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blood neoplasia

Validation of ELN 2024 genetic classification in patients with AML treated with HMA-based regimens: PETHEMA registry study

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Data are available from the PETHEMA AML group coordinator, Pau Montesinos (montesinos_pau@gva.es), on request.

The full-text version of this article contains a data supplement.

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Key Points

- ELN 2024 stratifies patients with less-intensive AML, and its prognostic accuracy may improve if cytogenetic data are incorporated.
- Its predictive performance is markedly diminished in patients with secondary myeloid neoplasms.

The 2024 European LeukemiaNet (ELN 2024) genetic risk classification was proposed to assess prognosis in patients with acute myeloid leukemia (AML) receiving less-intensive hypomethylating agent (HMA)–based regimens. However, its applicability to real-world patients remains unclear. We retrospectively analyzed 669 adult patients with AML from the PETHEMA registry treated in routine practice with HMA monotherapy (n = 414) or HMA-venetoclax (VEN) (n = 255). Molecular profiling was performed centrally among the Programa Español de Tratamientos en Hematología (PETHEMA) laboratory network. Median age was 75 years, and 48% had secondary AML (s-AML). Across the full cohort, ELN 2024 stratified patients into prognostic groups across both regimens, but overall survival (OS) was consistently shorter with HMA monotherapy than with HMA-VEN (median OS, 6.5 vs 11.2 months). Favorable risk patients treated with HMA-VEN achieved a median OS exceeding 18.4 months, whereas adverse risk patients had an OS of 7.7 months. ELN 2024 provides meaningful stratification in nonintensive AML, especially with HMA-VEN. However, prognostic accuracy is limited in HMA monotherapy and s-AML, particularly those arising from a myeloid neoplasm (sM-AML). Incorporating cytogenetic risk and sM-AML as adverse risk improved discrimination (area under the curve at 24 months, 0.71 vs 0.76). Refinement incorporating clinical history, cytogenetics, emerging mutations, and treatment response is needed to improve risk prediction in real-world populations.

Introduction

Acute myeloid leukemia (AML) is an aggressive hematologic malignancy with increasing incidence in older adults. Despite recent advances in the understanding of AML, outcomes remain suboptimal in older patients due to age-related comorbidities, poor tolerance to intensive chemotherapy, and adverse disease biology.[1]

Historically, therapeutic options for older patients were limited, with many receiving only supportive care or low-intensity regimens with marginal benefits. However, advances in drug development have not only led to improved survival in this population[2] but also exposed important limitations in traditional risk stratification systems. The European LeukemiaNet (ELN) stratification has been mainly developed and validated in patients treated with intensive chemotherapy, predominantly younger patients, and may not accurately reflect outcomes in older or unfit individuals, particularly those treated with low-intensity regimens.[3]

Emerging molecular data from clinical trials involving hypomethylating agent (HMA)-based regimens, either alone or in combination with the BCL-2 inhibitor venetoclax (HMA-VEN) or the IDH1 inhibitor ivosidenib (IVO), have revealed a distinct genetic landscape.[4] Notably, *DDX41* mutations have been associated with particularly favorable outcomes in patients receiving HMA or HMA-VEN combinations.[5] Similarly, *NPM1* and *IDH1/2* mutations have been linked to enhanced sensitivity to HMA-VEN.[6] Conversely, mutations affecting *TP53* and the RAS signaling pathway, such as *NRAS* and *KRAS*, are consistently associated with primary resistance to VEN-based regimens and inferior survival.[7]

Therefore, several groups have attempted to develop specific risk stratification systems for patients receiving less-intensive treatments.[8] The 2024 ELN risk classification (ELN 2024) is applicable to patients receiving HMA-based regimens alone or combined either with VEN or azacitidine (AZA) plus IVO for *IDH1*-mutated patients. Favorable-risk includes mutations in *NPM1*, *IDH1*, *IDH2*, and *DDX41*. Intermediate-risk encompasses patients with *FLT3*-ITD, *NRAS*, or *KRAS* mutations. Adverse-risk is defined by *TP53* mutations. This stratification correlates with overall survival (OS) outcomes, with favorable-risk patients experiencing median survival exceeding 24 months, whereas those in the adverse-risk category have a median survival of 5 to 8 months.[8]

Although the ELN 2024 classification represents the first formal attempt to provide a molecular risk stratification tailored to unfit patients with AML, the following key questions remain unresolved regarding its broader clinical applicability: (1) due to the predominant reliance on retrospective cohorts treated with HMA-VEN, applicability to patients treated with HMA monotherapy has not yet been established; (2) it remains unclear whether the current ELN 2024 risk categories can reliably predict outcomes in patients with secondary AML or those previously treated with HMAs; and (3) the prognostic impact of some genetic alterations has not been completely established and are tentatively categorized depending on the absence or presence of activating signaling mutations in a heterogeneous intermediate group.

Therefore, further validation in real-world settings is needed to confirm and refine this classification. In this paper, we analyze real-world data from patients receiving HMA-based regimens from the PETHEMA registry to validate the ELN 2024 risk stratification.

Patients and methods

Patients and inclusion criteria

The study included 669 adult (aged >18 years) patients with AML treated with HMA-based regimens, enrolled from October 2014 to February 2025 in the Programa Español de Tratamientos en

Hematología (PETHEMA) epidemiologic registry. Patients with prior HMA exposure and those with secondary AML arising from a myeloid neoplasm (sM-AML) or therapy-related AML (t-AML) were also included. The institutional ethics committee for clinical research of each institution approved this study. Written informed consent was obtained from all patients in accordance with the recommendations of the Declaration of Human Rights, Conference of Helsinki, and institutional regulations.

Molecular analysis

Molecular analyses were conducted using a standardized next-generation sequencing (NGS) panel by the PETHEMA group and implemented across 7 certified central laboratories.[9] The panel included, at least, the following key myeloid genes: *ASXL1*, *BCOR*, *BRAF*, *CALR*, *CBL*, *CEBPA*, *CSF3R*, *DNMT3A*, *ETV6*, *EZH2*, *FLT3*, *GATA2*, *HRAS*, *IDH1*, *IDH2*, *JAK2*, *KIT*, *KRAS*, *MPL*, *NPM1*, *NRAS*, *PTPN11*, *RUNX1*, *SETBP1*, *SF3B1*, *SRSF2*, *STAG2*, *TET2*, *TP53*, *U2AF1*, *WT1*, and *ZRSR2*. Sequencing quality metrics required a minimum uniformity of >85% and a mean read depth of ≥1000×.[9] Cytogenetic analyses were performed locally at each participating center.

Treatment

Treatment data from patients diagnosed with AML who received HMA-based regimens as frontline therapy were obtained from the PETHEMA registry. Patients were treated with either HMA monotherapy (389 with AZA and 25 with decitabine) or in combination with VEN (241 with AZA-VEN and 14 with decitabine-VEN), according to institutional protocols and physician discretion.

End points and statistics

Cytogenetic risk was stratified according to the Medical Research Council classification.[10] AML with myelodysplasia-related changes is defined in the World Health Organization (WHO) and International Consensus Classification (ICC) classifications by the presence of specific myelodysplasia-related (MR) gene mutations and/or cytogenetic abnormalities. MR-molecular mutations include *ASXL1*, *BCOR, RUNX1*, *SETBP1*, *SRSF2*, *STAG2*, *U2AF1*, and *ZRSR2*. MR-cytogenetics alterations include complex karyotype, −7 or del(7q), −5 or del(5q), i(17q) or t(17p), −13 or del(13q), del(11q), del(12p) or t(12p), idic(X)(q13), del 20q, and +8. Complete remission (CR) required the absence of extramedullary disease, <5% blast cells in the bone marrow, and absence of blasts in the peripheral blood, along with neutrophil and platelet counts of $\geq 1 \times 10^9$/L and $\geq 100 \times 10^9$/L, respectively. CR with incomplete hematologic recovery (CRi) was defined as the fulfillment of all morphologic CR criteria with incomplete recovery of either neutrophils or platelets.[11] Relapse was defined as the reappearance of ≥5% blast cells in the bone marrow or peripheral blood or documented extramedullary AML after achieving CR/CRi. OS time was measured from diagnosis to death. Patients were censored at the last follow-up date at which they were known to be alive. Disease-free survival (DFS) was defined as the time from the date of first CR/CRi to the earliest evidence of confirmed morphologic relapse or death. Cumulative incidence of relapse (CIR) was calculated from the date of first CR/CRi to the date of documented morphologic relapse. Death without prior relapse was considered a competing event.

The χ^2 or Fisher exact test was used to compare categorical variables, as appropriate, whereas continuous variables were analyzed using the Student *t* test or the Mann-Whitney *U* test depending on distributional assumptions. Survival outcomes were estimated using the Kaplan-Meier method and compared using a log-rank test. The Gray test was used to compare the cumulative incidence distributions. Cox proportional hazards models were fitted for univariate and multivariate analysis. Multivariate analysis was performed including factors in >5% of patients. Time-dependent receiver operating characteristic curves and corresponding area under the curve (AUC) with 95% confidence intervals (CI) were estimated using the riskRegression package. Analyses were performed for OS at 12 and 24 months for the original ELN classification and the refined models. All statistical analyses were performed using SPSS (version 30) and R software (version 4.4.2), with a significance threshold set at $P < .05$. Plots were generated with R software (version 4.4.2) using the ComplexHeatmap and ggplot2 packages and BioRender.

Results

Patients and treatment characteristics

This analysis included 669 patients with AML ineligible for intensive chemotherapy, of whom 414 were treated with HMAs and 255 with HMA-VEN. The median age in the HMA group was 76 years (range, 30-94). A total of 249 patients (60.1%) were male, and 220 patients (53.1%) had de novo AML, 142 (34.3%) had sM-AML, and 52 (12.6%) had t-AML. Prior HMA exposure was documented in 27 of 414 patients (6.5%). The median age in the HMA-VEN group was 75 years (range, 33-91); 150 patients (58.8%) were male, and 142 (55.7%) had de novo AML, 70 (27.5%) had sM-AML, and 43 (16.9%) had t-AML. A total of 20 of 255 patients (7.8%) received prior treatment with an HMA (Table 1).

Except for Eastern Cooperative Oncology Group performance status (ECOG) performance status (2-4 in 35.1% of HMA vs 17.2% of HMA-VEN patients; $P < .001$) and allogeneic transplantation (2.2% of HMA vs 5.1% of HMA-VEN patients; $P = .028$), characteristics were comparable between treatment cohorts. Baseline patient characteristics by treatment group are detailed in Table 1.

Molecular results

Comprehensive molecular profiling was available for all 669 patients. The most frequently mutated genes in HMA-treated patients were *TP53* (n = 109 [26.3%]), *TET2* (n = 101 [24.4%]) *RUNX1* (n = 99 [23.9%]), and *SRSF2* (n = 87 [21%]). In the HMA-VEN group, the most commonly mutated genes were *SRSF2* (n = 66 [25.9%]), *TP53* (n = 61 [23.9%]), *TET2* (n = 50 [19.6%]), and *RUNX1* (n = 49 [19.2%]). No significant differences in the frequency of gene mutations were observed between treatment groups, except for *DNMT3A* mutations, which were significantly less frequent in the HMA-VEN group (14.5% vs. 20.8%, $P = .027$) (Table 1; Figure 1). According to the ELN 2024 classification, in the HMA group, 200 of 414 (48.3%) patients were classified into the favorable-risk group, 105 of 414 (25.4%) into the intermediate-group, and 109 of 414 (26.3%) were allocated into the adverse-risk group. In HMA-VEN, 47.5% (121/255) were favorable-, 28.6% (73/255), intermediate-; and 23.9% (61/255), adverse-risk group. No statistically significant differences in the distribution of ELN 2024 risk groups were found between the HMA and HMA-VEN cohorts ($P = .602$; Figure 1). In addition, a detailed breakdown of the specific genetic alterations

Table 1. Baseline characteristics of the study patients

Feature	HMA (n = 414)	HMA-VEN (n = 255)	*P* value
Age, median (range), y	76 (30-94)	75 (33-91)	.071
Sex, n (%)			.742
Male	249 (60.1)	150 (58.8)	.727
Female	165 (39.9)	105 (41.2)	.912
Median WBC, $\times 10^9$ cells per L (range)	4.79 (0.1-321.4)	4.50 (0.4-323)	.381
Median Platelets, $\times 10^9$ cells per L (range)	59 (0.28-885)	65 (4-690)	.314
Bone marrow blasts, % (range)	46 (1-100)	45 (5-100)	.841
ECOG, n (%)			**<.001**
0	95 (22.9)	76 (29.8)	.066
1	175 (42.3)	111 (43.5)	.812
2	98 (23.7)	32 (12.5)	**<.001**
3	42 (10.1)	11 (4.3)	**.010**
4	2 (0.5)	1 (0.4)	.998
Unknown	2 (0.5)	24 (9.4)	<.001
Type of disease, n (%)			
De novo	220 (53.1)	142 (55.7)	.571
Secondary myeloid AML	142 (34.3)	70 (27.5)	.089
MDS	96 (23.2)	53 (20.8)	.532
MPN	32 (7.7)	11 (4.3)	.114
MDS/MPN	6 (1.4)	2 (0.8)	.693
Other/unknown	8 (1.9)	4 (1.6)	.967
Therapy-related	52 (12.6)	43 (16.9)	.151
Prior HMA treatment, n (%)	27 (6.5)	20 (7.8)	.546
Treatment, n (%)			
AZA	389 (94)		
Decitabine	25 (6)		
AZA + VEN		241 (94.5)	
Decitabine + VEN		14 (5.5)	
AlloTPH, n (%)	9 (2.2)	13 (5.1)	**.028**
Cytogenetic risk group, n (%)			
Favorable	8 (1.9)	7 (2.7)	.672
Intermediate	189 (45.6)	120 (47.1)	.788
Adverse	141 (34)	69 (27.1)	.074
Not available	76 (18.3)	59 (23.1)	.167
Mutation, n (%)			
TP53	109 (26.3)	61 (23.9)	.534
TET2	101 (24.4)	50 (19.6)	.478
RUNX1	99 (23.9)	49 (19.2)	.259
SRSF2	87 (21)	66 (25.9)	.112
DNMT3A	86 (20.8)	37 (14.5)	**.027**
ASXL1	86 (20.8)	47 (18.4)	.611
NPM1	77 (18.6)	45 (17.6)	.767
FLT3	67 (16.2)	49 (19.2)	.478
IDH2	66 (15.9)	50 (19.6)	.074
NRAS	49 (11.8)	39 (15.3)	.192
IDH1	46 (11.1)	26 (10.2)	.326

Gene mutation frequency >5%. Values that reached statistical significance are shown in bold.

AlloTPH, allogeneic hematopoietic progenitor cell transplantation; ECOG, Eastern Cooperative Oncology Group performance status; MDS, myelodysplastic syndrome; MPN, myeloproliferative neoplasm; WBC, white blood cell.

Table 1 (continued)

Feature	HMA (n = 414)	HMA-VEN (n = 255)	*P* value
JAK2	38 (9.2)	9 (3.5)	.094
U2AF1	38 (9.2)	13 (5.1)	.528
KRAS	28 (6.8)	12 (4.7)	.320
SF3B1	26 (6.3)	18 (7.1)	.632
EZH2	25 (6)	14 (5.5)	.929
CEBPA	24 (5.8)	12 (4.7)	.638
CBL	18 (4.3)	12 (4.7)	.315
PTPN11	12 (2.9)	11 (4.3)	.105

Gene mutation frequency >5%. Values that reached statistical significance are shown in bold.

AlloTPH, allogeneic hematopoietic progenitor cell transplantation; ECOG, Eastern Cooperative Oncology Group performance status; MDS, myelodysplastic syndrome; MPN, myeloproliferative neoplasm; WBC, white blood cell.

driving ELN 2024 risk assignment in each treatment cohort is provided in supplemental Tables 1 and 2.

Treatment response

Among patients treated with HMA monotherapy, the overall response rate (CR/CRi) was 17.4%. In contrast, patients receiving HMA-VEN achieved a significantly higher response rate of 56.9% ($P < .001$). Within the HMA group, response rates according to the ELN 2024 stratification were 19% for favorable, 19% for intermediate, and 12.5% for adverse risk groups (Figure 2A). Notably, the addition of VEN significantly improved response rates ($P = .007$) across all risk categories: 65.7% in the favorable-, 56.5% in the intermediate-, and 38.8% in the adverse-risk group (Figure 2B). No significant differences in the CR/CRi rates were observed in patients with de novo, sM-AML, or t-AML or patients with prior HMA exposure. CR/CRi rates were lower in the presence of *TP53* mutation compared with patients *TP53* wild type (38.8% vs 61.2%; $P = .005$). Moreover, patients with an adverse karyotype showed lower CR rates compared with those with favorable or intermediate karyotype (44.8% vs 65.7%; $P = .013$).

Survival outcomes in HMA

The median OS for the total HMA group was 6.5 months (95% CI, 5.2-7.4).

No significant differences in OS were observed among patients with de novo (7.8 months), sM-AML (6.4 months), t-AML (5.2 months), or prior HMA exposure (6.2 months) ($P = .160$).

According to the ELN 2024 risk stratification, median OS was 11.1 months (95% CI, 9.2-12.6), 4.9 months (95% CI, 3.7-6.8),

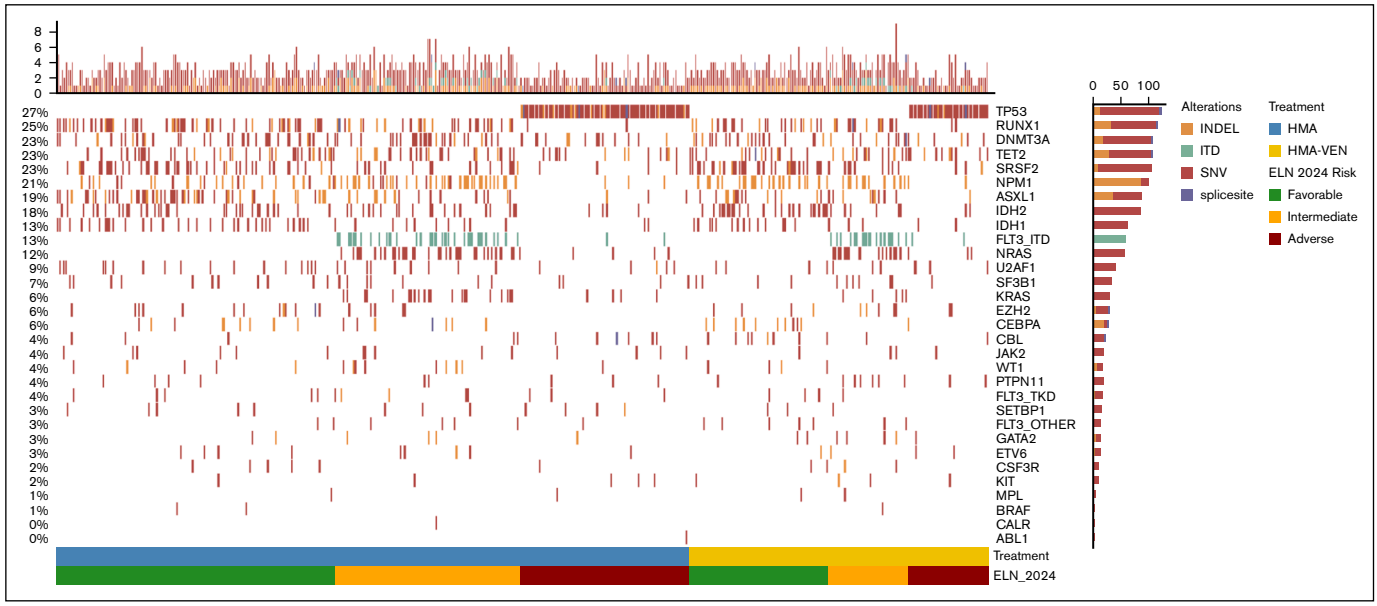

Figure 1. Oncoprint showing mutational landscape across patients stratified by treatment and ELN 2024 risk classification. The top bar plot indicates the number of mutations per patient. Each row represents a gene, and each colored block denotes a mutation type: SNV (red), INDEL (orange), ITD (green), or splice site (purple). Patients are grouped by treatment type (HMA in blue and HMA-VEN in yellow) and risk category according to the ELN 2024 classification (favorable, green; intermediate, orange; and adverse, dark red). The bar plot on the right shows the mutation frequency per gene across the cohort. INDEL, insertion/deletion; ITD, internal tandem duplication; SNV, single nucleotide variant.

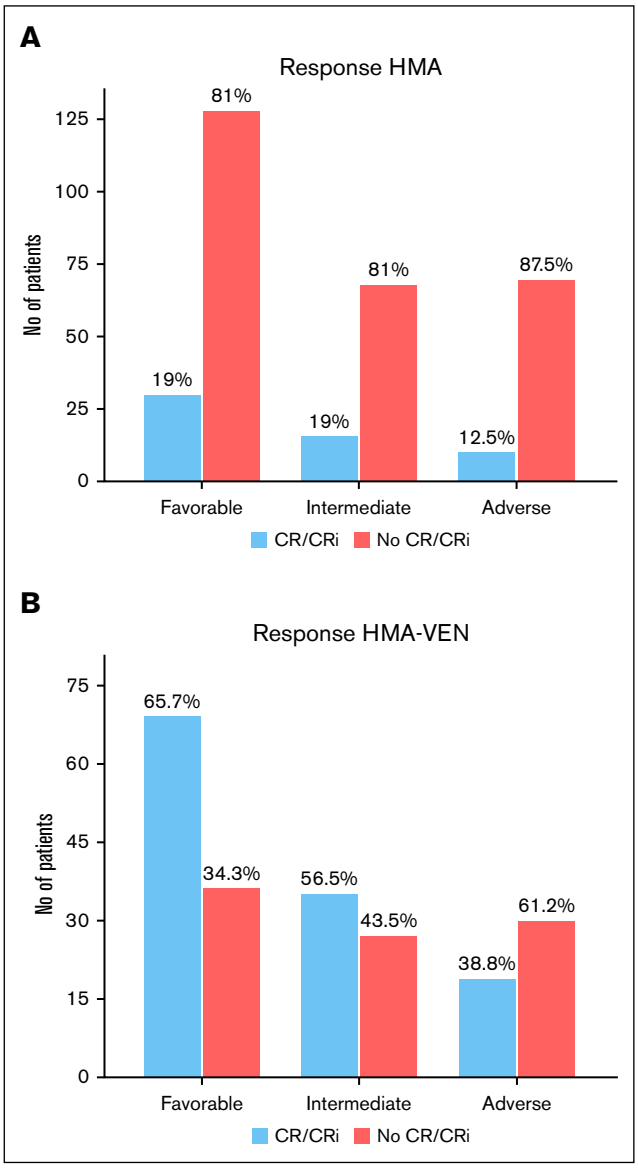

Figure 2. Response to treatment in unfit patients with AML stratified by ELN 2024 risk categories. (A) Patients treated with HMA. (B) Patients treated with HMA-VEN. The bars represent the number of patients achieving CR/CRi (blue) or no response (red) in each group; the percentages above the bars indicate the proportion of patients within each category.

and 2.8 months (95% CI, 2.2-4.2) in the favorable-, intermediate-, and adverse-risk groups, respectively ($P < .001$; Figure 3A).

When stratified by disease presentation in the HMA cohort, the ELN 2024 risk categories retained clear prognostic discrimination in patients with de novo AML and patients with sM-AML. However, in t-AML, survival differences across the ELN strata were less pronounced and did not reach statistical significance (supplemental Figure 1).

In patients who received HMA and achieved CR/CRi (n = 53), the median DFS was 13.7 months (95% CI, 6.5 to not reached). No significant differences in DFS were observed across the ELN 2024 risk groups ($P = .410$).

Survival outcomes in the HMA-VEN

Considering all patients treated with HMA-VEN in routine clinical practice, the median OS was 11.2 months (95% CI, 8.9-13.5). Patients with sM-AML had significantly poorer outcomes, with a median OS of 5.9 months (95% CI, 2.5-9.3) compared with 14.3 months (95% CI, 7.9-20.6) in those with de novo AML and 13.3 months (95% CI 9.9-16.7) in those with t-AML ($P < .001$).

According to ELN 2024, the median OS was 18.4 months (95% CI, 12.5-24.3), 13.5 months (95% CI, 6.9-20.1), and 7.7 months (95% CI, 4.9-10.3) in the favorable-, intermediate-, and adverse-risk groups, respectively ($P < .001$; Figure 3B).

When considering disease presentation, patients with de novo AML showed a median OS of 28.4 months (95% CI, not reached) in the favorable-risk group, 15.7 months (95% CI, 6.7-24.7) in the intermediate-risk group, and 7.7 months (95% CI, 5.9-9.4) in the adverse-risk group ($P < .001$; Figure 4A). In patients with t-AML, median OS was 16.2 months (95% CI, 7.4-24.9) in the favorable-risk group, 15 months (95% CI, 10.7-19.3) in the intermediate-risk group, and 9.2 months (95% CI, 0-18.7) in the adverse-risk group ($P = .039$; Figure 4B). In contrast, in patients with sM-AML, median OS was poorer across all risk groups (9.5, 5.4, and 5.5 months, respectively; $P = .481$; Figure 4C).

In the sM-AML group, 66 of 70 patients had documented information regarding a preceding myeloid malignancy; 53 patients had myelodysplastic syndrome antecedent, and 13 patients had prior myelodysplastic syndrome/myeloproliferative neoplasm. There were no statistically significant differences in OS between these 2 subgroups (5.3 vs 7.5 months, respectively) nor according to ELN 2024 risk stratification. Furthermore, 20 of 68 (29.4%) patients with sM-AML who had received prior HMA therapy did not show differences in survival compared with the OS of the sM-AML cohort or when stratified by ELN 2024 risk category.

Current AML classifications recognize AML arising from a preceding myeloid disorder not only based on clinical history but also by defining a specific set of MR-cytogenetic and -molecular alterations.

When all patients with secondary myeloid, defined by a clinical history of a myeloid malignancy and/or the presence of MR-cytogenetic and/or MR-molecular alterations, were grouped together, the vast majority of patients (76%) fulfilled any of these criteria (194/255 patients) and the ELN 2024 risk stratification showed a median OS of 14.3 months (95% CI, 5.7-22.8) for the favorable-risk group, 10.2 months (95% CI, 6.9-13.4) for the intermediate-risk group, and 7.2 months (95% CI, 4.4-10.0) for the adverse-risk group ($P < .001$).

However, only patients with clinical secondary and MR-cytogenetic alteration showed significantly poorer OS (5.9 months; 95% CI, 2.5-9.3 and 7.8 months; 95% CI, 5.2-10.3, respectively; $P < .001$). In contrast, the presence of MR-molecular mutations did not significantly affect OS (11.3 months; 95% CI, 7.5-15.1; $P = .632$; supplemental Figure 2).

Forest plot analysis showed that, when cytogenetic, genetic, and clinical criteria were analyzed separately, MR-cytogenetic alone (hazard ratio [HR], 5.76; 95% CI, 2.78-11.95; $P < .001$) and sM-AML alone (HR, 3.98; 95% CI, 1.10-14.46; $P = .036$) were significantly associated with inferior survival, whereas MR-molecular alone showed a trend toward worse outcome that did

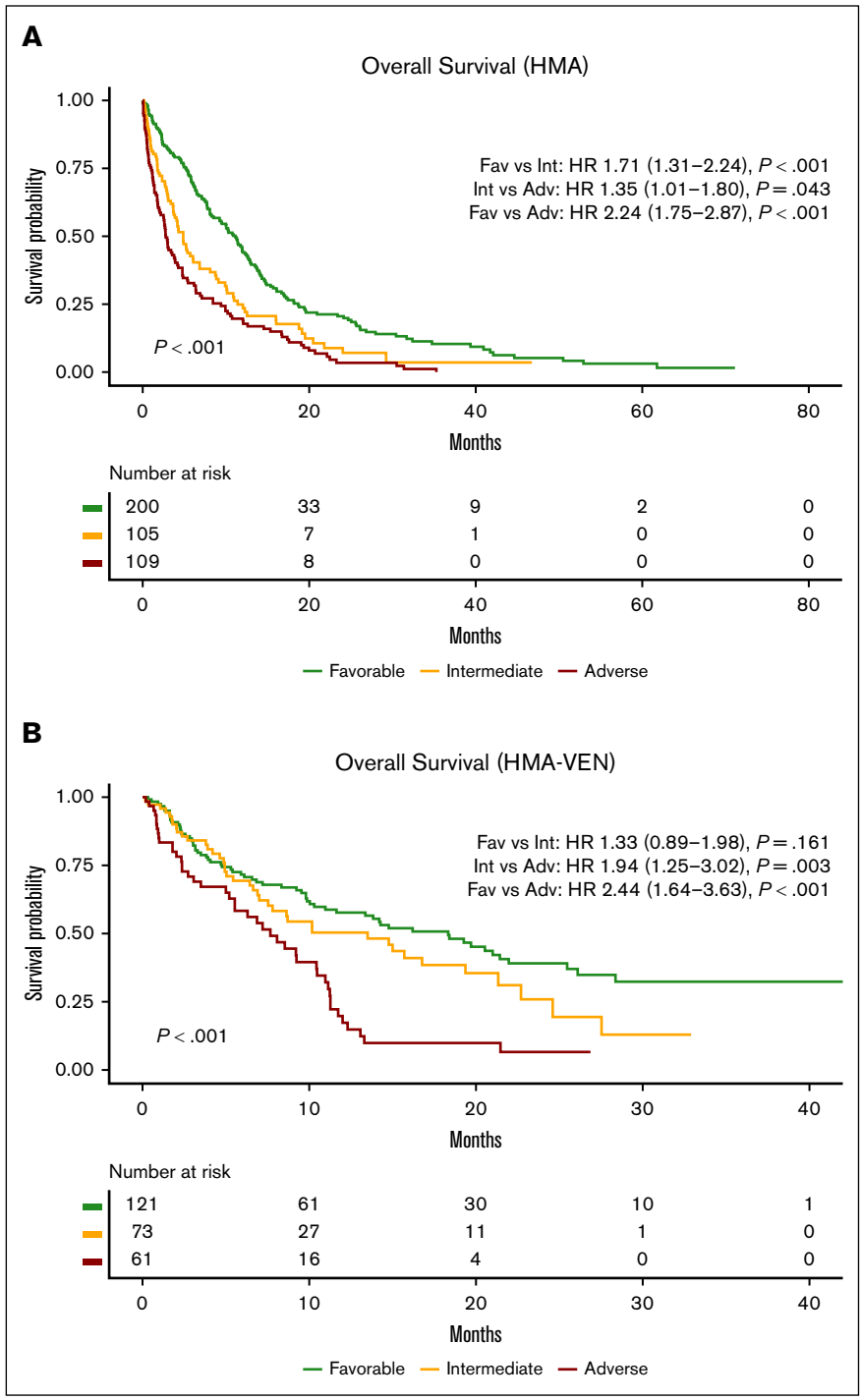

Figure 3. Kaplan-Meier OS curves stratified by ELN 2024 risk groups. HMA (A) and HMA-VEN (B) treatment in the entire real-world cohort. Survival probabilities are shown for favorable-risk (green), intermediate-risk (orange), and adverse-risk (dark red) categories. The numbers below the curves represent the patients at risk at different time points. The *P* values from the log-rank test indicate statistically significant differences in survival between risk groups in both treatment cohorts. Adv, adverse; Fav, favorable; Int, intermediate.

not reach statistical significance (HR, 1.97; 95% CI, 0.96-4.04; $P = .063$). Notably, patients presenting with the combination of all 3 conditions had the highest risk of death (HR, 11.12; 95% CI, 4.34-28.46; $P < .001$; supplemental Figure 3).

Among HMA-VEN patients who achieved CR/CRi (n = 114), the median DFS was 15.3 months (95% CI, 8.6-22.6). Within this cohort, patients classified as adverse risk had a significantly shorter median DFS of 6.3 months (95% CI, 2.5-10) compared with patients in the favorable-risk group (25 months; 95% CI, not reached) and intermediate-risk group (16 months; 95% CI, not reached) ($P < .001$; Figure 5A)

The 1-year CIR was 61.6% in the adverse-, 29.6% in the intermediate-, and 22.0% in the favorable-risk group ($P = .539$). At 2 years, the CIR was slightly higher in all groups, with 68.3% in the adverse-, 40.4% in the intermediate-, and 34.4% in the favorable-risk group ($P = .062$; Figure 5B).

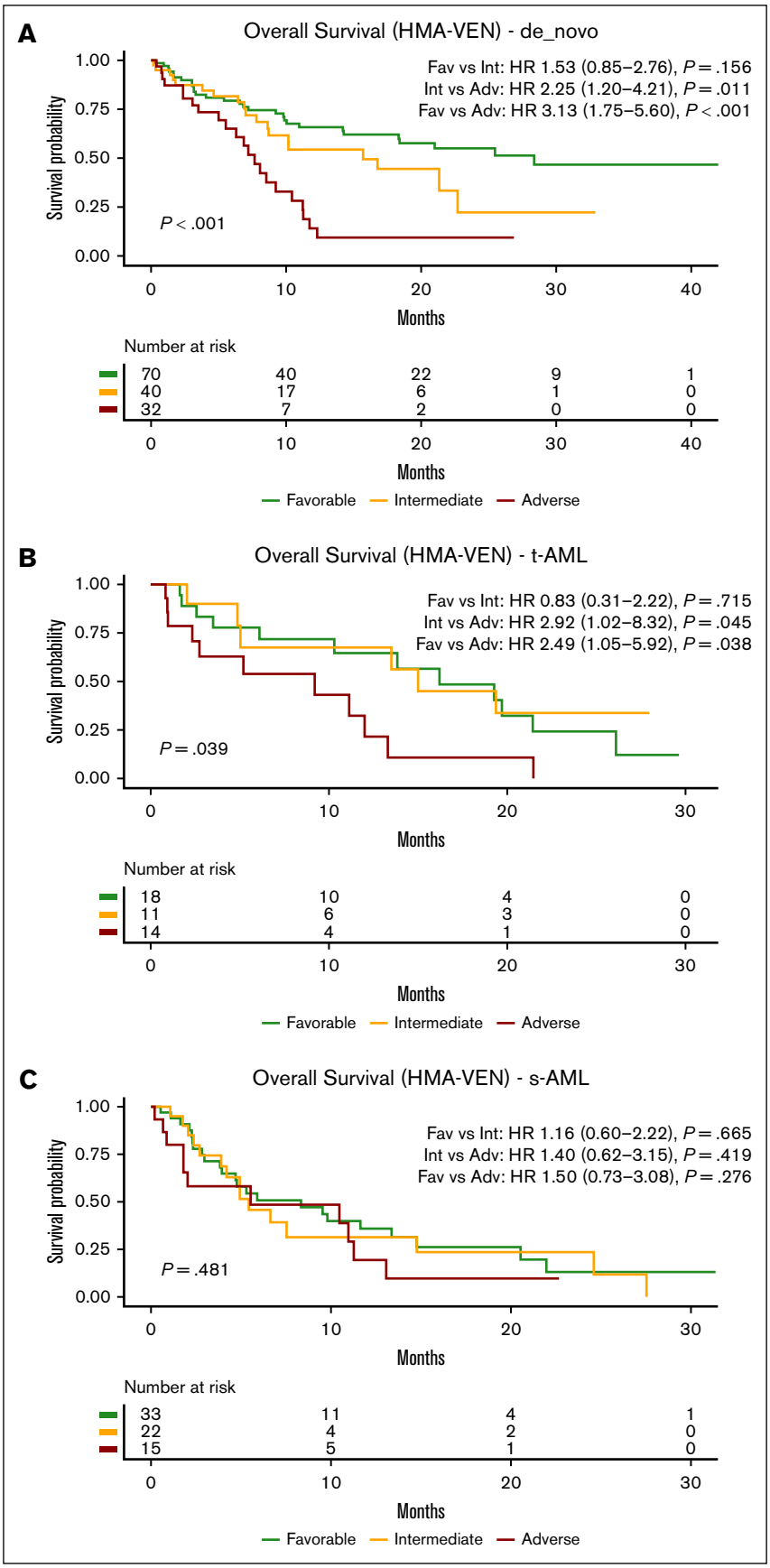

Figure 4. Kaplan-Meier OS curves stratified by ELN 2024 risk groups for patients treated with HMA-VEN according to disease presentations. Patients with de novo AML (A), t-AML (B), and sM-AML (C). Survival probabilities are shown for favorable-risk (green), intermediate-risk (orange), and adverse-risk (dark red) categories. The numbers below the curves represent the patients at risk at different time points. The *P* values from the log-rank test indicate statistically significant differences in survival between risk groups in both treatment cohorts. Adv, adverse; Fav, favorable; Int, intermediate.

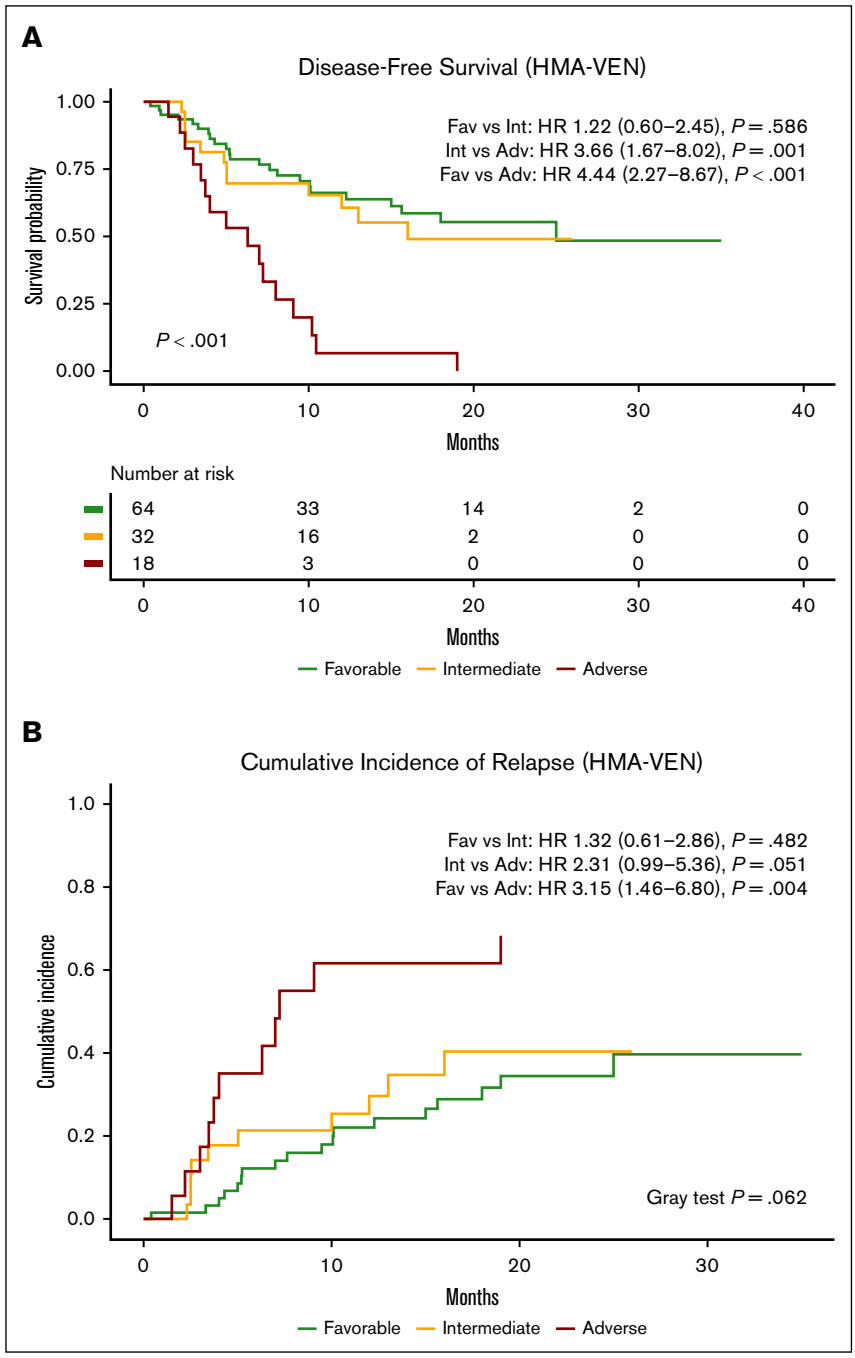

Figure 5. DFS and CIR in patients treated with HMA-VEN stratified by ELN 2024 risk group. (A) Kaplan-Meier curves depicting DFS from the time of achieving response (CR/CRi). (B) CIR analysis considering death as a competing event. Adv, adverse; Fav, favorable; Int, intermediate.

Prognostic factors for survival

In univariate Cox regression within the HMA-treated cohort, both intermediate- and adverse-risk groups had significantly worse survival than the favorable-risk group. Adverse cytogenetics was also independently associated with inferior prognosis. Regarding gene mutations, *JAK2* and *GATA2* predicted worse outcomes within the favorable- and intermediate-risk groups, respectively. In the adverse-risk group, *KRAS* mutations were linked to poorer outcomes, whereas *RUNX1* showed an improved survival (supplemental Tables 3 and 4). In the HMA-VEN group, sM-AML, MR-cytogenetics, adverse cytogenetics, and the ELN 2024 adverse-risk status were strongly associated with worse outcomes. Among gene mutations, *TET2* predicted poorer outcomes in the intermediate- and adverse-risk groups, whereas *NRAS* and *ETV6* were adverse in the intermediate- and adverse-risk groups, respectively; *NPM1* and *IDH2* showed improved survival in the favorable-risk group (supplemental Tables 5 and 6).

In multivariate analysis for the HMA group, the ELN 2024 intermediate- and adverse-risk groups retained an independent and statistically significant association with worse survival (HR, 1.66;

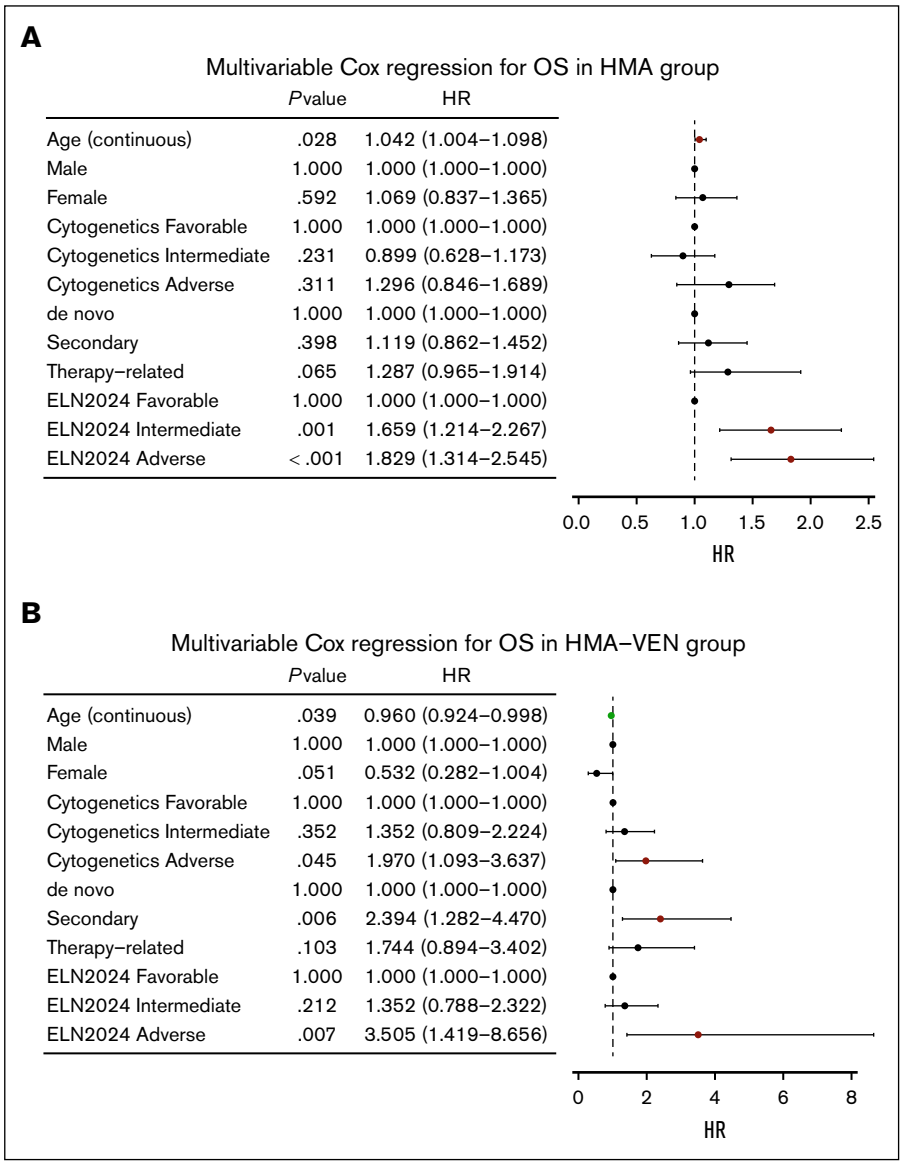

Figure 6. Multivariable and survival analysis of clinical and biological variables in patients with AML. (A) Multivariable Cox regression for OS in patients treated with HMA alone (n = 414). (B) Multivariable Cox regression for OS in the HMA-VEN cohort (n = 255). HR and 95% CI are shown for each variable. The green dots indicate variables independently associated with favorable outcome, and the red dots indicate variables independently associated with adverse outcome ($P < .050$).

95% CI, 1.21-2.27; $P = .001$ and HR, 1.83; 95% CI, 1.31-2.55; $P < .001$, respectively; Figure 6A). In the HMA-VEN group, the ELN 2024 adverse-risk group remained significant (HR, 3.51; 95% CI, 1.42-8.66; $P = .007$), whereas the intermediate-risk group did not reach statistical significance (HR, 1.35; 95% CI, 0.79-2.32; $P = .212$). Adverse cytogenetic risk also retained independent prognostic significance (HR, 1.98; 95% CI, 1.09-3.64; $P = .045$), supporting the continued prognostic relevance of cytogenetic abnormalities. In addition, sM-AML remained an independent adverse prognostic factor (HR, 2.39; 95% CI, 1.28-4.47; $P = .006$). No gene mutations remained statistically significant in the multivariable model. Age showed a statistically significant but modest association with survival (HR, 0.96 per year; 95% CI, 0.92-0.99; $P = .039$). Sex and t-AML did not reach statistical significance, although a trend toward improved survival was observed in female patients (HR, 0.53; 95% CI, 0.28-1.00; $P = .051$; Figure 6B).

Refined ELN 2024 proposal

Across all comparisons, patients classified as favorable risk consistently exhibited superior OS, whereas those assigned to the adverse-risk group had the poorest outcomes. In contrast, the intermediate-risk category remained clinically heterogeneous. Given the strong and independent adverse prognostic impact of cytogenetic risk and clinical secondary AML observed in both the univariate and multivariable analyses, we explored refined risk stratification strategies by sequentially reclassifying patients into the ELN 2024 adverse-risk group: first incorporating adverse cytogenetics, then secondary AML, and finally, the combination of both factors.

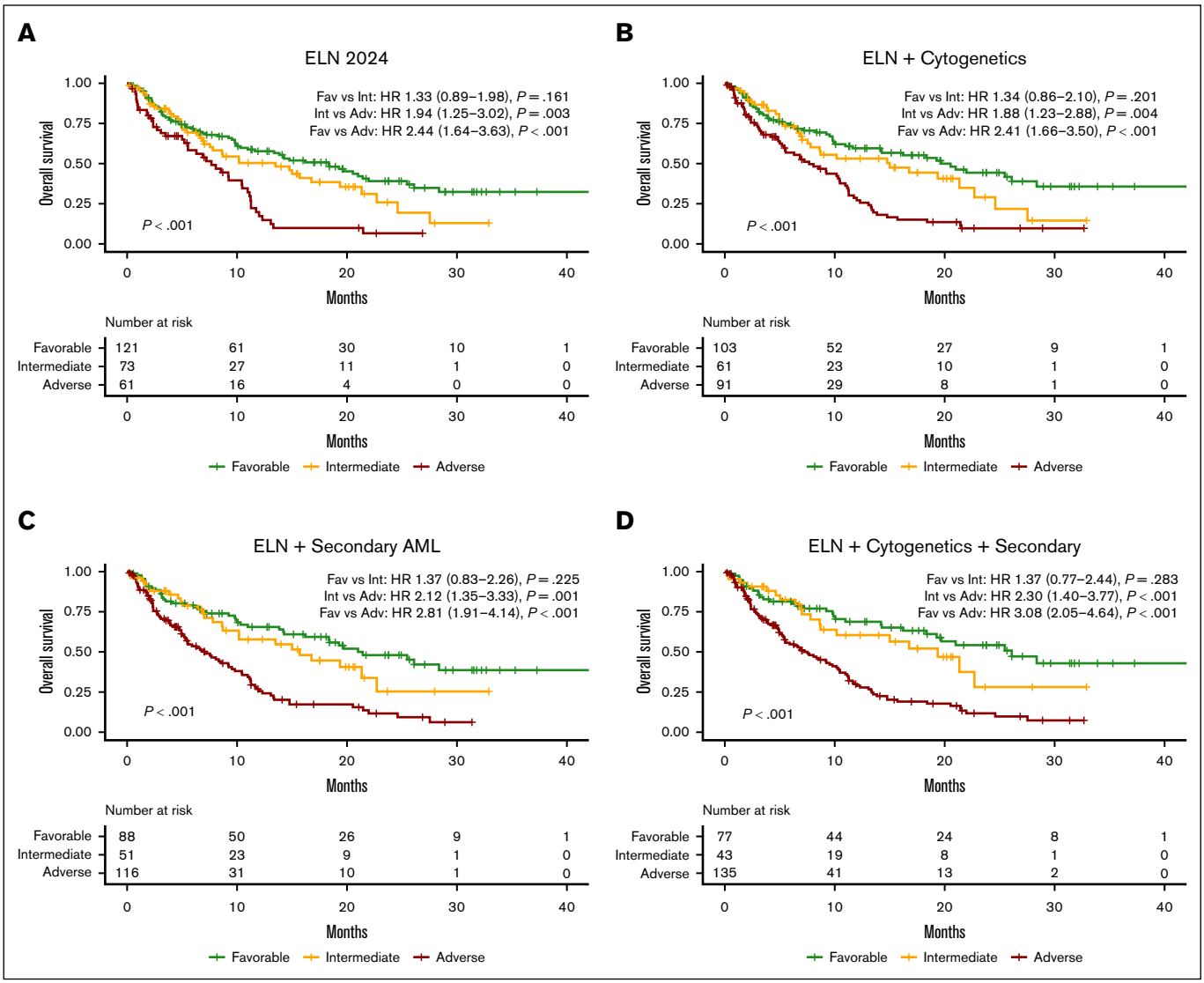

Figure 7. Kaplan-Meier OS curves stratified by ELN 2024 risk groups in patients treated with HMA-VEN. (A) ELN 2024 original. (B) Refined ELN 2024 including adverse cytogenetics in the adverse-risk group. (C) Refined ELN 2024 including sM-AML in the adverse-risk group. (D) Refined ELN 2024 including sM-AML and adverse cytogenetics in the adverse-risk group. Survival probabilities are shown for favorable-risk (green), intermediate-risk (orange), and adverse-risk (dark red) risk groups. The numbers below the curves indicate patients at risk at different time points. Adv, adverse; Fav, favorable; Int, intermediate.

Using the original ELN classification, median OS was 18.4 months (95% CI, 12.5-24.3), 13.5 months (95% CI, 6.9-20.1), and 7.7 months (95% CI, 4.9-10.3) in the favorable-, intermediate-, and adverse-risk groups, respectively ($P < .001$; Figure 7A). Reclassification based on adverse cytogenetics modestly improved risk separation, with a median OS of 19.7 months (95% CI, 14.2 to not reached) in the favorable group, 15.0 months (95% CI, 7.8-24.6) in the intermediate group, and 7.7 months (95% CI, 5.4-11.0) in the adverse group ($P < .001$; Figure 7B). A similar pattern was observed when reclassifying based on sM-AML alone, yielding a median OS of 21.0 months (95% CI, 16.2 to not reached), 15.7 months (95% CI, 10.2 to not reached), and 7.2 months (95% CI, 5.3-9.8) across the 3 risk categories ($P < .001$; Figure 7C). Further refinement incorporating sM-AML and adverse cytogenetics resulted in more pronounced survival discrimination, with a median OS of 26.1 months (95% CI, 19.3 to not reached), 19.4 months (95% CI, 8.7 to not reached), and 7.2 months (95% CI, 5.4-10.3) in the favorable-, intermediate-, and adverse-risk groups, respectively ($P < .001$; Figure 7D).

To compare the discriminative performance of the original and refined ELN based models, we performed time-dependent receiver operating characteristic analyses for OS. At 12 months, AUC values ranged from 0.64 to 0.70 across the different models. At 24 months, the original ELN classification showed an AUC of 0.71 (95% CI, 0.63-0.78), whereas models incorporating adverse cytogenetics or sM-AML status showed higher discrimination (AUC, 0.73; 95% CI, 0.64-0.81 and 0.74; 95% CI, 0.64-0.83, respectively). The refined model combining both adverse cytogenetics and sM-AML status achieved the highest discriminative

performance, with an AUC of 0.76 (95% CI, 0.66-0.85) at 24 months.

Discussion

In this study, we validated the ELN 2024 genetic risk classification in a real-world cohort of patients with AML treated with HMA-based therapy, including both monotherapy and combination regimens with VEN. Our findings confirm that ELN 2024 effectively stratifies patients with AML receiving less-intensive treatments and that its prognostic performance may be modestly improved when cytogenetic data are incorporated. However, its predictive performance is markedly diminished in patients with sM-AML. Therefore, we suggest that this subset of patients should be classified as high risk. These results highlight the challenges of applying clinical trial–derived risk models to heterogeneous, real-world populations.

ELN 2024 is fundamentally derived from clinical trial populations in which eligibility criteria excluded many high-risk or complex cases that do not fully reflect the heterogeneity observed in routine practice. Consequently, real-world outcomes after HMA-VEN are consistently inferior to those reported in the VIALE-A, as we demonstrate in our cohort and as has been noted by literature reviews and meta-analyses.[12,13] Moreover, the classification is derived almost exclusively from patients treated with AZA-VEN, thereby leaving its utility in other low-intensity regimens uncertain. Recently Othman et al[14] and Gangat et al[15] explored ELN 2024 in real-world cohorts, but their analyses were limited to patients receiving VEN-based low-intensity regimens, such as AZA or low-dose cytarabine combined with VEN. Consequently, the real-word applicability of ELN 2024 to patients treated with HMA monotherapy remained unexplored. In response, our cohort represents a broader, real-world population of 669 patients with AML, with a median age of ~75 years and a substantial proportion of secondary AML, all treated in routine clinical settings with HMA monotherapy or HMA-VEN combinations.

As previously reported,[2] we observed significantly inferior survival outcomes among patients treated with HMA monotherapy compared with those receiving HMA-VEN combinations (CR/CRi: 17.4% vs 56.9%; median OS: 6.5 vs 11.2 months). ELN 2024 classification successfully stratified prognostic groups within both treatment arms; however, OS was consistently shorter in the HMA-only group across all ELN risk categories. These results are in line with a recent paper by Roncador et al,[16] who conducted an external validation of the ELN 2024 using a publicly available data set[17] treated with various nonintensive regimens outside the context of HMA-based treatments and observed similarly diminished survival across all risk groups. In HMA-VEN treatment, ELN 2024 consistently stratified patients into prognostic groups, with the favorable-risk group achieving a median OS of 18.4 months in the entire cohort. These results are concordant with other real-world studies,[14,15] which reported slightly shorter median survivals for each risk group compared with the outcomes observed in clinical trial populations originally described by Döhner et al.[8]

These data highlight a critical limitation of ELN 2024 when applied to real-world patients, particularly those with secondary AML arising from antecedent myeloid neoplasms. Across our entire cohort, sM-AML patients consistently demonstrated poor survival outcomes, regardless of their ELN 2024 genomic risk. Moreover, these findings align with other real-world studies, including those by Gangat et al,[15] Pullarkat et al,[18] and Lloret et al,[19] which report similarly dismal outcomes in patients with sM-AML, even when treated with VEN-based regimens. Notably, in our cohort, t-AML did not have inferior survival relative to de novo AML, suggesting biological divergence between secondary AML subtypes. Current AML classifications increasingly recognize AML arising from a preceding myeloid disorder not only based on clinical history but also through the identification of specific MR-associated cytogenetic and molecular alterations. When we integrated clinical history and cytogenetic and molecular findings into a broader secondary myeloid population, ELN 2024 risk stratification retained its discriminatory capacity across risk groups. However, statistical analysis revealed that the prognostic impact of individual conditions was not uniform. MR-cytogenetic abnormalities and secondary AML defined by clinical history emerged as independent predictors of poor outcome, whereas MR-molecular alterations alone were not significantly associated with inferior survival. Our findings align with emerging evidence that the prognostic impact of MR-molecular alterations is context-dependent, particularly in the setting of lower-intensity therapies such as VEN combined with HMAs.[20]

Although HMA-VEN therapy is associated with high initial response rates, long-term remissions remain limited to a subset of patients. In our cohort, patients in the favorable-risk group demonstrated frequent long-term survivors beyond 2 years, whereas intermediate- and adverse-risk groups showed markedly fewer survivors beyond 1 year. These findings highlight that durable remission is achievable in a subset of older patients with AML when treated with HMA-VEN, whereas such outcomes are rarely observed with HMA monotherapy.

The ELN 2024 nonintensive classification, although an important advance, is built upon a limited set of molecular markers. In particular, the intermediate-risk category is defined exclusively by signaling pathway mutations (*FLT3-ITD*, *KRAS*, and *NRAS*). To enhance the discriminatory power of the ELN 2024 classification, our study, along with others, explored the integration of additional gene mutations beyond those currently used for categorical risk assignment.[14,15,21] Notably, in our cohort, the prognostic impact of individual gene mutations was not fully consistent with these previous reports, underscoring the need for larger, prospective studies to better define the prognostic relevance of specific molecular alterations in the context of less-intensive treatment regimens.

Multivariate analysis identified adverse cytogenetics as a powerful independent prognostic factor, demonstrating a stronger association with poor survival outcomes than any individual gene mutation. Furthermore, our data demonstrate that other simple pretreatment clinical characteristics, such as previously discussed sM-AML, remained relevant prognostic factors. Reclassifying sM-AML into the adverse-risk group improved the performance of the ELN 2024 system in our cohort. These findings reinforce the idea that the further refinement of prognostic models should not exclude clinical features especially in real-world settings where patient populations are older, enriched with secondary AML, and more heterogeneous than those represented in clinical trials.

By reclassifying patients with adverse cytogenetics and sM-AML into the ELN adverse group, we observed improved separation of median OS by group and a higher predictive value. This ELN 2024 refinement proposal could be clinically meaningful because it more accurately identifies patients at the highest risk of poor outcomes, in whom the HMA-VEN combination could be less worthy. Importantly, these results highlight the value of incorporating clinical, genetic, and cytogenetic variables into risk stratification models to better reflect disease heterogeneity and support more precise, biology-driven treatment strategies.[17,22]

Our study has the following limitations: (1) the sample size of the HMA-VEN cohort was relatively limited and we could not deeply analyze the role of all NGS panel mutations when dissecting AML in smaller subgroups and low statistical power; (2) the follow-up of the HMA-VEN cohort is relatively short compared with that of the HMA monotherapy group; (3) we had no patients treated with IVO and we could not explore the prognostic role of *IDH1* mutations under this agent; and (4) although *DDX41* was recently recognized in the ELN 2024 classification as a favorable prognostic marker, we were unable to assess its impact because this gene was not routinely included in the NGS panel used by PETHEMA laboratories.

In conclusion, the ELN 2024 nonintensive classification remains a valuable tool, especially for patients with de novo AML and patients receiving HMA-VEN, but we suggest that patients with unfavorable cytogenetic risk and sM-AML should be allocated into the high-risk category. Our findings emphasize the need to account for disease ontogeny and cytogenetic risk when stratifying AML in real-world settings. The next-generation AML prognostic models should move beyond static, genomics-only frameworks and embrace the complexity of nonintensive and older patient populations.

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