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

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*-internal tandem duplication (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. In order 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 *Online Supplementary Table S1*.[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 the *Online Supplementary Table S2*.

Univariate analyses adjusting for ELN-2017 or ELN-2022 risk yielded similar statistical results for all outcomes: AUC of 0.7 for CR and C-statistics of 0.63 and 0.61 for OS and RFS, respectively (Table 1; Figures 1A, B; *Online Supplementary Figure S1A, B*). 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 (*Online Supplementary Table S1*). Restricting the analyses to age of patients >55 years old, 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, D) and RFS (ELN-2022=0.61 *vs.* ELN-2017=0.60; *Online Supplementary Figure 1C, D*). 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, F) and RFS (ELN-2022=0.60 and ELN-2017=0.60; *Online Supplementary Figure 1E, F*). As we previously described with ELN-2017, the ELN-2022 risk had greater prognostic

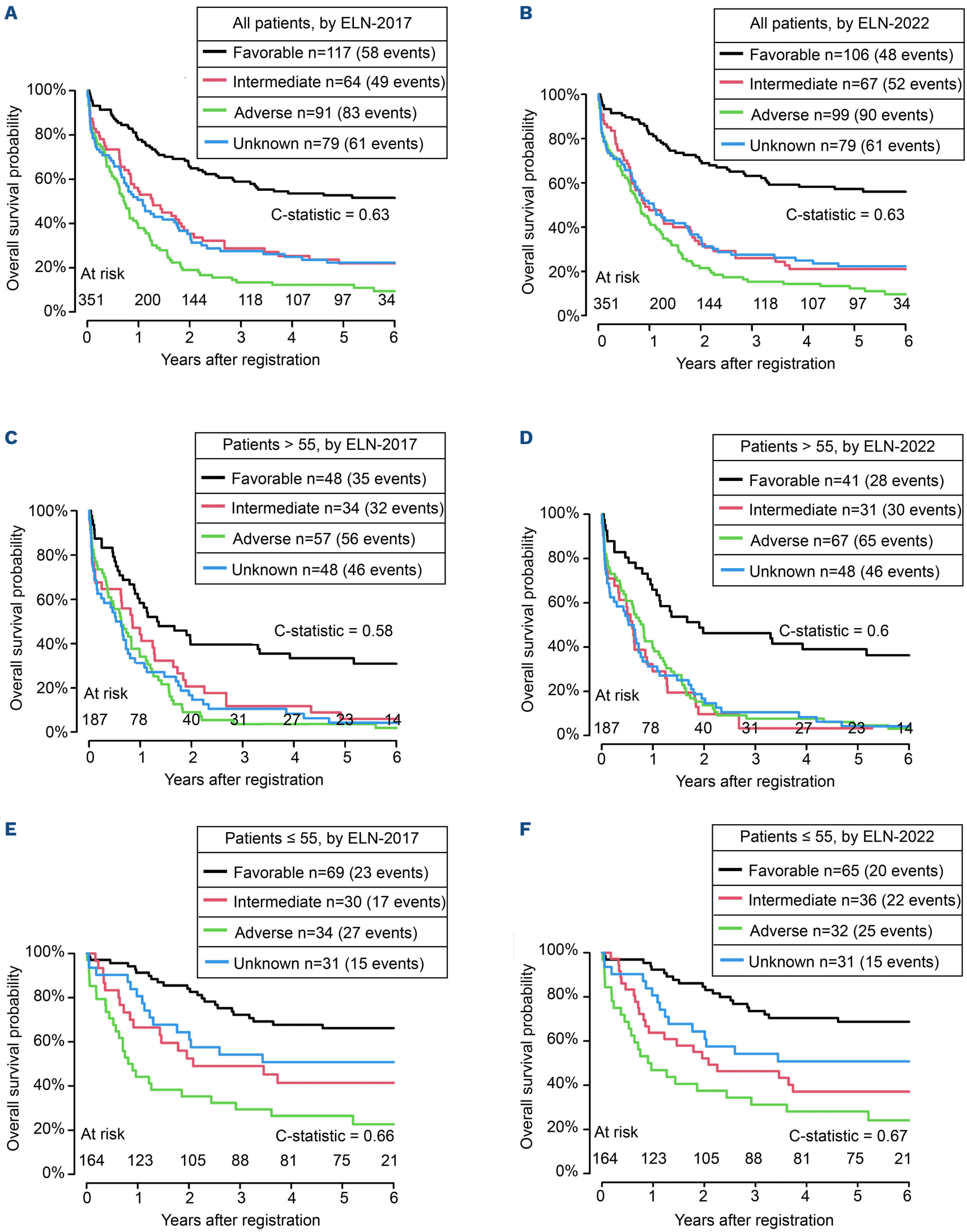

Figure 1. Similar survival probability is seen in older patients analyzed using ELN-2017 and ELN-2022. Overall survival probability was analyzed for all patients classified into favorable, intermediate, adverse, or unknown risk groups based upon (A) ELN-2017 and (B) ELN-2022 guidelines. Overall survival 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.

Table 1. Age minimally changes the 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).

Model	AUC or C-statistic	AUC or C-statistic (excluding unknowns)
Complete response (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 (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 (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

AUC: area under the curve; ELN: European LeukemiaNet.

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 the 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*-ITD mutations, given that examined patients did not receive an FLT3 inhibitor (*Online Supplementary Table S3*). 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 (*Online Supplementary Table S3*).

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 reclassified for their risk stratification category under the ELN-2022 guidelines (*Online Supplementary Table S1*). 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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Disclosures

No conflicts of interest to disclose.

Contributions

CMT, AM, MO, and DLS developed the concept. CMT, AM, MO, FRA, TRC, HPE, JEG, MF, JN, ELPA, CLW, FW, SM and DLS provided resources. CMT, AM, MO, FRA, TRC, MF, JEG, JN, ELPA, CLW, FW and DLS cured data. CMT, AM, MO, ELPA, FW and DLS performed formal analysis using software. CMT, AM, MO, ELPA, FW and DLS performed formal analysis. CMT, AM, MO, HPE, MF and DLS supervised the research. MO, SM and DLS acquired funding. CMT, MO, ELPA, FW and DLS developed the methodology. CMT, AM, MO, FRA, TRC, HPE, JEG, MF, SCL, JN, ELPA, JPR, CLW, FW, SM and DLS wrote, reviewed and edited the manuscript.

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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 *Online Supplementary Appendix*. 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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