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Real-world survival analysis of elderly patients with acute myeloid leukemia

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Abstract

Acute myeloid leukemia (AML) predominantly affects the elderly, who often have a poor prognosis due to age-related comorbidities, adverse genetic features, and limited tolerance to standard therapies. This study aimed to evaluate real-world survival outcomes and prognostic factors in elderly patients with AML to improve clinical management. A retrospective analysis was conducted on 179 elderly AML patients across multiple centers over 6 years. Clinical features, bone marrow characteristics, vital status, and prognostic factors were analyzed. Kaplan–Meier was used to estimate overall survival, while univariate and multivariate regression analyzes identified prognostic factors. The median overall survival (mOS) of the cohort was 5.3 months. Patients in the chemotherapy group (n = 126) showed better mOS than those in the support therapy group (n = 53) (7.567 vs. 3 months; p<0.0001). Among chemotherapy patients, those treated with hypomethylating agents (HMAs) (n = 54) had better mOS compared to cytotoxic chemotherapy (n = 72) (10.17 vs. 4.1 months; p<0.0001). Within the HMA group, no significant difference in mOS was found between HMA monotherapy (n = 9) and HMA plus venetoclax (VEN) (n = 45) (9.117 vs. 10.17 months; p=0.3407). In patients eligible for intensive chemotherapy, the HMA group had a superior mOS than the cytotoxic chemotherapy group (9.4 vs. 3.933 months; p<0.0001). The top five mutations identified were *NPM1 (*29.59%), *FT3*-internal tandem duplication (ITD) (26.53%), *DNMT3A* (25.51%), *IDH2 (*20.41%), and *CEBPA* (14.29%), with *DNMT3A-FLT3*-ITD, *NPM1-FLT3*-ITD, and *NPM1-DNMT3A* showing significantly higher co-mutation frequencies than the other combinations. In addition, infection was the most frequent complication (60%). Elderly AML patients have poor mOS and a high burden of adverse genetic features. Chemotherapy, especially HMAs alone or combined with VEN, is associated with improved survival and better clinical outcomes compared to supportive care or intensive regimens. These findings provide real-world evidence to inform treatment strategies.

Keywords: Elderly; Acute myeloid leukemia; Hypomethylating agents; Cytotoxic chemotherapy; Survival analysis; Prognostic factors

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1. Introduction

Acute myeloid leukemia (AML) is a malignant disorder of myeloid hematopoietic stem/progenitor cells, characterized by the abnormal proliferation of immature myeloid cells in the bone marrow and peripheral blood. It commonly affects the elderly with a peak incidence between 65 and 70 years of age.[1] Approximately 14,500 patients are diagnosed with AML in the United States annually, with the majority being over 60 years old and one-third being over 75.[2] The treatment efficacy of AML notably declines with age,[3] attributed to various adverse factors including high expression of *MDR1*, P-glycoprotein-mediated multidrug resistance, specific cytogenetic abnormalities, and the frequent comorbidities and complications associated with older patients.[4] Consequently, the therapy for elderly AML patients faces significant challenges.[5]

Hematopoietic stem cell transplantation (HSCT) is a pivotal method for treating AML, significantly improving disease-free survival rates in high- and intermediate-risk patients by leveraging the graft-versus-leukemia effect to enhance immunosurveillance against residual leukemia cells and reduce relapse risk.[6] However, not all AML patients are eligible for HSCT, particularly the elderly who face higher risks and complications. The complex HSCT procedure can lead to severe side effects including infections and organ dysfunction.[7] Although 40 – 60% of AML patients over 60 achieve complete remission with cytotoxic chemotherapy, 80 – 90% will eventually relapse.[8]

In recent years, the therapeutic landscape for elderly AML patients has been revolutionized by the combination of hypomethylating agents (HMAs) with the B-cell leukemia/lymphoma 2 inhibitor, venetoclax (VEN). The VIALE-A trial demonstrated that azacitidine (AZA) plus VEN significantly improved median overall survival (mOS) (14.7 vs. 9.6 months) and complete remission rates (66.4% vs. 28.3%) compared to AZA monotherapy in newly diagnosed elderly AML patients.[9] Subsequent real-world studies have corroborated these findings, showing that HMAs-VEN regimens achieve comparable efficacy in broader patient populations, including those with high-risk cytogenetic profiles.[10] The synergistic mechanism involves HMAs downregulating myeloid cell leukemia 1 expression while VEN selectively inhibits B-cell leukemia/lymphoma 2, collectively promoting apoptosis in leukemic cells.[11]

Extensive clinical evidence confirms that the HMAs-VEN combination not only overcomes drug resistance but also significantly improves survival outcomes in elderly AML patients who are ineligible for intensive chemotherapy.[12] For patients with poor health status, the primary treatment goal is to improve quality of life and extend lifespan. In this context, the HMAs-VEN combination has emerged as the preferred first-line regimen for unfit elderly AML patients, supported by Level 1 evidence from randomized controlled trials and real-world evidence.[13]

This study aims to conduct a multicenter retrospective study to delve into the overall survival (OS) of elderly AML patients in the real world, evaluate the most promising treatment strategies for elderly AML, and analyze risk factors that exacerbate poor prognoses in this patient population.

2. Materials and methods

2.1. Data source and ethics approval

In this study, we included 320 elderly AML patients aged ≥60 years from Tongji Hospital of Tongji Medical College of Huazhong University of Science and Technology and Shanxi Bethune Hospital from January 2018 to December 2024 as potential study subjects. With the inclusion and exclusion criteria, we finally identified 179 patients who were eligible for the study (Figure A1). This is a retrospective study using data from the Departments of Hematology of Tongji Hospital of Huazhong University of Science and Technology and Shanxi Bethune Hospital.

2.2. Study population

The eligibility criteria for the study were patients who: (i) met the diagnostic criteria for AML in the 2022 European Leukemia Network guidelines for diagnosis and treatment,[14] (ii) were diagnosed with AML at Tongji Hospital of Huazhong University of Science and Technology from January 2018 to July 2024, and (iii) were aged ≥60 years old. The exclusion criteria were as follows: (i) age <60 years, (ii) diagnosis of secondary AML, (iii) diagnosis of acute promyelocytic leukemia, (iv) co-existing malignant blood disorders, such as chronic lymphocytic leukemia or lymphoma, (v) co-existing malignant tumor diseases, such as liver cancer, lung cancer, or intestinal cancer, and (vi) presence of severe reactions caused by serious infections, such as systemic inflammatory response syndrome or sepsis. The cutoff date for follow-up was December 15, 2024.

2.3. Therapy group

The patients were divided into three groups based on the therapies: supportive therapy, cytotoxic drug chemotherapy, and HMA chemotherapy. The HMA chemotherapy group was further divided into the group receiving HMAs alone (nine cases) and the group receiving combination therapy with VEN (45 cases). The supportive therapy group included hydroxyurea monotherapy, component blood transfusions, and anti-infective therapy. Chemotherapy

groups for HMAs included decitabine alone, AZA alone, or in combination with VEN. Cytotoxic drug chemotherapy was administered for at least one cycle with idarubicin + cytarabine (IA), homosophocarpine + cytarabine (HA), daunorubicin + cytarabine (DA), or decitabine +homosophocarpine/aclarubicin, cytarabine, and G-CSF (DHAG/DCAG) regimen. Treatment selection was based on patient preference. Further details are provided in the Appendix. Eligibility for intensive therapy criteria was assessed using the Ferrara criteria,[15] and prognostic risk stratification was determined according to the European Leukemia Network 2022 guidelines.[16]

2.4. Statistical analysis

Baseline characteristics of patients were expressed as medians and ranges, and categorical data were presented as frequencies and percentages. Survival curves were plotted using the Kaplan–Meier method and compared between groups using the log-rank test. Univariate and multivariate survival analyses were performed using Cox proportional risk regression models to assess hazard ratios (HR) and 95% confidence intervals. Categorical data on complications were presented as pie charts, and gene co-mutation relationships were visualized using chord plots. Statistical analyses were conducted using the Statistical Package for the Social Sciences software (version 22.0) and R software (version 3.3.0).

3. Results

3.1. Characteristics of the study patients

As shown in Table 1, a total of 179 elderly AML patients were enrolled in this study. According to the French–American–British classification, they were divided into M0 – M7, with type M5 accounting for 40% (n = 72), type M2 for 30% (n = 54), type M4 for 20% (n = 36), and type M1 for 10% (n = 18), showing a distribution pattern of M5>M2>M4>M1. In addition, Table 1 presents the clinical characteristics of these 179 elderly AML patients, grouped by three treatment modalities: supportive therapy (n = 53), HMA therapy (n = 54), and cytotoxic chemotherapy (n = 72).

3.2. Adverse events of elderly AML patients after chemotherapy

In elderly AML patients, the adverse events of cytotoxic chemotherapy (n = 72) were compared with those of HMAs chemotherapy (n = 54). According to the Common Terminology Criteria for Adverse Events grading statistics, the incidence of adverse events was generally higher in the cytotoxic chemotherapy group. As shown in Table 2, the incidence of fever ≥Grade 3 reached 100.0% in the cytotoxic chemotherapy group and 68.5% in the HMA chemotherapy group. For neutropenia ≥Grade 3, the rates in the two groups were 100.0% and 81.4%, respectively. In terms of thrombocytopenia ≥Grade 3, anemia ≥Grade 3, nausea ≥Grade 2, alopecia ≥Grade 2, oral mucositis ≥Grade 3, diarrhea ≥Grade 3, and liver function impairment ≥Grade 3, the HMA chemotherapy group demonstrated a lower incidence of adverse events than the cytotoxic chemotherapy group. Evidently, in elderly AML patients, cytotoxic chemotherapy was associated with more extensive and severe than Grade 3 adverse events compared to HMAs chemotherapy.

3.3. Survival outcomes of elderly AML patients

The mOS for the entire cohort was 5.3 months (Figure 1A). Patients receiving chemotherapy exhibited a significantly improved mOS compared to those in the supportive therapy group (7.567 vs. 3 months; p<0.05; Figure 1B). In addition, the mOS was superior in the HMA group relative to the cytotoxic chemotherapy group (10.17 vs. 4.1 months; p<0.05; Figure 1C). Among patients fit for intensive chemotherapy, the HMAs group has better mOS than the cytotoxic chemotherapy group (9.4 vs. 3.933 months; p<0.05; Figure 1D). Moreover, patients with a white blood cell (WBC) count of <20×10^9/L had a higher mOS compared to those with a WBC count of 20×10^9/L or more (7.3 vs. 4.3 months; p<0.05; Figure 1E). In the HMA subgroup, there was no statistically significant difference between the two types of HMA therapies (9.117 vs. 10.17 months; p>0.05; Figure 2).

3.4. Univariate and multivariable regression analysis of elderly AML patients

We analyzed the effects of age, WBC count, blast cell percentage, therapies, and cytogenetics on the prognosis of elderly AML patients, and found that high WBC count was associated with an increased risk of survival, which was statistically significant in univariate analyses (HR=1.50, p=0.029) but did not reach statistical significance in multivariate analyses (HR=1.41, p=0.062) (Table 3). The HRs for HMAs and cytotoxic drug chemotherapy were significantly lower than 1 (HR=0.28, p<0.001) and (HR=0.52, p=0.007), respectively, indicating that both therapies resulted in a statistically significant reduction in the risk of survival. However, HMA chemotherapy was associated with a reduced survival risk among elderly AML patients, suggesting improved survival and prognosis.

4. Discussion

AML is a hematological malignancy resulting from the malignant cloning of hematopoietic stem progenitor cells. The hallmark of AML is the uncontrolled

Table 1. Baseline table of characteristics of elderly acute myeloid leukemia patients

Characteristics	Supportive therapy (n = 53)	Hypomethylating agents (n = 54)	Cytotoxic chemotherapy (n = 72)	p-value
Median age (years, range)	68 (60 – 88)	68 (60 – 82)	65 (60 – 86)	0.0871
≥75 years old	11 (20.7)	5 (9.2)	8 (11.1)	0.1771
Sex (female/male)	17/36	20/24	35/37	0.1648
Median white blood cell count (1×10^9/L, range)	9.03 (0.1 – 213.34)	4.10 (0.38 – 158.69)	5.85 (0.20 – 198.47)	0.3271
≥20×10^9/L	20 (37.7)	14 (25.9)	26 (36.1)	0.361
Median hemoglobin count (g/L, range)	75 (39 – 108)	71 (36 – 139)	66 (39 – 133)	0.7429
<60 g/L	15 (28.3)	9 (16.7)	22 (30.6)	0.184
Median platelet count (1×10^9/L, range)	38 (5 – 505)	47 (6 – 388)	33 (1 – 265)	0.5240
<20×10^9	15 (28.3)	12 (22.2)	13 (18.1)	0.397
Median albumin count (g/L, range)	36.2 (19.6 – 47.4)	35 (21.6 – 45.4)	35.4 (22.6 – 48.7)	0.3838
<35 g/L	7 (13.2)	5 (9.3)	9 (12.5)	0.79
Median blast cell percentage (%, range)	45 (7 – 97)	46.5 (1 – 93.5)	48 (5 – 96)	0.2565
Gene abnormality				
NPM1	5 (9.4)	9 (16.7)	15 (20.8)	0.6312
TP53	1 (1.9)	4 (7.4)	1 (1.4)	0.3044
FLT3-internal tandem duplications	7 (13.2)	7 (13.0)	12 (16.7)	0.5339
DNMT3A	3 (5.7)	8 (14.8)	14 (19.4)	0.2851
ASXL1	3 (5.7)	2 (3.7)	3 (4.2)	0.5095
CEBPA	3 (5.7)	6 (11.1)	5 (6.9)	0.8213
IDH2	5 (9.4)	10 (18.5)	5 (6.9)	0.1895
Chromosome abnormality	41 (77.4)	30 (55.6)	44 (61.1)	0.2273
Myelofibrosis	17 (32.1)	21 (38.9)	16 (22.2)	0.1218
Myelodysplasia	8 (15.1)	9 (16.7)	13 (18.1)	0.9672
Prognostic grade				
High	17 (32.1)	20 (37.0)	28 (38.9)	0.7402
Moderate	33 (62.3)	34 (63.0)	37 (51.4)	0.3431
Low	3 (5.7)	0 (0.0)	7 (9.7)	0.0285
Fit for intense chemotherapy	0 (0.00)	29 (53.7)	52 (72.2)	0.0625
Complication				
Infections	26 (49)	28 (51.8)	38 (52.9)	0.9277
Organ failure	0 (0)	23 (42.7)	22 (30.5)	<0.0001
Infections combined with organ failure	25 (47.3)	1 (1.8)	9 (12.5)	<0.0001
None	2 (3.7)	2 (3.7)	3 (4.1)	0.9988

Note: Data are presented as n (%), unless stated otherwise.

proliferation of WBC and impaired cell differentiation, a condition particularly prevalent among the elderly. Elderly patients often exhibit reduced physical function, making them more susceptible to chemotherapy resistance and adverse reactions. In addition, many elderly patients have comorbid systemic organ lesions; consequently, the OS of elderly AML patients is notably poor. These findings underscore the urgent need for targeted therapies and personalized treatment strategies to improve outcomes and enhance quality of life for this vulnerable population.

A study conducted in Sweden indicated that elderly AML patients who underwent chemotherapy achieved better efficacy compared to those receiving support therapy, with a higher proportion of patients attaining complete remission.[17] The results of our survival analysis (Table 4) showed that patients in the chemotherapy group had better OS than the supportive therapy group.

Table 2. Adverse events after chemotherapy of elderly acute myeloid leukemia patients

Common terminology criteria for adverse events	Cytotoxic chemotherapy (n = 72)	Hypomethylating agent chemotherapy (n = 54)	p-value
Fever (≥Grade 3)	72 (100.0)	37 (68.5)	<0.0001
Neutropenia (≥Grade 3)	72 (100.0)	44 (81.4)	0.0001
Thrombocytopenia (≥Grade 3)	55 (76.3)	20 (37.0)	<0.0001
Anemia (≥Grade 3)	50 (60.4)	15 (27.7)	<0.0001
Nausea (≥Grade 2)	55 (76.3)	8 (14.8)	<0.0001
Alopecia (≥Grade 2)	68 (94.4)	9 (16.6)	<0.0001
Oral mucositis (≥Grade 3)	35 (48.6)	8 (14.8)	<0.0001
Diarrhea (≥Grade 3)	18 (25.0)	5 (9.2)	0.0346
Liver function impairment (≥Grade 3)	15 (20.8)	6 (11.1)	0.2266

Note: Data are presented as n (%), unless stated otherwise.

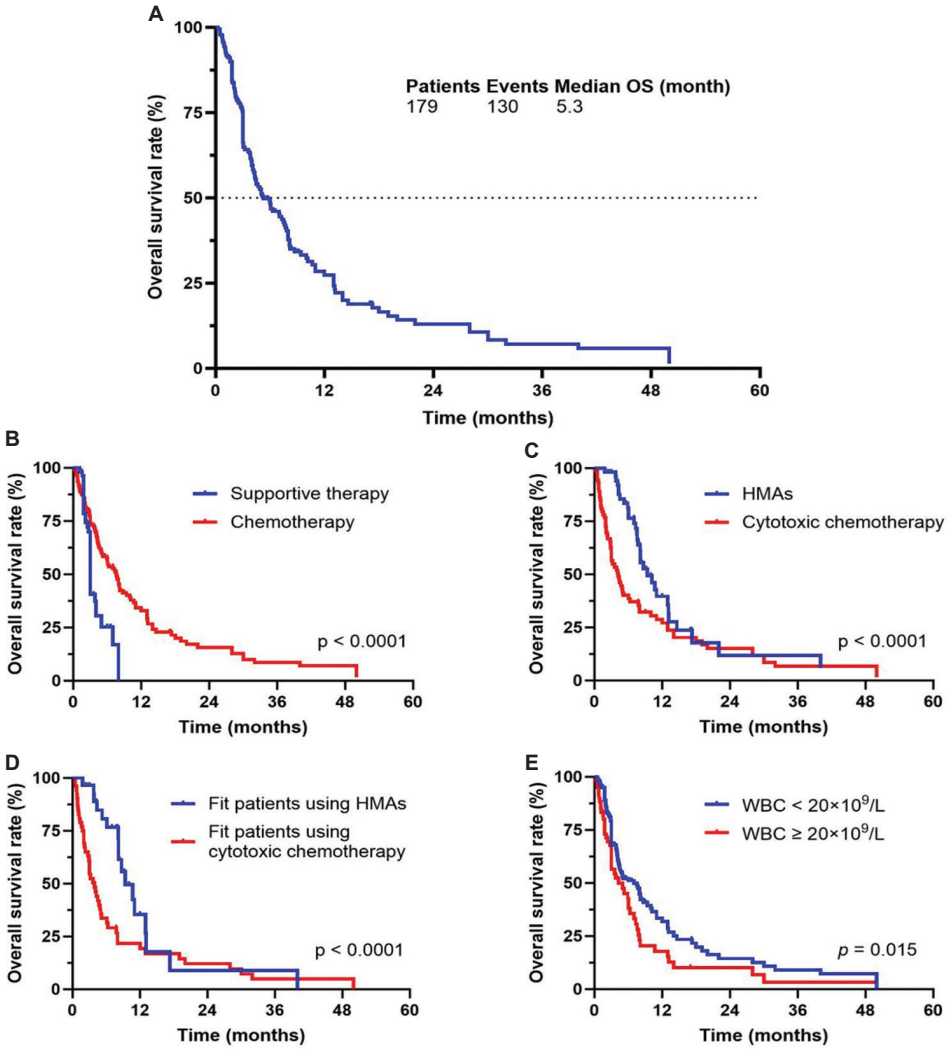


Figure 1. Kaplan–Meier curve analysis. Kaplan–Meier curves for (A) OS of the entire cohort, (B) survival in elderly AML patients receiving supportive therapy versus chemotherapy, (C) survival in elderly AML patients receiving HMAs versus cytotoxic drugs, (D) different therapies selected for patients fit for intense chemotherapy, and (E) WBC count <20×10^9/L group and WBC ≥ 20×10^9/L group.
Abbreviations: AML: Acute myeloid leukemia; OS: Overall survival; HMA: Hypomethylating agent; WBC: White blood cell.

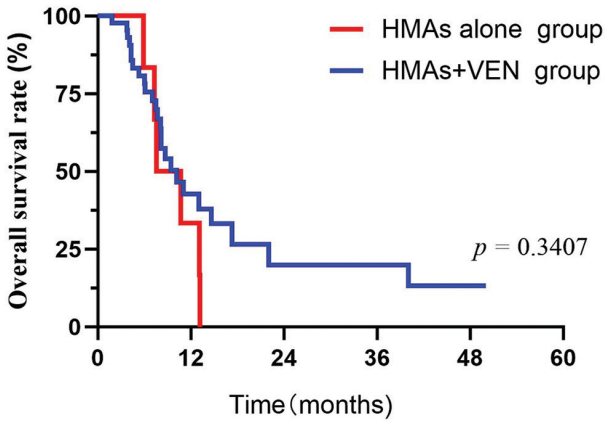


Figure 2. Kaplan–Meier curve of hypomethylating agents (HMAs) chemotherapy subgroups.
Abbreviation: VEN: Venetoclax.

While supportive therapy effectively alleviates symptoms and enhances patient comfort, it primarily focuses on symptom management and may fail to adequately address serious complications such as infections, bleeding, and organ failure. If these complications are not managed appropriately, they can lead to faster disease progression and accelerated mortality.

Recent comparative studies have further established the superiority of HMAs over conventional chemotherapy in elderly AML patients. The phase III QUAZAR AML-001 trial demonstrated that oral AZA maintenance therapy significantly improved mOS compared to placebo (24.7 vs. 14.8 months) in remission patients, with a favorable safety profile.[18] A 2023 multinational retrospective study analyzing 2,145 untreated elderly AML patients (age ≥75 years) found that frontline HMAs-based regimens

Table 3. Univariate or multivariate analysis of factors affecting prognosis

Risk factors	Univariate Cox regression			Multivariate Cox regression		
	HR	95% CI	*p*-value	HR	95% CI	*p*-value
Age ≥75 years old	0.65	0.38 – 1.11	0.137			
White blood cell count ≥20×10^9/L	1.50	1.04 – 2.15	0.029	1.41	0.98 – 2.03	0.062
Hemoglobin count ≥60g/L	1.14	0.77 – 1.70	0.509			
Platelet count ≥20×10^9/L	0.90	0.60 – 1.36	0.617			
Albumin count ≥35g/L	0.91	0.53 – 1.57	0.729			
Blast cell percentage ≥50%	1.05	0.74 – 1.49	0.785			
Gene abnormality						
NPM1	1.07	0.65 – 1.76	0.803			
FLT3-internal tandem duplications	1.47	0.88 – 2.47	0.143			
DNMT3A	1.11	0.66 – 1.85	0.701			
CEBPA	1.25	0.65 – 2.38	0.503			
IDH2	0.89	0.50 – 1.59	0.693			
TP53	1.28	0.51 – 3.19	0.603			
ASXL1	1.13	0.49 – 2.62	0.773			
Chromosome abnormality	1.12	0.77 – 1.64	0.542			
Myelofibrosis	0.75	0.51 – 1.10	0.137			
Myelodysplasia	0.98	0.63 – 1.51	0.923			
Prognostic grade						
High						
Moderate	1.30	0.90 – 1.88	0.163			
Low	0.71	0.31 – 0.62	0.417			
Fit for intense chemotherapy	1.50	0.98 – 2.30	0.063			
Therapy						
Supportive therapy						
HMAs	0.28	0.17 – 0.48	< 0.001	0.29	0.17 – 0.49	< 0.001
Cytotoxic chemotherapy	0.52	0.32 – 0.83	0.007	0.52	0.32 – 0.84	0.007

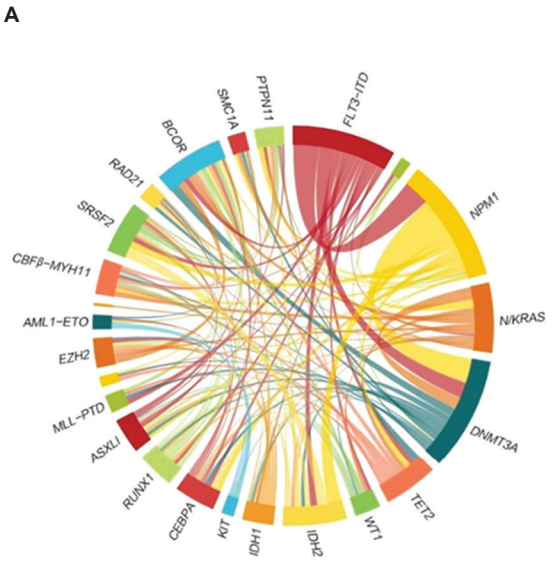
Abbreviations: CI: Confidence interval; HMA: Hypomethylating agent; HR: Hazard ratio.

Table 4. Survival analysis table for acute myeloid leukemia in the elderly

Characteristics	Number	Median overall survival (months)	*p*-value
Age ≥75 years old	24	7.8	0.1423
White blood cell count ≥20×10^9/L	60	4.3	0.015
Albumin count <35g/L	84	5.3	0.9902
Blast cell percentage ≥50%	87	6.3	0.8059
Gene abnormality			
NPM1	29	7.3	0.8371
FLT3-internal tandem duplications	26	6.1	0.1584
DNMT3A	25	8.1	0.7966
CEBPA	14	7.6	0.4957
IDH2	20	8.2	0.6954
TP53	6	7.3	0.5587
ASXL1	8	11.0	0.7822
French–American–British classification			
M1	18	4.5	0.3968
M2	53	7.7	
M4	36	5.0	
M5	72	4.4	
Chromosome abnormality	115	5.0	0.4448
Myelofibrosis	54	7.0	0.1277
Myelodysplasia	30	8.0	0.7899
Prognostic grade			
High	65	8.1	0.109
Moderate	104	4.4	
Low	10	4.0	
Type of therapy			
Chemotherapy	126	7.6	<0.0001
Supportive therapy	53	3.0	
Type of chemotherapy			
Hypomethylating agents (HMAs)	54	10.2	<0.0001
Cytotoxic chemotherapy	72	4.1	
Type of HMA			
Alone	9	9.2	
Combined with venetoclax	45	10.2	0.3407
Unfit for intense chemotherapy			
Cytotoxic chemotherapy/HMAs	21/24	10.0/7.7	0.683
Fit for intense chemotherapy			
Cytotoxic chemotherapy/HMAs	52/29	3.9/9.4	<0.0001

achieved longer mOS than intensive chemotherapy (9.2 vs. 5.6 months), with fewer severe adverse events.[19] Our real-world study showed that, compared with cytotoxic chemotherapy, HMA chemotherapy led to better OS, potentially due to the higher incidence of adverse events in cytotoxic chemotherapy.

The phase III clinical trial conducted by DiNard *et al.*[20] showed that, for AML patients who are ineligible for intensive chemotherapy, the combination of AZA and VEN significantly improved outcomes compared to AZA monotherapy. The mOS increased from 9.6 months to 14.7 months, and the complete remission rate surged



Gene	Mutation frequency(%)
NPM1	29.59%
FLT3-ITD	26.53%
DNMT3A	25.51%
IDH2	20.41%
CEBPA	14.29%
NKRAS	12.24%
TET2	12.24%
SRSF2	11.22%
BCOR	10.20%
RUNX1	9.18%
ASXL1	8.16%
MLL-PTD	6.12%
TP53	6.12%
WT1	5.10%
EZH2	5.10%
IDH1	4.08%
KIT	4.08%
RAD21	4.08%
PTPN11	4.08%
FLT3-TKD	3.06%
AML1-ETO	2.04%
CBFß-MYH11	2.04%
SMC1A	2.04%
MLL-AF6	1.02%

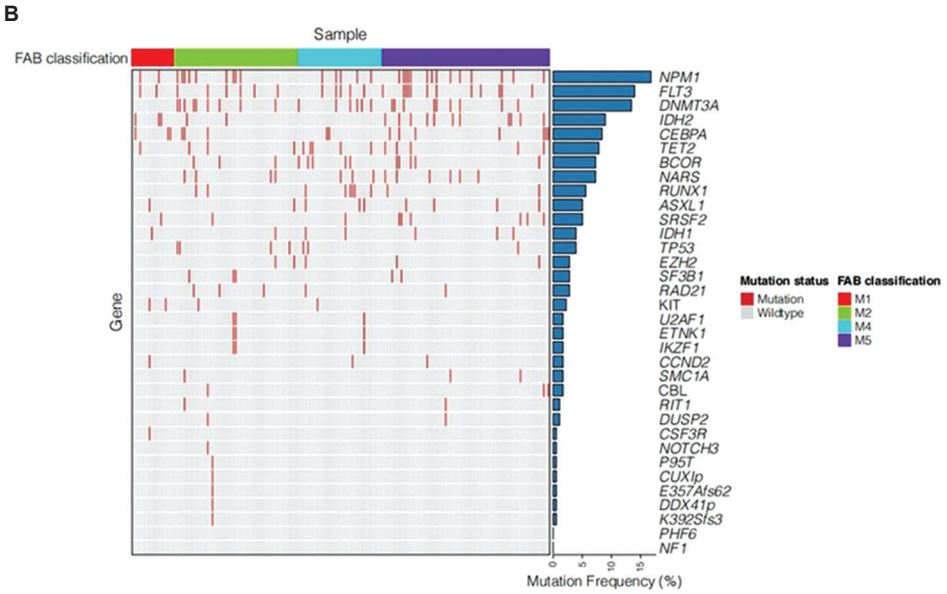


Figure 3. Mutational complexity of acute myeloid leukemia in the elderly. (A) A Circos diagram depicts the relative frequency and pairwise co-occurrence of mutations in patients with 179 cases of acute myeloid leukemia in the elderly. The length of the arc corresponds to the frequency of mutations in the first gene, and the width of the ribbon corresponds to the percentage of patients who also had a mutation in the second gene. Pairwise co-occurrence of mutations is denoted only once, beginning with the first gene in the clockwise direction. (B) Gene mutation status according to French–American–British (FAB) classification.

from 28.3% to 66.4%.[20] The results of the phase Ib/II study conducted by Wei *et al.*[12] showed that the treatment regimen of decitabine combined with VEN in treating AML achieved a complete remission rate of 54%. Compared with the conventional control, the complete remission rate of decitabine monotherapy was only 20 – 30%, further emphasizing the significant advantage of the combination regimen.[12] In our real-world study, the OS of patients treated with HMAs and VEN was significantly shorter than previously reported studies. In real-world settings, persistent low blood cell counts and various complications in patients significantly restricted the duration of VEN. Through further analysis, we found that 20 patients received VEN treatment for only 28 days, while 25 patients received it for merely 14 days. Such an insufficient treatment duration of VEN ultimately may lead to poor treatment outcomes.

The studies conducted by Greenwood *et al.*[21] and Bocchia *et al.*[22] suggest that a higher WBC count at initial diagnosis is associated with a poor prognosis. An excessive increase in WBC count levels at diagnosis can lead to systemic bone pain and WBC stasis. These, in turn, raise blood viscosity, which can potentially cause tissue embolism, impair blood supply, and result in tissue hypoxia, affecting the function of vital organs.[23] In this study, WBC count was categorized into two groups: WBC<20×10^9/L and WBC≥20×10^9/L. The results showed that the mOS was better in the WBC<20×10^9/L group than in the WBC≥20×10^9/L group. Further univariate analyses confirmed that an initially high WBC count was strongly associated with poor prognosis in elderly AML patients.

Previous studies have demonstrated that cytogenetics serves as an independent risk factor for guiding the treatment of elderly patients with AML.[24] Research has also confirmed that both chromosomal karyotype and gene mutation types are critical factors influencing the prognosis of AML patients.[25] However, neither chromosomal karyotype nor prognostic stratification reflected prognostic correlations in this study.[26] This may be related to sample differences. Elderly AML patients may have significant differences in biological characteristics and disease progression than younger patients, resulting in an insignificant predictive role of karyotypic abnormalities and prognostic stratification in older patients. Elderly patients often have multiple concomitant chronic conditions, and these comorbid conditions may have a greater impact on prognosis, masking the role of karyotypic abnormalities and prognostic stratification. Moreover, the choice of therapies may also influence this discrepancy.

The influence of gene mutations on the prognosis of AML patients is complex and multifaceted. Molecular genetics posits that mutations in genes such as *FLT3*-internal tandem duplication (ITD), *TP53*, *RUNX1*, and *ASXL1*, along with high expression of *FLT3*-ITD in *NPM1* wild-type, are indicative of a poor prognosis.[27] In the present study, we observed that the co-mutation frequencies of *DNMT3A-FLT3*-ITD, *NPM1-FLT3*-ITD, and *NPM1-DNMT3A* were significantly higher than the other combinations (Figure 3), suggesting that there may be an important biological association between these genes.[28] DNA methyltransferase 3 alpha is an enzyme involved in DNA methylation, whereas *NPM1* is involved in the assembly and translocation of ribosomes. Mutations in *FLT3*-ITD activate the FMS-like receptor tyrosine kinase-3 receptor signaling, leading to enhanced cell proliferation and survival. Mutations in *DNMT3A* and *NPM1* may further enhance the effects of *FLT3*-ITD mutations by affecting DNA methylation patterns and normal protein trafficking, thereby promoting tumor development. Research has shown that AML patients with *DNMT3A* and *FLT3*-ITD mutations face a higher risk of recurrence and exhibit significantly reduced OS rates.[26] Recent data suggest that *FLT3*-ITD gene mutations are regarded as one of the independent adverse prognostic factors for AML patients.[29] In addition, our analysis revealed that co-mutations in *DNMT3A-FLT3*-ITD and *NPM1-FLT3*-ITD were significantly associated with poorer prognosis,[30] suggesting that the combination of these mutations may be an important biomarker for evaluating patient prognosis.[31]

Comorbidities are prevalent among elderly AML patients. Our study identified infection as the most common comorbidity in this population (Figure 4). This is primarily attributed to chemotherapy-related side effects, which significantly compromise the patients' immune status and increase their risk of infection. In addition, organ failure emerged as another common comorbidity. The incidence of organ failure in the HMA and cytotoxic chemotherapy groups was significantly higher than that in the supportive therapy group (Table 1), which may be due to the mechanism of action of the drugs. HMA and cytotoxic chemotherapies may affect bone marrow hematopoiesis. Their long-term use may lead to immunosuppression and increase the risk of organ failure. In addition, cytotoxic chemotherapy causes damage to normal cells by directly killing the growth of cancer cells, especially rapidly dividing cells, increasing the risk of organ failure. The incidence of infections combined with organ failure was significantly higher in the supportive therapy group than in the other two groups. This could be attributed to a combination of factors such as poorer baseline condition of the patients, immunosuppressive status, lack of effective anticancer therapy, poor nutritional and physical status, and inadequate quality and timeliness of supportive therapies.

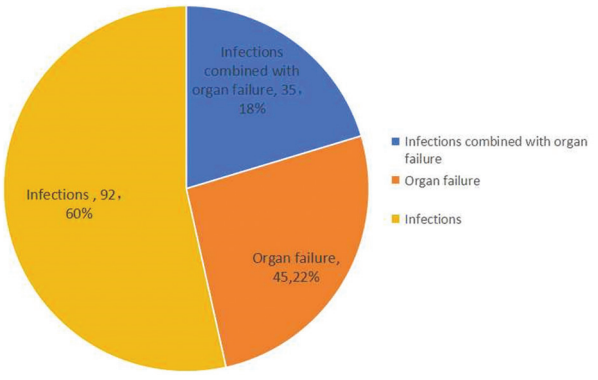


Figure 4. Proportional distribution of comorbidities. Comorbidities of 172 patients were mainly divided into three categories: Infection, organ failure, and infection combined with organ failure. A total of 92 patients had infections only, which accounted for 60% of the total, while 45 patients had organ failure only, which accounted for 22%. The number of patients with infections combined with organ failures was 35, which accounted for 18% of the total.

5. Conclusion

The elderly AML patients had extremely poor mOS and a significantly higher incidence of aberrant cytogenetic profiles and mutations. Univariate and multifactorial analyses showed that chemotherapy, especially HMAs alone or in combination with VEN, can better improve patient survival and prognosis. *DNMT3A-FLT3*-ITD, *NPM1-FLT3*-ITD, and *NPM1-DNMT3A* were significantly associated with poorer prognosis, suggesting that the combination of these mutations may be an important biomarker for evaluating patient prognosis.

Acknowledgments

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Conflict of interest

Jia Wei is an Associate Editor of this journal, but was not in any way involved in the editorial and peer-review process conducted for this paper, directly or indirectly. Separately, other authors declared that they have no known competing financial interests or personal relationships that could have influenced the work reported in this paper.

Author contributions

Conceptualization: All authors
Investigation: All authors
Methodology: All authors
Writing – original draft: Yuanyuan Wang, Shaoli Zhang
Writing – review & editing: All authors

Ethics approval and consent to participate

The retrospective study involving human participants was reviewed and approved by the Medical Ethics Committee of Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, and Shanxi Bethune Hospital (Ethical approval: TJ-IRB202412027 and YXLL-2025-142). Participants provided informed consent to participate in this study. All procedures involving human participants were in accordance with ethical standards and relevant regulations.

Consent for publication

The study subjects gave consent to publish their data in this study.

Availability of data

Data used in this work are available from the corresponding author on reasonable request.

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Appendix

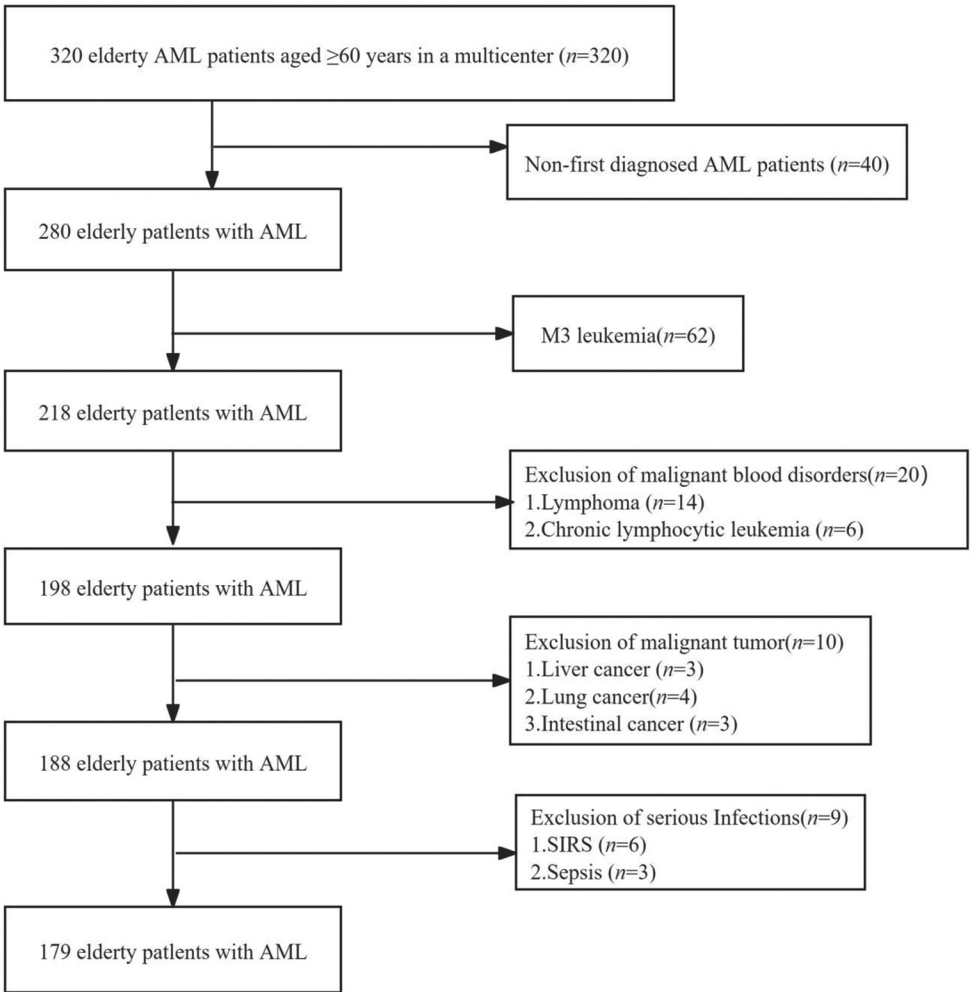

Figure A1. Flow diagram of the screening process of 320 elderly (≥60 years old) AML patients in a multicenter study. After sequentially excluding patients with non-initial diagnoses, acute promyelocytic leukemia (M3), other malignant hematologic disorders, malignant tumors, and serious infections, a total of 179 patients were included in the final analysis.
Abbreviations: AML: Acute myeloid leukemia; SIRS: Systemic inflammatory response syndrome.

1. Supportive therapy group
   (i) Hydroxyurea: When a white blood cell (WBC) count was higher than 10×10^9/L, 0.5 g of hydroxyurea was used twice or thrice daily to reduce a WBC count to a normal level (4.5×10^9/L – 10×10^9/L).
   (ii) Component transfusion: When hemoglobin<60 g/L, de-whitened suspended erythrocytes were transfused, and when a platelet count was $<20\times10^9$, platelets were transfused.
   (iii) Granulocyte-colony stimulating factor (G-CSF): When the neutrophil count was $<0.5\times10^9$/L, 200 μg/m^2 of G-CSF was given subcutaneously.
   (iv) Anti-infective medication: Pathogenetic and drug sensitivity tests and appropriate imaging were performed in case of infection and fever, and broad-spectrum antibiotics were promptly administered.
2. Cytotoxic chemotherapy group
   (i) IA regimen: Idarubicin 8 – 12 mg/m^2×D1 – 3 + cytarabine 100 mg/m^2×D1 – 7
   (ii) DA regimen: Daunorubicin 45 – 60 mg/m^2×D1 – 3 + cytarabine 100 mg/m^2×D1 – 7
   (iii) HA regimen: Homosophocarpine 2.5 mg/m^2×D1 – 7 + cytarabine 100 mg/m^2×D1 – 7
   (iv) DHAG regimen: Decitabine 20 mg/m^2×D1 – 5, homosophocarpine 1 mg/m^2×D5 – 7 + cytarabine 20 mg/m^2×D1 – 14 + G-CSF 200~400 ug×D1 – 14
   (v) DCAG regimen: Decitabine 20 mg/m^2×D1 – 5, aclarubicin 10 mg/m^2×D5 – 7 + cytarabine 10 mg/m^2×D1 – 14 + G-CSF 200~400 ug×D1 – 14
3. Hypomethylating agent groups
   (i) Azacitidine (AZA) or decitabine (DEC) alone: AZA 75 mg/m^2×D1 – 7 or DEC 20 mg/m^2×D1 – 5
   (ii) DEC combined with venetoclax (VEN) group: DEC 20 mg/m^2×D1 – 5 + VEN (100 mg×D1, 200 mg×D2, and 400 mg×D3 – 14 or – 28)
   (iii) AZA combined with VEN group: AZA 75 mg/m^2×D1 – 7 + VEN (100 mg×D1, 200 mg×D2, and 400 mg×D3 – 14 or – 28)