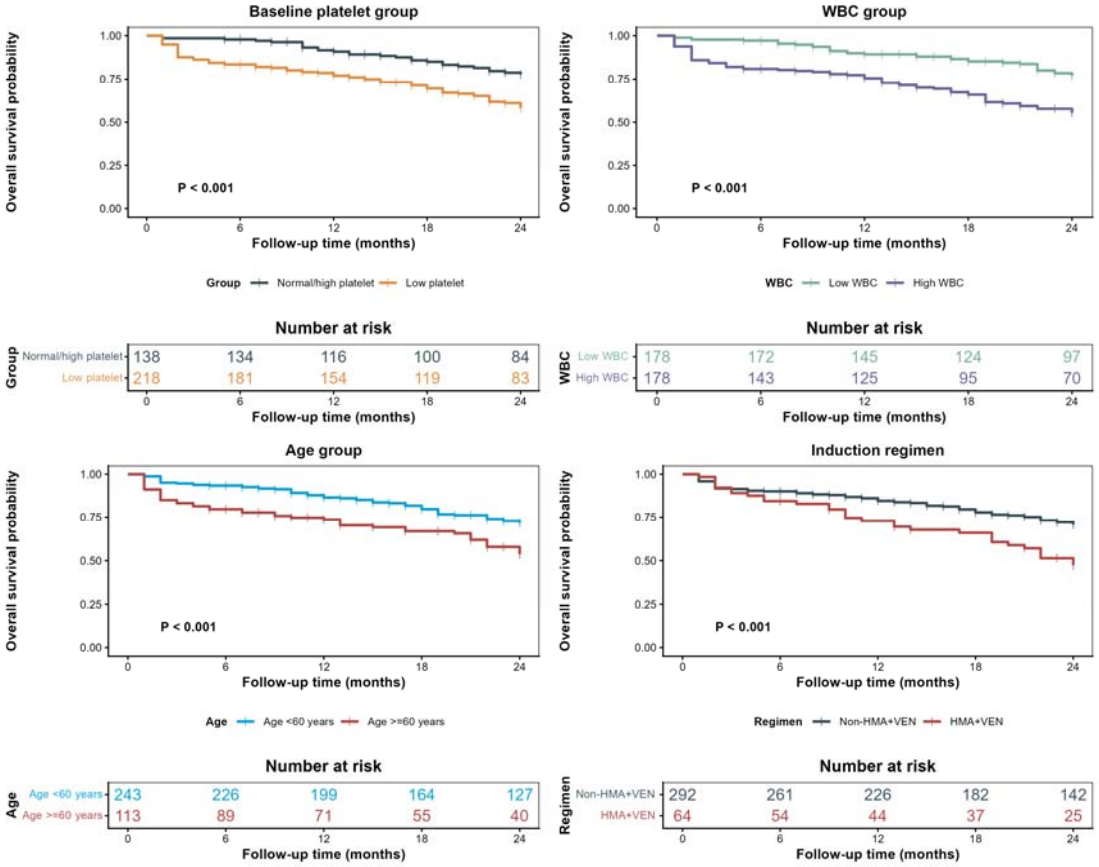

Figure 2. Kaplan–Meier survival curves. Kaplan–Meier curves for OS administratively censored at 24 months. (**A**) Baseline platelet group; (**B**) age group; (**C**) WBC group; and (**D**) induction-treatment class. P values are from log-rank tests. Numbers at risk are shown below the curves at 0, 6, 12, 18, and 24 months. These curves do not classify patients lost before 24 months as survivors.
Abbreviations: OS, overall survival; PLT, platelet count; WBC, white blood cell count; HMA+VEN, hypomethylating agent plus venetoclax regimen; DA, daunorubicin plus cytarabine regimen; HR, hazard ratio; CI, confidence interval.

Age (HR=1.025 per year, 95% CI 1.009–1.041, P=0.002), WBC (HR=1.009 per 10 × 10⁹/L, 95% CI 1.005–1.014, P<0.001), and lower-intensity HMA+VEN treatment versus intensive DA/IA (HR=1.868, 95% CI 1.210–2.885, P=0.005) were independently associated with the hazard of death through 24 months. ECOG performance status ≥2 versus 0–1 (HR=1.158, 95% CI 0.761–1.763, P=0.493) and secondary/therapy-related AML versus de novo AML (HR=1.270, 95% CI 0.773–2.088, P=0.345) were not independently associated with 24-month OS in this model. Bone marrow blast percentage and cytogenetic risk category were also not significant in the adjusted model (**Table 4**).

The full-follow-up Cox model was examined only as a supplementary analysis. Its global Schoenfeld-residual test was significant (P=0.034), with evidence of non-proportionality for WBC (P=0.007); therefore, it was not used as the primary effect estimate or as a substitute for the explicitly defined 24-month survival estimand.

Censoring Assessment. The median follow-up time by reverse Kaplan-Meier was 30.0 months. Among 88 patients censored before 24 months (24.7%: 27.5% of the low-platelet group and 20.3% of the normal/high group, P=0.148), baseline characteristics were generally comparable to those with adequate follow-up, except that early-censored patients were younger (50.7 vs. 54.6 years, P=0.018; **Supplementary Table 2**). In common-outcome scenario analyses, the low-platelet HR for 24-month OS was 2.012 (95% CI 1.472–2.750, P<0.001) under the assumption that all patients censored before 24 months died, and 2.276 (95% CI 1.469–3.526, P<0.001) under the assumption that all survived (**Supplementary Table 3**). Both common-outcome scenarios produced hazard ratios in the same direction as the primary analysis; however, these scenarios do not address differential informative censoring between platelet groups.

WBC Functional-Form Diagnostics. Martingale-residual loess plots showed mild curvature at higher WBC values (**Supplementary Figure 2**), but formal comparisons did not demonstrate a statistically significant improvement over the linear specification. AIC values were 1143.40 for linear WBC, 1142.40 for log (WBC+0.1), and 1142.68 for the spline model. The likelihood-ratio test comparing the linear and spline specifications yielded χ^2=2.71 (P=0.0996), and the spline-based test for the nonlinear component was not statistically significant (P=0.0779). The adjusted HR for the low-platelet group

Table 4. Parsimonious univariable and multivariable Cox proportional hazards analyses of 24-month overall survival.

Variable	Univariable			Multivariable		
Variable	HR	95% CI	P value	HR	95% CI	P value
PLT group (Low vs. Normal/High)	2.276	1.469–3.526	<0.001	1.811	1.145–2.864	0.011
Age, years	1.029	1.014–1.044	<0.001	1.025	1.009–1.041	0.002
WBC, × 10⁹/L	1.012	1.007–1.016	<0.001	1.009	1.005–1.014	<0.001
BM blast, %	1.019	1.007–1.031	0.001	1.006	0.993–1.019	0.376
Cytogenetic risk: Intermediate (vs. Favorable)	1.269	0.718–2.244	0.412	1.077	0.602–1.927	0.803
Cytogenetic risk: Adverse (vs. Favorable)	1.346	0.735–2.465	0.336	1.306	0.706–2.413	0.395
Lower-intensity HMA+VEN (vs. intensive DA/IA)	2.039	1.331–3.121	0.001	1.868	1.210–2.885	0.005
Other regimen (vs. intensive DA/IA)	1.111	0.534–2.313	0.778	1.481	0.704–3.114	0.300
ECOG ≥2 (vs. 0–1)	1.256	0.832–1.894	0.278	1.158	0.761–1.763	0.493
Secondary/therapy-related AML (vs. de novo)	1.202	0.739–1.956	0.458	1.270	0.773–2.088	0.345

Note: The primary model included 356 patients and 106 deaths within 24 months (approximately 10 degrees of freedom; EPV=10.6). Follow-up was administratively censored at 24 months. C-index=0.717; global Schoenfeld-residual P=0.209. Intensive DA/IA and favorable cytogenetic risk were reference categories. ECOG and AML type were added per the covariate-selection rationale in the Methods. **Abbreviations**: HR, hazard ratio; CI, confidence interval; PLT, platelet count; WBC, white blood cell count; HMA+VEN, hypomethylating agent plus venetoclax; ECOG, Eastern Cooperative Oncology Group.

Table 5. Twenty-four-month overall survival after propensity score matching.

Outcome	Statistical method	OR/HR	95% CI	P value	N
24-month OS	Cox + cluster-robust SE	1.981	1.228–3.193	0.005	228

Note: One-to-one nearest-neighbor matching yielded 114 pairs (228 patients). A 24-month Cox model with cluster-robust standard errors was used for OS. Residual |SMD|>0.1 remained for the propensity score, age, WBC, Hb, and bone marrow blast percentage; PSM is therefore a secondary sensitivity analysis. The matched severe-bleeding analysis was not reported because the matched bleeding risk set (which excluded patients with bleeding at diagnosis) differed from that used for matching and contained too few events (n=146, 8 events) to be informative. **Abbreviations**: PSM, propensity score matching; HR, hazard ratio; CI, confidence interval; OS, overall survival.

was stable across the linear, log-transformed, and spline specifications (1.811, 1.766, and 1.768, respectively), supporting retention of linear WBC in the primary model.

Sensitivity Analysis: Intensive Induction Subgroup. In the subgroup of 264 patients receiving intensive induction (DA or IA), low baseline platelet count was associated with 24-month OS (adjusted HR=2.402, 95% CI 1.273–4.532, P=0.007; 67 deaths within 24 months). The severe-bleeding association in the intensive subgroup was directionally consistent with the primary analysis but was not statistically significant (adjusted OR=1.821, 95% CI 0.462–10.038, P=0.407; n=174, 9 events) (**Supplementary Table 4**).

Center and Calendar-Period Analyses. After additional adjustment for participating center, low baseline platelet count remained associated with a higher hazard of death through 24 months (HR=1.896, 95% CI 1.192–3.017, P=0.007; n=356, 106 deaths). The center-by-platelet-group interaction was not statistically significant (P=0.186), although this analysis had limited power to detect center-specific heterogeneity. In calendar-period analyses, the adjusted association with 24-month OS was directionally consistent but imprecise in both 2020–2022 (HR=1.614, 95% CI 0.975–2.672, P=0.063; n=279, 88 deaths) and 2023–2025 (HR=3.048, 95% CI 0.880–10.560, P=0.079; n=77, 18 deaths). Period-specific severe-bleeding estimates were likewise highly imprecise: OR=1.253 (95% CI 0.413–4.178, P=0.696; n=181, 16 events) for 2020–2022 and OR=4.994 (95% CI 0.419–1385.252, P=0.224; n=50, 4 events) for 2023–2025. These period-stratified results were exploratory and do not establish the presence or absence of calendar-period heterogeneity (**Supplementary Table 5**).

Subgroup Analysis. Subgroup analysis based on 24-month censored Cox regression (stratification variables: age <60/≥60 years, sex, cytogenetic risk category, infection/fever at diagnosis, induction regimen, CR achievement, severe bleeding) demonstrated that HRs for the low baseline platelet group were >1 across all strata defined by the seven subgroup variables, with a consistent direction of association. Interaction tests showed that all interaction P values were >0.05 (only the interaction P for CR achievement showed a borderline trend of 0.069), providing no statistical evidence that the observed association differed across the examined subgroups. These descriptive subgroup estimates do not establish consistent prognostic performance. The largest point estimate was observed in the adverse cytogenetic risk subgroup (HR=3.516, 95% CI 1.593–7.761,

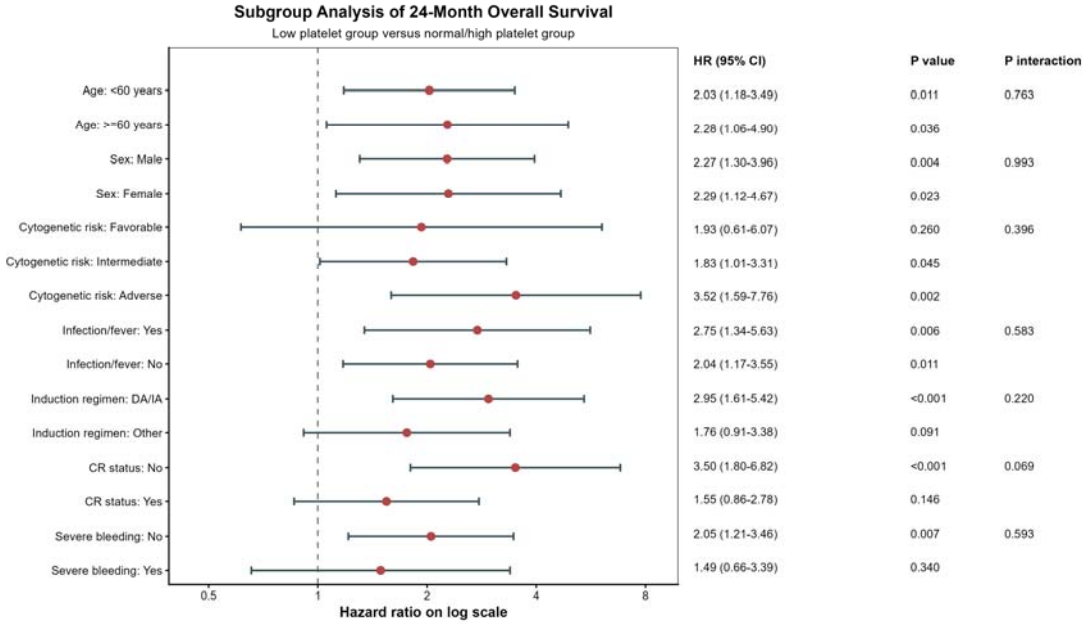

Figure 3. Forest plot for subgroup analysis. Subgroup analysis of the association between the low baseline platelet group (vs. normal/high platelet group) and 24-month overall survival. HRs and 95% CIs are based on 24-month censored Cox regression models. Interaction P values test the interaction between baseline platelet group and each subgroup variable. The vertical dashed line indicates HR=1 (null effect line).
Abbreviations: HR, hazard ratio; CI, confidence interval; OS, overall survival; CR, complete remission; PLT, platelet count; DA, daunorubicin plus cytarabine regimen; IA, idarubicin plus cytarabine regimen.

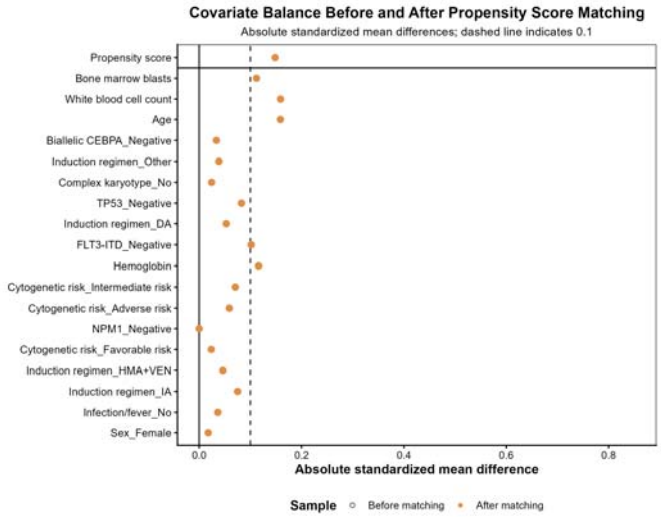

Figure 4. Assessment of covariate balance before and after propensity score matching (Love plot). Absolute SMDs before and after PSM. The dashed line indicates |SMD|=0.1. Residual imbalance after matching remained for the propensity score, age, WBC, Hb, and bone marrow blast percentage; therefore, the matched sample was not considered fully balanced.
Abbreviations: PSM, propensity score matching; SMD, standardized mean difference; WBC, white blood cell count; Hb, hemoglobin; BM_blast, bone marrow blast percentage; PLT, platelet count; FLT3-ITD, Fms-like tyrosine kinase 3–internal tandem duplication; NPM1, nucleophosmin 1; CEBPA, CCAAT/enhancer-binding protein alpha; TP53, tumor protein p53; DA, daunorubicin plus cytarabine regimen; IA, idarubicin plus cytarabine regimen; HMA+VEN, hypomethylating agent plus venetoclax regimen.

P=0.002), and the association estimate was also statistically significant in the subgroup without CR achievement (HR=3.503, P<0.001). The forest plot for the subgroup analysis is shown in **Figure 3**.

Propensity Score Matching and Sensitivity Analyses. One-to-one nearest-neighbor PSM matched 114 low-platelet patients to 114 normal/high-platelet patients (228 patients). Matching improved most SMDs but did not fully balance the groups. Residual absolute SMDs >0.1 remained for the propensity score, age, WBC, Hb, and bone marrow blast percentage (**Figure 4**). Accordingly, the matched analysis was treated as a secondary sensitivity analysis rather than as evidence that all baseline confounding had been eliminated.

After matching, low baseline platelet count remained associated with poorer 24-month OS in the cluster-robust Cox model (HR=1.981, 95% CI 1.228–3.193, P=0.005; 58 events) (Table 5). The severe-bleeding association could not be reliably evaluated in the matched sample because the primary bleeding analysis excluded patients with bleeding at diagnosis, the matched bleeding risk set differed from that used for matching, and only 8 events were observed (OR=1.000, 95% CI 0.141–7.099, P=1.000); this estimate was uninformative. No binary mortality model at 24 months was performed.

Continuous and alternative-threshold analyses supported the survival association but not the severe-bleeding association. Per 10 × 10⁹/L higher baseline platelet count, the adjusted odds of severe bleeding decreased by 16.8% (OR=0.832, 95% CI 0.701–0.988, P=0.036) in the continuous analysis, suggesting a potential dose-response relationship. However, this finding was not confirmed by the categorical analysis using the 50 × 10⁹/L threshold (OR=1.761, P=0.287) or by the restricted cubic spline analysis (overall association P=0.218; nonlinear P=0.130). The

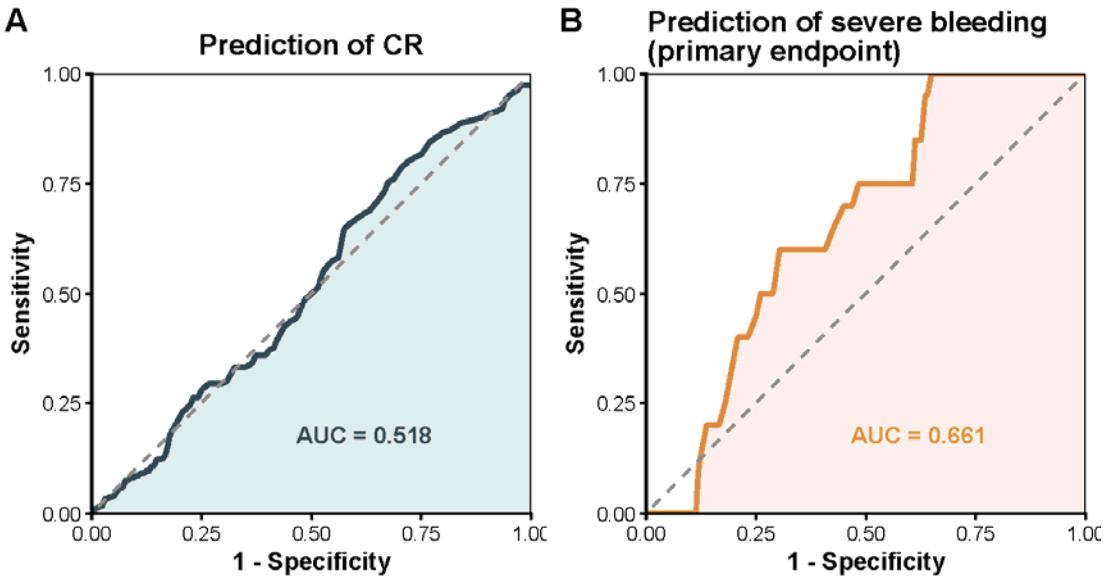

Figure 5. ROC curves for the association of baseline platelet count with CR and severe bleeding. Ordinary ROC curves describing the discrimination of baseline platelet count for (A) complete remission (n=356) and (B) severe bleeding using the primary endpoint (n=231, excluding patients with bleeding at diagnosis). Ordinary ROC analysis was not performed for 24-month OS because censoring must be considered.
Abbreviations: ROC, receiver operating characteristic; AUC, area under the curve; CR, complete remission; CTCAE, Common Terminology Criteria for Adverse Events; CI, confidence interval; PLT, platelet count.

discordance between the continuous, categorical, and spline analyses indicates that the severe-bleeding result should be interpreted cautiously and may reflect limited statistical power (only 20 events in the primary analysis) rather than a true absence of association. For 24-month OS, all three approaches were concordant: categorical HR=1.811 (P=0.011), continuous HR per 10 × 10⁹/L higher platelet count = 0.887 (P<0.001), and RCS overall association P<0.001 (nonlinear P=0.069), indicating a robust, approximately linear relationship.

ROC Analysis. Ordinary ROC analysis was limited to binary, non-censored outcomes. The AUC was 0.518 (95% CI 0.458–0.579) for CR and 0.661 (95% CI 0.563–0.759) for severe bleeding using the primary endpoint (n=231, excluding patients with bleeding at diagnosis; **Figure 5**). No ordinary ROC curve was calculated for 24-month OS because survival is subject to censoring.

Discussion. In this cohort of 356 adults with newly diagnosed non-APL AML, baseline platelet count was not associated with induction CR or CR/CRi. A count <50 × 10⁹/L was associated with poorer OS through 24 months across multiple sensitivity analyses, but its association with severe bleeding was sensitive to endpoint definition and was not statistically significant after excluding patients with bleeding already present at diagnosis. Continuous, spline, and alternative-threshold analyses supported the survival association. The matched analysis retained residual covariate imbalance, and all results remain associational and hypothesis-generating.

No statistically significant differences were detected between groups in the CR rate (53.7% vs. 50.7%) or CR/CRi rate (63.3% vs. 68.8%), and multivariable logistic regression did not identify low baseline platelet status as an independent factor associated with CR (OR=1.254, P=0.346) or CR/CRi (OR=1.175, P=0.526). These null findings do not establish equivalence, but they provide no evidence that diagnostic thrombocytopenia alone should determine expectations of induction response. Zhang et al.[10] reported that a high diagnostic platelet count was associated with a lower CR rate. At the same time, another study of 633 patients[19] found that a high-platelet group had a higher proportion of leukemia stem cells and immunosuppressive factors. Together, these observations suggest that platelet count may reflect heterogeneous biological features rather than functioning as a direct determinant of remission. HMA+VEN was associated with a higher CR/CRi rate in the present model (OR=1.939, P=0.035), consistent in direction with VIALE-A;[20] however, treatment was not randomly assigned, so this estimate is susceptible to indication selection and should not be interpreted as a comparative treatment effect.

Severe bleeding occurred in 22.5% of the low-platelet group and 8.7% of the normal/high group in the full cohort. However, among the 61 severe-bleeding events, 41 occurred in patients who also had bleeding at diagnosis; because the CTCAE grade could not distinguish baseline from treatment-emergent events, the primary analysis excluded these 125 patients and found no independent association between low baseline platelet count and subsequent severe bleeding (Firth OR=1.761,

P=0.287). The full-cohort sensitivity analysis, which removed the baseline-bleeding covariate to avoid circularity, showed a significant association (OR=2.753, P=0.007). This discrepancy indicates that the bleeding association was sensitive to endpoint definition and may partially reflect inclusion of baseline-state bleeding rather than a treatment-emergent event. The bleeding findings should therefore not be interpreted as establishing a definitive relationship between diagnostic platelet count and subsequent induction bleeding. WBC and DIC also contributed to bleeding risk, emphasizing that platelet count should not be interpreted in isolation. This finding is compatible with previous evidence that baseline platelet count contributes to bleeding-risk stratification in AML.[5] Still, it highlights the methodological importance of distinguishing baseline from treatment-emergent events in retrospective bleeding analyses.

Low baseline platelet count was associated with lower 12- and 24-month OS and an adjusted 24-month HR of 1.811. The similar center-adjusted estimate (HR=1.896) supports robustness to measure between-center differences, but neither this adjustment nor the non-significant center interaction eliminates the possibility of unmeasured center-level confounding. Calendar-period estimates were directionally consistent but statistically non-significant and imprecise, especially in 2023–2025 and should be regarded as exploratory. These data do not establish that thrombocytopenia causes death or that early mortality mediates the platelet-OS association. A low count may instead be a concurrent marker of aggressive disease burden, marrow failure, coagulation abnormalities, infection, and treatment selection. Bleeding, treatment interruption, and delayed platelet recovery are clinically plausible contributors, but causal mediation cannot be inferred from this retrospective dataset. The 30- and 60-day mortality models contained few events and therefore provide only exploratory, imprecise estimates.

Subgroup point estimates were directionally consistent, but non-significant interaction tests do not prove equivalence across strata, and the subgroup findings should be considered descriptive. In 114 matched pairs, the 24-month OS estimate remained significant (HR=1.981). In contrast, the severe-bleeding association could not be reliably evaluated because the matched bleeding risk set differed from that used for matching and contained too few events to be informative. Age, WBC, Hb, bone marrow blasts, and the propensity score remained imbalanced after matching. Consequently, the PSM estimates remain susceptible to residual confounding and should not be considered confirmatory for either outcome.

The continuous analysis was retained because dichotomization discards information. Each 10 × 10⁹/L higher platelet count was associated with 16.8% lower adjusted odds of severe bleeding in the primary analysis and an 11.3% lower adjusted 24-month death hazard. Three-knot RCS analyses showed a non-significant overall association for severe bleeding and a significant, approximately linear association for 24-month OS. The severe-bleeding estimates at 40, 30, and 20 × 10⁹/L thresholds did not reach statistical significance in the primary analysis. These analyses reduce concern that the survival association is solely an artifact of the 50 × 10⁹/L split. Still, they do not identify a biologically definitive threshold or demonstrate incremental prediction beyond ELN risk classification.

This study has several limitations. First, its multi-center retrospective design limits external validity and permits residual confounding; treatment was not randomized, and patients receiving intensive induction and lower-intensity HMA+VEN differ in age, frailty, comorbidity, and disease features. Second, platelet transfusion thresholds, prophylactic versus therapeutic practice, refractoriness, and supportive-care policies were not captured uniformly and may have differed among centers or changed during the six-year study period. Adjustment for center cannot account for all unmeasured institutional differences. Calendar-period analyses contained only 18 deaths and 4 severe-bleeding events in 2023–2025, yielding wide confidence intervals; they were exploratory and cannot exclude temporal heterogeneity. Third, bleeding grades were reconstructed retrospectively from electronic records by two independent investigators; minor mucosal or cutaneous bleeding may not have been recorded, leading to underestimation and misclassification, and even severe events may be influenced by local transfusion and intervention practices. Assessors were not blinded to baseline platelet count. The bleeding observation window (diagnosis to end of induction) was defined clinically and applied during data abstraction; because bleeding events were recorded without separate event-level dates in the extracted dataset, automated date-based confirmation of window adherence was not possible. Fourth, the molecular testing panel was limited to FLT3-ITD, NPM1, CEBPA, and TP53, detected by PCR and Sanger sequencing (with a subset evaluated by next-generation sequencing). Myelodysplasia-related gene mutations required by ELN 2022 (ASXL1, BCOR, EZH2, RUNX1, SF3B1, SRSF2, STAG2, U2AF1, ZRSR2) were not systematically tested; a uniformly complete ELN 2022 molecular panel was not available. The use of ELN 2017 risk classification may therefore misclassify some patients with adverse-risk features as intermediate-risk, and the direction and magnitude of bias arising from this misclassification cannot be determined. Fifth, MRD status, post-remission consolidation intensity, allogeneic stem-cell transplantation, and treatments after relapse were not uniformly available; these are major determinants of OS,

so the 24-month OS estimates cannot fully isolate the association of baseline platelet count. Sixth, PSM left clinically relevant imbalance in age, WBC, Hb, bone marrow blasts, and the propensity score, so the matched analysis did not eliminate all between-group differences. Seventh, the full-follow-up Cox model violated the global proportional-hazards assumption and was treated as supplementary; although the 24-month primary model had a non-significant global PH test, bone marrow blast percentage showed a variable-specific departure, so proportional-hazard estimates warrant caution. Eighth, early-death analyses were underpowered, and the observational design cannot support mediation or other causal claims. Ninth, reasons for early discontinuation of follow-up were not consistently documented; therefore, informative censoring cannot be excluded. Finally, all primary-model variables were complete within their respective analysis populations, so missing-data bias from complete-case exclusion did not arise in those models; predefined zero coding was used for supportive-care variables, whereas genuinely unrecorded values were retained as missing. Prospective multicenter studies with standardized, independently adjudicated bleeding ascertainment, contemporary genomic profiling, and complete post-remission treatment data are needed.

Conclusions. a baseline platelet count <50 × 10⁹/L was associated with poorer 24-month OS but not with induction CR in newly diagnosed AML. The association with severe bleeding was not statistically significant after excluding patients with bleeding at diagnosis (Firth OR=1.761, P=0.287), although the continuous analysis (OR=0.832 per 10 × 10⁹/L higher, P=0.036) suggested a possible dose-response relationship that merits further assessment in larger cohorts. The OS association was directionally consistent across multivariable adjustment, propensity-score matching, and common-outcome censoring scenarios, and was directionally consistent in the intensive-induction subgroup. The divergence between bleeding and survival findings suggests that baseline thrombocytopenia may influence prognosis through pathways beyond hemorrhagic complications.

Ethics Approval and Consent to Participate. The study protocol was reviewed and approved by the institutional review boards / Medical Ethics Committees of all participating hospitals. Owing to the retrospective nature of this study, which involved only anonymized historical medical record data with no additional interventions imposed on patients, the requirement for written informed consent was waived in accordance with the ethical principles of the Declaration of Helsinki.

Consent for Publication. All authors consent to the publication of this manuscript. No identifiable personal information of participants is included in this article.

Authors' Contributions. Tao Zhou: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Writing – original draft, Writing – review & editing. Zengfeng Ni: Data curation, Methodology, Validation. Wenjing Fan, Jing Xu, Jing Qin, Kaiyue Wang, Rui Wang: Data curation, Investigation, Validation, Resources. Yaping Li: Conceptualization, Funding acquisition, Project administration, Supervision, Writing – review & editing. All authors meet the International Committee of Medical Journal Editors (ICMJE) authorship criteria: they made substantial contributions to the conception or design of the work, or the acquisition, analysis, or interpretation of data; drafted the work or revised it critically for important intellectual content; provided final approval of the version to be published; and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Data Availability Statement. The de-identified dataset generated and analyzed during the current study is available from the corresponding author (Yaping Li, email: Liyaping881018@126.com) upon reasonable request, subject to restrictions imposed by patient privacy protection regulations and the ethics approval of the study. The core analysis code used in this research can also be provided by the corresponding author on reasonable request.

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