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Examining the impact of age on the prognostic value of ELN-2017 and ELN-2022 acute myeloid leukemia risk stratifications: a report from the SWOG Cancer Research Network

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Title: Examining the impact of age on the prognostic value of ELN-2017 and ELN-2022 acute myeloid leukemia risk stratifications: a report from the SWOG Cancer Research Network

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Running title: Impact of age on ELN-2017 and ELN-2022

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Data sharing statement: The datasets generated and/or analyzed during the current study are available in the dbGaP repository, dbGaP, under accession number phs002805.v1.p1. Investigators can apply to access sequencing data through standard dbGaP request procedures as described by NIH and found at dbgap_request_process.pdf (nih.gov). Additional data generated or analyzed during this study are included in the supplementary information files. Data and code to reproduce the analyses presented here are available upon request from SWOG following SWOG's data sharing policy and process: https://www.swog.org/sites/default/files/docs/2019-12/Policy43_0.pdf

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Recent revisions to the European LeukemiaNet (ELN) recommendations have redefined how acute myeloid leukemia (AML) is classified, monitored, treated, and risk stratified (1, 2). Some of the most significant risk stratification changes involve reclassification for some previously utilized mutations and the inclusion of additional mutations. The ELN-2022 guidelines have removed the *FLT3*-ITD ratio as a major risk classifier while promoting a single *CEPBA* mutation within the Zip domain as sufficient to convey a favorable risk. In the absence of favorable risk genomic alterations, the new ELN-2022 guidelines also recommend that mutations associated with myelodysplasia (i.e., myelodysplastic syndrome (MDS), or MDS-related) be considered adverse risk factors, even in patients without a history of MDS.

The median age of AML patients at diagnosis is 68 years, highlighting that most AML patients are older (3), and these older patients frequently harbor MDS-related mutations despite not having documentation for antecedent MDS. It remains uncertain whether the "*de novo*" older patients with MDS-related mutations had an undiagnosed preceding MDS or not, but the MDS-related mutations in older AML patients are associated with an adverse risk (2). We and others have shown that age remains a major adverse risk factor, even after accounting for other age-related factors: type of therapy, performance status, cytogenetics, specific favorable-risk mutations, and even ELN-2017 (4, 5). Moreover, models incorporating age with ELN-2017 risk performed better than models with ELN-2017 risk alone (6). With the inclusion of MDS-related mutations into ELN-2022 guidelines, we hypothesized that ELN-2022 would outperform ELN-2017 - especially in older adults with AML, who tend to have a higher frequency of many of these MDS-related mutations. To examine this question, we compared the prognostic performance of the two versions of ELN guidelines. Since neither version incorporates age into its risk stratification, we evaluated whether a model with ELN-2022 risk and age would improve the prognostic value of ELN-2022 as it does for ELN-2017. These models were evaluated in a well-defined cohort of patients treated with intensive chemotherapy as part of the SWOG Cancer Research Network clinical trials.

Thus, we examined the molecular and clinical data from 351 patients previously enrolled in protocols SWOG-9031, SWOG-9333, S0106, and S0112 and treated as previously described (6-10). Details of the patients and utilized specimens have been published and can be found in **Supplementary Table 1** (6-10). All participants provided written informed consent to participate in correlative research in compliance with the Declaration of Helsinki. All studies were conducted with the approval of Fred Hutch Cancer Center's Institutional Review Board. ELN risk for patients was assigned based on previously described guidelines (1,2). Univariate and multivariable analyses of complete response (CR, logistic regression), overall survival (OS, Cox regression), and relapse-free survival (RFS, Cox regression) were used to evaluate the prognostic value of the ELN-2017 and ELN-2022 risk stratification. OS, CR, and RFS were defined as previously described (6). Multivariable analyses included age (modeled as a quantitative covariate) in addition to ELN risk. Note that there was no model or covariate selection performed in the analyses reported here. The objective was to describe how model performance changed by adding the covariate of age based on prior work. Therefore, we did not perform cross-validation. The Area under the Receiver Operating Characteristic curve (AUC) and C-statistics were calculated to assess model performance. Molecular mutation and cytogenetic profiles are specified in **Supplementary Table 2**.

Univariate analyses adjusting for ELN-2017 or ELN-2022 risk yielded similar statistical results for all outcomes: AUCs of 0.7 for CR and C-statistics of 0.63 and 0.61 for OS and RFS, respectively (**Table 1, Figures 1A, 1B, Supplementary Figures 1A & 1B**). Specifically, 9% of all patients were reclassified based on their risk categorization when the ELN-2022 guidelines were used instead of the ELN-2017 guidelines (**Supplementary Table 1)**. Restricting the analyses to age of patients > 55, the models incorporating ELN-2022 or ELN-2017 risk had similar prognostic value as measured by C-statistics for OS (ELN-2022=0.60 vs. ELN-2017=0.58, **Figure 1C & 1D**) and RFS (ELN-2022=0.61 vs. ELN-2017=0.60, **Supplementary Figure 1C & 1D**). Restricting age of patients to ≤ 55 years old showed a similar prognostic value as measured by C-statistics for OS (ELN-2022=0.67 and ELN-2017=0.66, **Figure 1E & 1F**) and RFS (ELN-2022=0.60 and ELN-2017=0.60, **Supplementary Figures 1E & 1F**). As we previously described with ELN-2017, the ELN-2022 risk had greater prognostic value with respect to OS in younger patients (≤ 55) than in their older counterparts (**Figure 1**). We then examined the impact of incorporating age into the ELN-2022 risk model. Overall, incorporating age improved prognostic value for CR, OS, and RFS – whether the model was based on ELN-2022 or ELN-2017. Moreover, the improvement was similar for ELN-2022 and ELN-2017 (**Table 1**), with the greatest improvement being for OS (Δ=0.08-0.09), followed by RFS (Δ=0.06), and then CR (Δ=0.03-0.04). Omitting patients with unknown risk group status from our analyses resulted in similar increases in the model performance when age was included for OS (Δ=0.06-0.07), RFS (Δ=0.06), and CR (Δ=0.03-0.02) (**Table 1**). We also performed similar analyses excluding those patients with FLT3- internal tandem duplication (FLT3-ITD) mutations, given that examined patients did not receive an FLT3 inhibitor (**Supplementary Table 3**). When FLT3-ITD patients were removed from our analyses, we detected a slightly worse prognostic value of ELN-2022 compared to ELN-2017 for CR (Δ=0.02) and OS (Δ=0.01) when age was incorporated into the model, while RFS was unchanged (**Supplementary Table 3**).

Taken together, these findings show a similar prognostic value of risk stratification for ELN-2022 and ELN-2017, which is consistent with only 9% of the patients in our cohort being re-classified for their risk stratification category under the ELN-2022 guidelines (**Supplementary Table 1**). Incorporating age into the ELN-2022 and ELN-2017 models resulted in a similar magnitude of improved performance over the univariate models. Although the analyses included over 350 patients, we recognize that additional studies with even more patients will be required to examine the performance of the ELN-2022. However, it is unlikely that the changes to ELN-2022 will dramatically improve risk stratification compared to ELN-2017. There are multiple reasons that likely contribute to our current lack of highly accurate prognostic and predictive biomarkers – with the lack of highly efficacious targeted therapy being just one. With the advent of more targeted therapies, investigators will hopefully be able to better refine and adapt risk models to incorporate more therapy-specific predictors, which will likely improve risk stratification and care.

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Table 1:

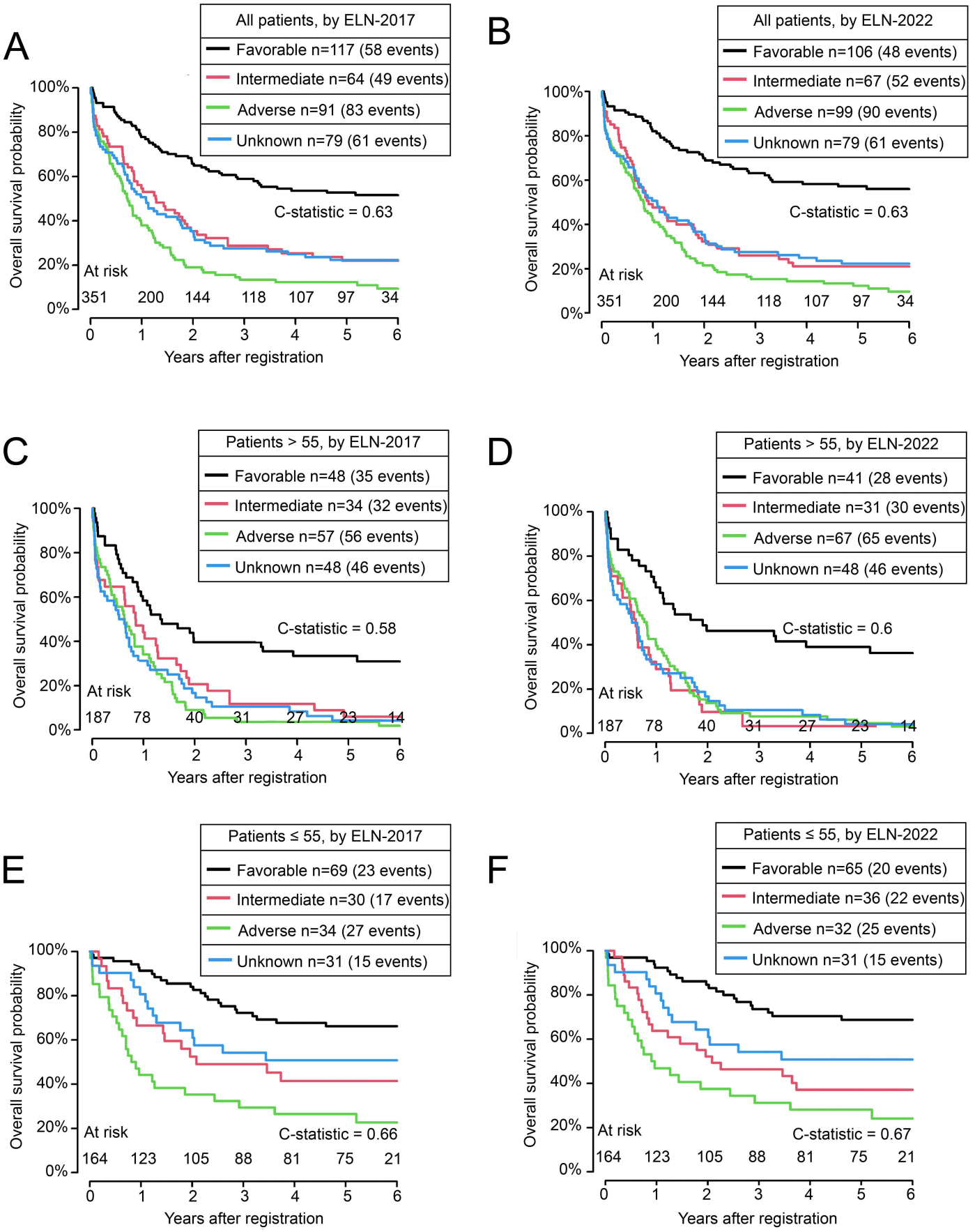
Table 1: Age minimally changes prognostic value of ELN-2017 and ELN-2022 guidelines.		
Model	AUC or C-statistic	AUC or C-statistic (excluding unknowns)
Complete Response (CR, AUC)		
ELN-2017	0.7	0.72
ELN-2022	0.7	0.72
Age + ELN-2017	0.74	0.75
Age + ELN-2022	0.73	0.74
Overall Survival (OS, C-Statistic)		
ELN-2017	0.63	0.65
ELN-2022	0.63	0.65
Age + ELN-2017	0.71	0.71
Age + ELN-2022	0.72	0.72
Relapse-free Survival (RFS, C-Statistic)		
ELN-2017	0.61	0.61
ELN-2022	0.61	0.62
Age + ELN-2017	0.67	0.67
Age + ELN-2022	0.67	0.68

Table 1: Age minimally changes prognostic value of ELN-2017 and ELN-2022 guidelines. Comparison of age as a prognostic factor using ELN-2017 and ELN-2022 guidelines. (n=351 total patients; n=272 patients with unknowns omitted).

FIGURE LEGENDS

Figure 1: Similar survival probability is seen in older patients analyzed using ELN-2017 and ELN-2022. Overall survival probability was analyzed for all patients classified into favorable, intermediate, adverse, or unknown risk groups based upon (A) ELN-2017 and (B) ELN-2022 guidelines. Overall survival was analyzed for patients > 55 years old classified into favorable, intermediate, adverse, or unknown risk groups based on (C) ELN-2017 and (D) ELN-2022 guidelines. Overall survival was analyzed for patients ≤ 55 years old classified into favorable, intermediate, adverse, or unknown risk groups based on (E) ELN-2017 and (F) ELN-2022 guidelines. (n=351 total patients). Kaplan-Meier curves are shown for each group of patients; C-statistics are based on Cox proportional hazards models.

Figure 1


A
All patients, by ELN-2017
Favorable n=117 (58 events)
Intermediate n=64 (49 events)
Adverse n=91 (83 events)
Unknown n=79 (61 events)
C-statistic = 0.63
At risk
351 200 144 118 107 97 34
Overall survival probability
Years after registration
B
All patients, by ELN-2022
Favorable n=106 (48 events)
Intermediate n=67 (52 events)
Adverse n=99 (90 events)
Unknown n=79 (61 events)
C-statistic = 0.63
At risk
351 200 144 118 107 97 34
Overall survival probability
Years after registration
C
Patients > 55, by ELN-2017
Favorable n=48 (35 events)
Intermediate n=34 (32 events)
Adverse n=57 (56 events)
Unknown n=48 (46 events)
C-statistic = 0.58
At risk
187 78 40 31 27 23 14
Overall survival probability
Years after registration
D
Patients > 55, by ELN-2022
Favorable n=41 (28 events)
Intermediate n=31 (30 events)
Adverse n=67 (65 events)
Unknown n=48 (46 events)
C-statistic = 0.6
At risk
187 78 40 31 27 23 14
Overall survival probability
Years after registration
E
Patients ≤ 55, by ELN-2017
Favorable n=69 (23 events)
Intermediate n=30 (17 events)
Adverse n=34 (27 events)
Unknown n=31 (15 events)
C-statistic = 0.66
At risk
164 123 105 88 81 75 21
Overall survival probability
Years after registration
F
Patients ≤ 55, by ELN-2022
Favorable n=65 (20 events)
Intermediate n=36 (22 events)
Adverse n=32 (25 events)
Unknown n=31 (15 events)
C-statistic = 0.67
At risk
164 123 105 88 81 75 21
Overall survival probability
Years after registration

Supplemental Table 1: Characteristics of patients analyzed using ELN-2017 and ELN-2022 guidelines. Data was procured from n=351 patients. Abbreviations: CR, complete remission.

Factor	Level	Number (%) of patients (n=351)	
Age	Age	Median 56 years (range 18-88)	
SWOG Study ID	S0106	205 (58)	
	S0112	24 (7)	
	S9031	57 (16)	
	S9333	65 (19)	
Hispanic Ethnicity	Hispanic	14 (4)	
	Not Hispanic	288 (82)	
	Hispanic ethnicity unknown	49 (14)	
FLT3 Status	FLT3-ITD mutated	110 (31)	
	FLT3-ITD not mutated	238 (68)	
	FLT3 ITD not tested	2 (1)	
NPM1 status	NPM1 mutated	124 (35)	
	NPM1 not mutated	223 (64)	
	NPM1 not tested	2 (1)	
	NPM1 statust unknown	1 (0)	
Cytogenic risk (ELN2017)	Favorable	42 (12)	
	Intermediate	184 (52)	
	Unfavorable	49 (14)	
	Unknown	76 (22)	
Cytogenic risk (ELN2022)	Favorable	43 (12)	
	Intermediate	184 (52)	
	Unfavorable	48 (14)	
	Unknown	76 (22)	
			5-year overall survival
ELN2017	Favorable	117 (33)	53% (95% CI 44% - 63%)
	Intermediate	64 (18)	22% (95% CI 14% - 35%)
	Unfavorable	91 (26)	12% (95% CI 7% - 21%)
	Unknown	79 (23)	22% (95% CI 15% - 34%)
ELN2022	Favorable	106 (30)	57% (95% CI 49% - 68%)
	Intermediate	67 (19)	21% (95% CI 13% - 34%)
	Unfavorable	99 (28)	12% (95% CI 7% - 21%)
	Unknown	79 (23)	22% (95% CI 15% - 34%)
ELN changed 2017-2022	Changed from 2017-2022	33 (9)	
	Did not change from 2017-2022	318 (91)	
Response to therapy	CR/Unconfirmed CR	210 (60)	
	No CR	141 (40)	
Overal survival	Overal survival	Median 1.4 years (95% CI 1.1-1.8)	

Supplemental Table 2: Molecular mutation profiles of patients analyzed with ELN-2017 and ELN-2022.		
Factor	Level	Number (%) of patients (n = 351)
ASXL1	ASXL1 mutated	33 (9)
	ASXL1 not mutated	314 (89)
	ASXL1 not tested	3 (1)
	ASXL1 status unknown	1 (0)
RUNX1	RUNX1 mutated	40 (11)
	RUNX1 not mutated	307 (87)
	RUNX1 not tested	3 (1)
	RUNX1 status unknown	1 (0)
TP53	TP53 mutated	26 (7)
	TP53 not mutated	321 (91)
	TP53 not tested	3 (1)
	TP53 status unknown	1 (0)
BCOR	BCOR mutated	12 (3)
	BCOR not mutated	335 (95)
	BCOR not tested	3 (1)
	BCOR status unknown	1 (0)
EZH2	EZH2 mutated	12 (3)
	EZH2 not mutated	335 (95)
	EZH2 not tested	3 (1)
	EZH2 status unknown	1 (0)
SF3B1	SF3B1 mutated	15 (4)
	SF3B1 not mutated	332 (95)
	SF3B1 not tested	3 (1)
	SF3B1 status unknown	1 (0)
SRSF2	SRSF2 mutated	36 (10)
	SRSF2 not mutated	311 (89)
	SRSF2 not tested	3 (1)
	SRSF2 status unknown	1 (0)

STAG2	STAG2 mutated	7 (2)
	STAG2 not mutated	340 (97)
	STAG2 not tested	3 (1)
	STAG2 status unknown	1 (0)
U2AF1	U2AF1 mutated	11 (3)
	U2AF1 not mutated	336 (96)
	U2AF1 not tested	3 (1)
	U2AF1 status unknown	1 (0)
ZRSR2	ZRSR2 mutated	1 (0)
	ZRSR2 not mutated	346 (99)
	ZRSR2 not tested	3 (1)
	ZRSR2 status unknown	1 (0)

Supplemental Table 3: Univariate and multivariate analyses with ELN-2017 and ELN-2022 with FLT3 patients removed. Univariate analyses for complete response, overall survival, and relapse-free survival for patients excluding those with FLT3 mutations. Multivariate analyses for complete response, overall survival, and relapse-free survival for patients excluding those with FLT3 mutations. Analyses were performed using data from n= 238 patients.

Univariate analyses				
Variable	**Level**	**Complete Response OR (95% CI; P-value)**	**Overall Survival HR (95% CI; P-value)**	**Relapse-free Survival HR (95% CI; P-value)**
Age	Continuous	0.96 (0.94-0.98; <0.01)	1.05 (1.04-1.06; <0.01)	1.03 (1.02-1.05; <0.01)
	By decade	0.66 (0.55-0.80; <0.01)	1.61 (1.43-1.81; <0.01)	1.39 (1.20-1.62; <0.01)
Cytogenetic risk 2017[1]	Favorable	5.47 (1.58-18.93; <0.01)	0.26 (0.13-0.50; <0.01)	0.51 (0.29-0.89; 0.017)
	Unfavorable	0.16 (0.07-0.36; <0.01)	2.57 (1.73-3.82; <0.01)	1.70 (0.84-3.45; 0.14)

	Unknown	0.34 (0.17-0.71; <0.01)	1.36 (0.89-2.06; 0.15)	1.02 (0.55-1.91; 0.95)
Cytogenetic risk 2022[1]	Favorable	3.94 (1.30-11.91; 0.015)	0.28 (0.15-0.53; <0.01)	0.50 (0.29-0.87; 0.014)
	Unfavorable	0.14 (0.06-0.32; <0.01)	2.64 (1.77-3.94; <0.01)	1.51 (0.72-3.17; 0.28)
	Unknown	0.33 (0.16-0.68; <0.01)	1.36 (0.90-2.07; 0.14)	1.00 (0.54-1.88; 0.99)
Performance Status	Numeric	0.90 (0.65-1.24; 0.51)	1.17 (0.98-1.41; 0.089)	1.02 (0.78-1.32; 0.89)
	2-3 v 0-1	0.70 (0.36-1.38; 0.31)	1.45 (0.98-2.14; 0.06)	1.12 (0.65-1.96; 0.68)
AML Onset	Yes v No	0.06 (0.01-0.26; <0.01)	3.34 (2.03-5.50; <0.01)	0.90 (0.13-6.49; 0.92)
	S0106	2.64 (1.17-5.96; 0.019)	0.25 (0.16-0.38; <0.01)	0.30 (0.16-0.54; <0.01)

Study[2]	S0112	0.71 (0.23-2.26; 0.57)	0.94 (0.53-1.69; 0.84)	0.76 (0.31-1.88; 0.55)
	S9333	0.87 (0.34-2.19; 0.76)	0.77 (0.48-1.25; 0.29)	0.81 (0.41-1.62; 0.56)
ELN 2017[1]	Favorable	2.78 (1.13-6.85; 0.026)	0.42 (0.25-0.70; <0.01)	0.59 (0.33-1.05; 0.072)
	Adverse	0.26 (0.11-0.65; <0.01)	1.80 (1.10-2.92; 0.018)	1.26 (0.63-2.52; 0.52)
	Unknown	0.41 (0.16-1.07; 0.07)	1.09 (0.63-1.87; 0.76)	0.85 (0.40-1.82; 0.68)
ELN 2022[1]	Favorable	2.33 (0.86-6.25; 0.094)	0.41 (0.24-0.71; <0.01)	0.55 (0.29-1.05; 0.069)
	Adverse	0.26 (0.10-0.69; <0.01)	1.69 (1.00-2.86; 0.049)	1.27 (0.63-2.57; 0.5)
	Unknown	0.35 (0.12-1.00; 0.049)	1.09 (0.61-1.95; 0.77)	0.84 (0.38-1.86; 0.66)

ELN 2017 (excluding unknowns)[1]	Favorable	2.78 (1.13-6.85; 0.026)	0.41 (0.25-0.68; <0.01)	0.58 (0.33-1.04; 0.069)
	Adverse	0.26 (0.11-0.65; <0.01)	1.82 (1.12-2.95; 0.016)	1.26 (0.63-2.52; 0.52)
ELN 2022 (excluding unknowns)[1]	Favorable	2.33 (0.86-6.25; 0.094)	0.40 (0.23-0.69; <0.01)	0.55 (0.29-1.03; 0.063)
	Adverse	0.26 (0.10-0.69; <0.01)	1.70 (1.01-2.88; 0.047)	1.26 (0.62-2.55; 0.52)
[1]Reference level = Intermediate				
[2]Reference level = S9031				

Multivariate analyses		
Model	**AUC or C-statistic**	**AUC or C-statistic (excluding unknowns)**
Complete Response (CR, AUC)		
ELN 2017	0.75	0.75
ELN 2022	0.74	0.74
Age + ELN 2017	0.79	0.78

Age + ELN 2022	0.77	0.77
Overall Survival (OS, C-Statistic)		
ELN 2017	0.66	0.67
ELN 2022	0.66	0.67
Age + ELN 2017	0.73	0.73
Age + ELN 2022	0.72	0.72
Relapse-free Survival (RFS, C-Statistic)		
ELN 2017	0.57	0.57
ELN 2022	0.58	0.59
Age + ELN 2017	0.65	0.66
Age + ELN 2022	0.65	0.67