REGULAR ARTICLE

blood advances

A revised prognostic model for patients with acute myeloid leukemia and first relapse

Niek G. van der Maas,[1] Dimitri Breems,[2] Clara P. W. Klerk,[3] Thomas Pabst,[4,5] Patrycja Gradowska,[1,6] Abin Thomas,[7] Bart J. Biemond,[8] Jurgen Kuball,[9] Catharina H. M. J. Van Elssen,[10] Otto Visser,[11] Marie-Christiane Vekemans,[12] Carlos Graux,[13] Johan Maertens,[14] Steven Knapper,[15] Mike Dennis,[16] Sylvie Freeman,[17] Ian Thomas,[7] H. Berna Beverloo,[18] Gerwin Huls,[19] Charles Craddock,[20] Peter J. M. Valk,[1] Paresh Vyas,[21,22] Nigel Russell,[23] Gert Ossenkoppele,[8] Bob Löwenberg,[1] Jan J. Cornelissen,[1] and Jurjen Versluis[1]

[1]Department of Hematology, Erasmus University Medical Center Cancer Institute, Rotterdam, The Netherlands; [2]Department of Hematology, Ziekenhuis aan de Stroom, Cadix Hospital, Antwerp, Belgium; [3]Department of Internal Medicine, Dijklander Hospital, Amsterdam, The Netherlands; [4]Department of Medical Oncology, University Hospital, Inselspital, Bern, Switzerland; [5]Swiss Group for Clinical Cancer Research, SAKK, Bern, Switzerland; [6]HOVON Foundation, Rotterdam, The Netherlands; [7]Centre for Trials Research, College of Biomedical & Life Sciences, Cardiff University, Cardiff, United Kingdom; [8]Department of Hematology, Amsterdam University Medical Center, Cancer Center Amsterdam, University of Amsterdam, Amsterdam, The Netherlands; [9]Department of Hematology, University Medical Centre Utrecht, Utrecht University, Utrecht, The Netherlands; [10]Division Hematology, Department of Internal Medicine, GROW institute for Oncology and developmental Biology, Maastricht University Medical Center, Maastricht, The Netherlands; [11]Department of Hematology, Isala Hospital, Zwolle, The Netherlands; [12]Department of Hematology, Cliniques Universitaires Saint-Luc, Brussels, Belgium; [13]Department of Hematology, Université Catholique de Louvain, University Hospital Center Namur (Godinne), Yvoir, Belgium; [14]Department of Hematology, University Hospital Gasthuisberg, Leuven, Belgium; [15]School of Medicine, Cardiff University, Cardiff, United Kingdom; [16]Department of Haematology, The Christie NHS Foundation Trust, Manchester, United Kingdom; [17]Department of Immunology and Immunotherapy, University of Birmingham, Birmingham, United Kingdom; [18]Department of Clinical Genetics, Erasmus University Medical Center, Rotterdam, The Netherlands; [19]Department of Hematology, University Medical Center, University Groningen, Groningen, The Netherlands; [20]Warwick Clinical Trials Unit, University of Warwick, Warwick, United Kingdom; [21]MRC Molecular Haematology Unit, Weatherall Institute of Molecular Medicine, University of Oxford, Oxford, United Kingdom; [22]Department of Haematology, Oxford University Hospitals NHS Trust and Oxford Biomedical Centre, Oxford, United Kingdom; and [23]Guy's and St Thomas' NHS Foundation Trust, London, United Kingdom

Key Points

- The revised AML relapse model includes 9 predictors, grouped into 3 risk categories that are each associated with distinct OS.
- The model outperformed previous scoring systems and was validated in an independent cohort of patients with AML relapse.

Most patients with acute myeloid leukemia (AML) may obtain remission upon induction chemotherapy, but relapse is frequent and associated with poor survival. Previous prognostic models for outcomes after relapse lacked analysis of comprehensive molecular data. A validated prognostic model integrating clinical, cytogenetic, and molecular variables may support treatment decisions. We studied 943 patients with AML who relapsed after intensive induction treatment in a development cohort (HOVON-SAKK). A random survival forest algorithm was used to evaluate the association of clinical parameters, cytogenetic abnormalities, and molecular variables at diagnosis with overall survival (OS). Relapsing patients (n = 377) who were enrolled in the NCRI-AML18 trial were used for validation. In the development cohort, the median age at relapse was 58 years, and patients were classified as 2022 European LeukemiaNet favorable (22%), intermediate (31%), and adverse risk (48%). One-third underwent allogeneic transplantation in the first complete remission. Variable selection yielded 9 variables associated with 1-year OS, including relapse-free interval, age, white blood cell count, mutated *TP53*, *FLT3* internal tandem duplication, core-binding factor abnormalities, t(v;11q23)/*KMT2A* rearrangement, and complex/monosomal karyotype, which were assigned points according to their estimated hazard ratios. Three prognostic groups were defined with distinct 1-year OS in both development (favorable, 51% ± 3%; intermediate, 29% ± 3%; and poor, 14% ± 2%,

Submitted 6 January 2025; accepted 15 April 2025; prepublished online on *Blood Advances* First Edition 22 May 2025; final version published online 28 July 2025. https://doi.org/10.1182/bloodadvances.2025015797.

Data are available on request from the corresponding author, Jurjen Versluis (j.versluis.1@erasmusmc.nl).

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

respectively) and validation cohorts (51% ± 4%, 26% ± 5%, and 14% ± 3%, respectively). Validation confirmed the improved accuracy in predicting outcomes for patients with AML in first relapse. The revised AML relapse model improved on previous prognostic models for outcomes after first relapse. It provides stratification that might support tailoring second line treatment.

Introduction

Disease recurrence is the most common cause of treatment failure in patients with acute myeloid leukemia (AML). Treatment of relapsed AML remains challenging, and outcome has been traditionally poor with median overall survival (OS) of <6 months.[1-5] Although outcome has been improved with novel targeted treatments,[6-9] allogeneic hematopoietic cell transplantation (allo-HCT) remains the only curative treatment for relapsing patients.[10,11] Risk models for these patients might support decision making for reinduction treatment and consolidation treatment with allo-HCT, whereas alternative experimental strategies might be considered for high-risk patients.

Prognostic factors associated with survival after relapse in AML have previously been identified.[1,2,5,12-14] These include the time between the first complete remission (CR1) and relapse, age at relapse, the presence of favorable and unfavorable karyotypes, the presence of *FLT3* internal tandem duplications (ITDs), and previous allo-HCT.[1,2,5,12-14] Earlier developed prognostic model groups[1,2] have highlighted these factors as significant predictors associated with survival after first AML relapse. Since the development of these risk models, an increasing number of molecular and cytogenetic alterations has been recognized affecting outcome in patients with newly diagnosed AML,[11,15] which might also affect survival after first relapse. Models that allow for risk stratification after first relapse using cytogenetic and molecular variables established at initial diagnosis in a recently treated AML patient cohort are currently lacking.

We set out to study a large cohort of patients with AML who relapsed after intensive induction treatment and for whom baseline comprehensive clinical, cytogenetic, and molecular variables were available. We developed a revised stratification system that was validated in an independent cohort of older patients with AML.

Methods

Clinical cohorts

The complete cohort consisted of 5086 patients aged 18 years and older enrolled in 8 consecutive HOVON-SAKK clinical trials (HO42, HO42A, HO43, HO81, HO92, HO102, HO103, and HO132; supplemental Materials) between 2000 and 2018 with an intensive induction chemotherapy backbone for newly diagnosed AML and high-risk myelodysplastic syndrome (MDS) with International Prognostic Scoring System of ≥1.5, Revised International Prognostic Scoring System risk score of >4.5, or excess blasts of ≥10% (see supplemental Figure 1A-H for trial details).[16-23] Postremission treatment with additional chemotherapy, high-dose chemotherapy followed by autologous HCT, or allo-HCT was based on AML risk in evolving classifications.[11,24] Patients were excluded because of no next-generation sequencing (NGS) data available at diagnosis (n = 2543), no CR or CR with incomplete count recovery after 2 cycles of induction chemotherapy (n = 416), and no relapse (n = 1184). The final development cohort consisted of 943 patients who developed a first relapse (Figure 1). The validation cohort included newly diagnosed AML and patients with high-risk MDS with excess blasts of ≥10% aged 60 years and older enrolled in the NCRI-AML18 trial who were treated with intensive induction chemotherapy between 2014 and 2018 (supplemental Figure 1I).[25] Patients were excluded because of no CR or CR with incomplete count recovery after 2 cycles of induction chemotherapy (n = 245) and no relapse (n = 354). The final validation cohort consisted of 377 patients who developed a first relapse (Figure 1). All trial participants provided a written informed consent in accordance with the Declaration of Helsinki.

Genetic analysis

High-molecular-weight genomic DNA was extracted from bone marrow samples or peripheral blood. Diagnostic samples at first AML diagnosis underwent gene resequencing using either a 97-gene panel (Oxford for UK-AML18) or a 54-gene panel (Erasmus MC, Rotterdam, for HOVON-SAKK), containing the most frequently mutated genes in myeloid malignancies. Targeted NGS used liquid-phase capture of molecule-barcoded libraries, with custom-designed probes targeting AML-associated genes for UK-AML18 (Roche, Basel, Switzerland) or the Illumina TruSight Myeloid panel for HOVON-SAKK (Illumina, San Diego, CA). Genomic libraries were sequenced on the Illumina platform, ensuring a minimum mean target coverage of 500×. Details of cytogenetic analysis, NGS, and additional molecular analyses have been previously published.[15]

Statistical methods

The analysis adhered to the Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis guideline for prediction model development and validation.[26] A total of 45 variables (supplemental Table 1) were considered for the association with 1-year OS in model development: age at relapse (≥60 vs <60 years), relapse-free interval (≤12 months vs >12 months) defined as the time between CR1 and relapse, number of treatment cycles needed to obtain CR1 (1 vs >1), sex (male vs female), white blood cell count (WBC) at diagnosis (≥10 × 10^9/L vs <10 × 10^9/L), previous allo-HCT (yes vs no), previous autologous HCT (yes vs no), 29 different gene mutations (presence vs absence), and 9 different cytogenetic abnormalities (presence vs absence) (see supplemental Table 1 for details of mutations and cytogenetic variables). Complex and monosomal karyotypes were grouped owing to their frequent co-occurrence in this cohort (94% concordant). During variable selection, we evaluated different thresholds for age, relapse-free interval, and WBC and found that the most optimal cutoffs were 60 years, 12 months,

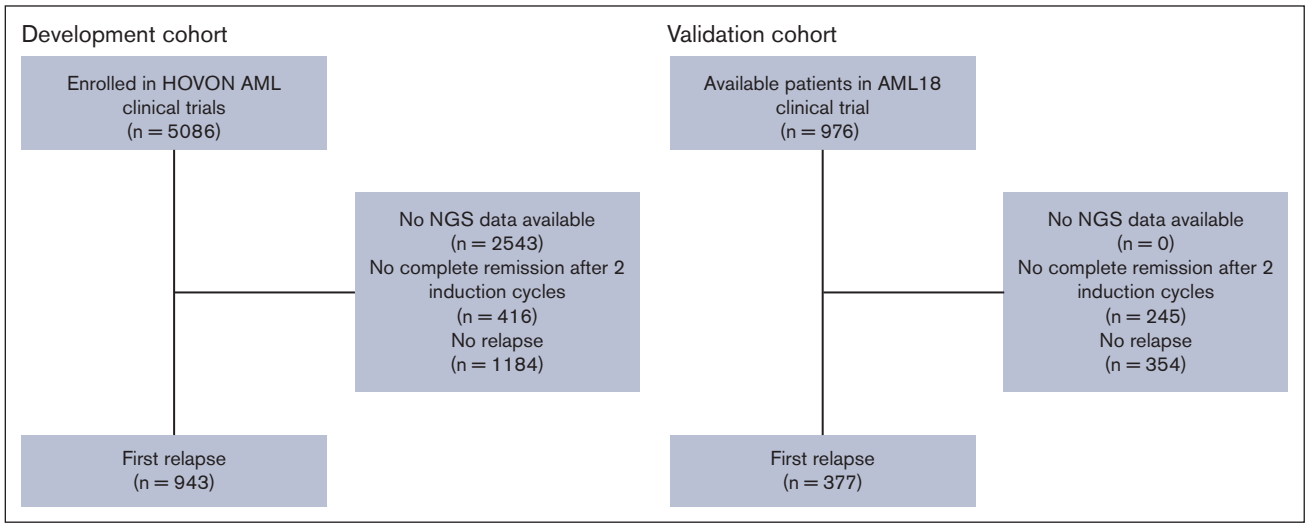

Figure 1. Consort diagram of patients included in this study.

and 10 × 10^9/L, respectively. Gene mutations and cytogenetic abnormalities were only evaluated if present in 10 or more patients (supplemental Table 1). OS was defined as the time from the date of first relapse to either the date of death from any cause or the date of last contact while still alive. OS curves were estimated using the Kaplan-Meier method and compared using the log-rank test. Model development consisted of 3 sequential stages, which included (1) variable selection using a random survival forest, (2) Cox regression analysis with backward selection ($P < .10$) to define the optimal model, and (3) assignment of weights and defining groups based on significantly different OS compared with a lower score to construct the final prognostic model. Further details are available in the supplemental Materials. The impact of allo-HCT after relapse was assessed using a time-dependent Cox regression allowing the allo-HCT covariate to change the state at the time of allo-HCT. Fine-Gray models were used to estimate the probability of an event accounting for competing risks, nonrelapse mortality (NRM), and relapse. Prognostic accuracy of existing models and the revised model was evaluated using Harrell's C-index. Cytogenetic data were not available in 38 patients (4.0%) owing to failed karyotyping and 3 patients (0.3%) because of missing WBC at diagnosis in the development cohort. Missing cytogenetics data were uniformly imputed as absent, consistent with real-world clinical practice, and with the median WBC count for missing WBC. All analyses were performed in R version 4.4.1. The R script of the analyses can be found online (https://github.com/niekvandermaas/AML-relapse-model).

Results

Patient characteristics

The development cohort consisted of 943 patients who relapsed after having obtained CR1 upon initial intensive treatment (Table 1). In this cohort, 1-year OS was similar across treatment periods (<2010 vs ≥2010; supplemental Figure 2) and disease type (AML vs high-risk MDS; supplemental Figure 3). In addition, no difference was observed for 1-year OS between missing and nonmissing NGS data (supplemental Figure 4). The median age of patients at relapse in this cohort was 58 years (range, 18-81 years; Table 1). At diagnosis, 22% of the patients were classified as having a favorable risk according to the European LeukemiaNet (ELN) 2022 AML classification, 31% as intermediate risk, and 48% as adverse risk (Table 1).[11] In this cohort, 33% of patients received postremission treatment with allo-HCT, whereas 14% underwent autologous HCT in first CR (Table 1). A total of 95% relapsing patients had at least 1 cytogenetic abnormality or genetic mutation at diagnosis (median, 3), with 62% of patients having molecular mutations only, 3% having karyotype alterations

Table 1. Patient characteristics at first AML diagnosis

Characteristic	Development cohort (N = 943)
Age at relapse, median (range), y	58.0 (18.0-81.0)
Sex, n (%)	
Male	523 (55.5)
Female	420 (44.5)
WBC (at diagnosis), median (range), ×10^9/L	8.45 (0-510)
ELN risk at diagnosis, n (%)	
Favorable	204 (21.6)
Intermediate	289 (30.6)
Adverse	450 (47.7)
Best response within 2 induction cycles, n (%)	
CR	889 (94.3)
CRi	54 (5.7)
HCT in first CRi, n (%)	
No	506 (53.7)
Allogeneic	310 (32.9)
Autologous	127 (13.5)
Relapse-free interval, median (range), mo	8 (0-124)
Follow-up of patients alive after first relapse, median (range), mo	49 (0-128)

CRi, CR with incomplete count recovery.

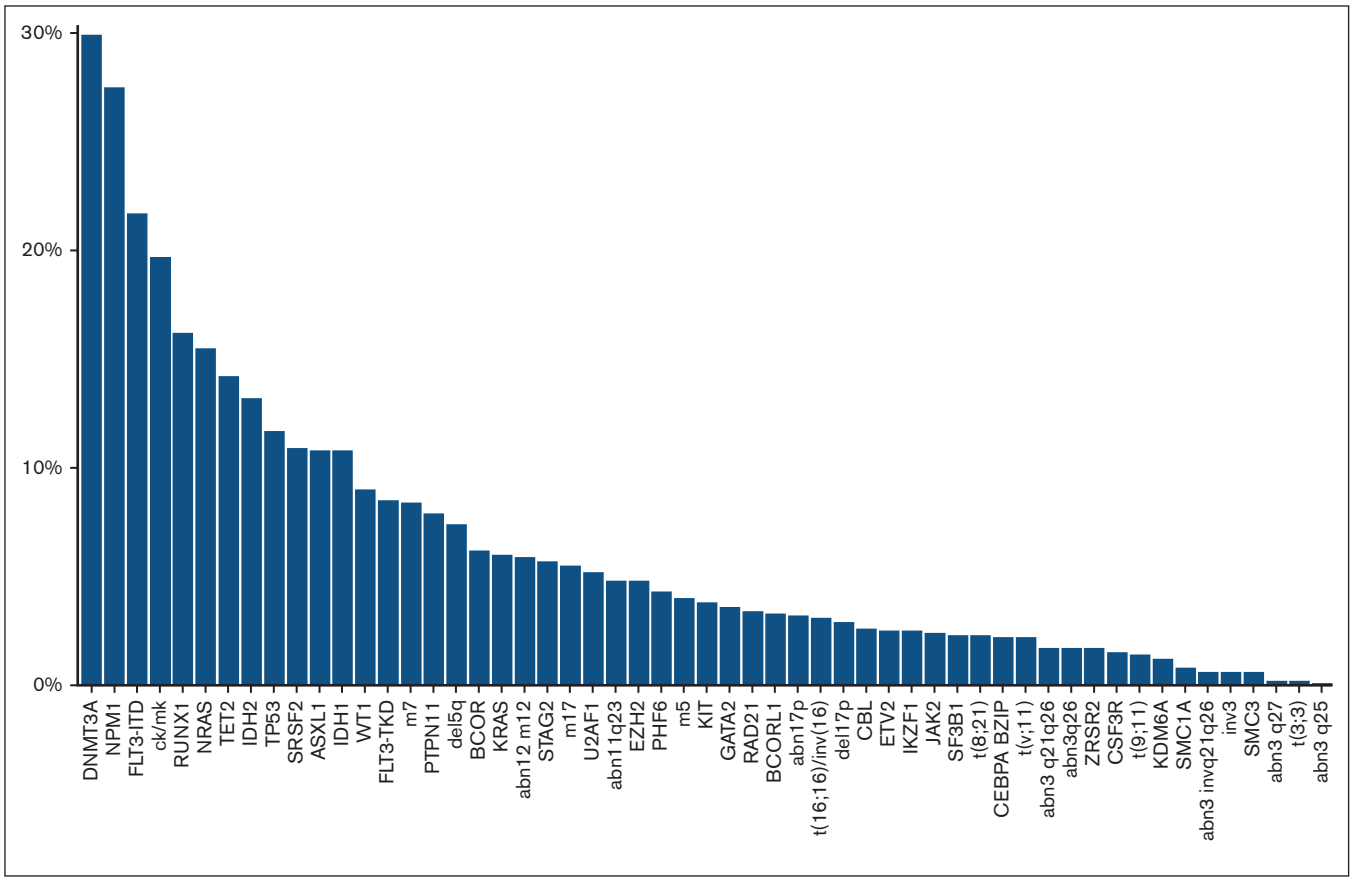

Figure 2. Mutational landscape of the development cohort at first AML diagnosis. Driver events found at diagnosis in 943 patients with relapsed AML. Each bar represents a driver lesion, including gene mutations, and chromosomal abnormalities. abn, abnormality in; ck, complex karyotype (annotated according to the 2022 ELN risk classification); del, deletion in; inv, inversion of; mk, monosomal karyotype; m, monosomy; t, translocation of.

only, and 32% having both. Most mutations at diagnosis were found in the following genes: *DNMT3A* (30%), *NPM1* (27%), and *FLT3* ITD (22%). Mutated *TP53* was found in 12% of patients. Complex or monosomal karyotype according to ELN 2022 was the most frequent cytogenetic abnormality in these patients (19%), whereas core-binding factor (CBF) abnormalities [t(16;16)/inv(16) (3%) and t(8;21) (2%)] were relatively infrequent (Figure 2).[27] The development cohort had a median follow-up from relapse of 49 months for patients alive (range, 0-128 months; Table 1). OS rates at 1 and 4 years after first relapse in the development cohort were 33% ± 2% and 16% ± 1%, respectively.

Patient outcomes by previous prognostic models

Previous prognostic models were assessed for their predictive performance in the development cohort. The HOVON-SAKK model[1] was associated with a C-index of 0.65 ± 0.016 for 1-year OS. Most patients were classified as adverse risk in that model (684 of 943, 73%). One-year OS after relapse was clearly distinct estimating 74% ± 7% for the favorable group, 54% ± 3% for the intermediate group, and 24% ± 2% for the adverse group, respectively (Figure 3A). Similarly, the GOELAMS model[2] was associated with a C-index of 0.64 ± 0.017, outcomes of which were distinct in the 3 risk groups associated with survival probabilities at 1 year: 49% ± 3% for the favorable group, 29% ± 2% for the intermediate group, and 11% ± 3% for the adverse group (Figure 3B).

Development of a revised prognostic model for patients in first relapse

To determine the optimal patient-specific and genetic variables for risk stratification of OS, we used a random survival forest algorithm, which revealed the hierarchy of each clinical, genetic, and cytogenetic variable for stratifying 1-year OS (details in the supplemental Materials). A total of 45 candidate variables were considered (supplemental Table 1), of which 18 were identified as significantly affecting ($P < .01$) 1-year OS (supplemental Figure 5). These were included in a multivariable Cox regression analysis using a stepwise backward selection, which resulted in a final model of 9 predictors. The 3 most important variables for 1-year OS after relapse were the absence of CBF abnormalities (hazard ratio [HR], 2.07; 95% confidence interval [CI], 1.38-3.12; $P < .001$), mutated *TP53* (HR, 1.99; 95% CI, 1.48-2.67; $P < .001$), and relapse-free interval of ≤12 months (HR, 1.76; 95% CI, 1.46-2.12; $P < .001$) (Figure 4A). Notably after adjustment for covariates, including mutated *TP53*, complex or monosomal karyotype was independently correlated with adverse OS (HR, 1.40; 95% CI, 1.08-1.82; $P = .01$; Figure 4A). Each of the 9 variables

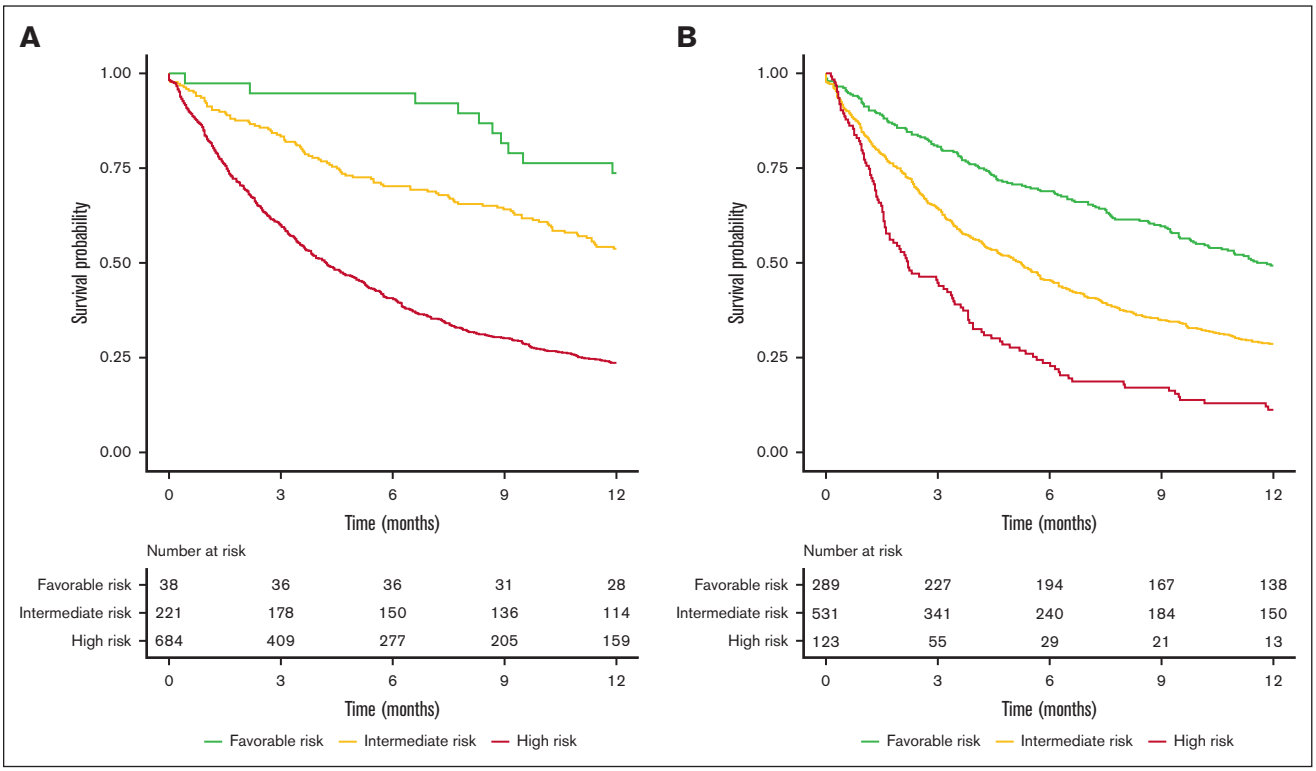

Figure 3. OS after 1 year by previous prognostic models. OS in the development cohort by HOVON-SAKK (A) and GOELAMS (B) prognostic models.

was assigned points based on their rounded HRs (Figure 4A) resulting in 3 points for either no CBF abnormalities or a *TP53* mutation. Similarly, relapse-free interval of ≤12 months, previous allo-HCT, t(v;11q23)/*KMT2A* rearrangement, and age at relapse ≥60 years were each assigned 2 points, whereas WBC of ≥10 × 10^9/L, complex and/or monosomal karyotype, and *FLT3* ITD were assigned 1 point. These points were subsequently used to derive the total score for each patient. The median total score in the development cohort was 7 points (range, 1-14). OS decreased with increasing scores (supplemental Figure 6). Based on significantly different OS, we collapsed the development cohort into 3 groups: favorable (≤6 points; n = 389, 42%), intermediate (7 points; n = 197, 21%), and poor (≥8 points; n = 357, 38%; supplemental Figure 7).

Favorable-risk patients in the revised model had a 1-year OS of 51% ± 3% (Figure 4B). Intermediate-risk patients had a 1-year OS of 29% ± 3%, which was 14% ± 2% in the poor-risk subgroup (Figure 4B). The C-index of the prognostic model in the development cohort was 0.71 ± 0.016 with excellent calibration (supplemental Figure 8). Four-year OS was also significantly different among the 3 subgroups (29% ± 2%, 11% ± 2%, 5% ± 1%, respectively; supplemental Figure 9A). The model restratified 57% and 49% of patients from the previous HOVON-SAKK and GOELAMS risk groups, respectively. Most patients in the large HOVON-SAKK poor-risk group were reclassified as favorable (26%) or intermediate (24%), whereas 30% and 42% of patients in the large GOELAMS intermediate-risk group were reclassified to the favorable- and poor-risk group of the revised model, respectively (Figure 4C-D).

Model validation

The model was validated in an independent data set derived from the NCRI-AML18 trial, consisting of 976 older patients with newly diagnosed AML aged 60 years and older who also received intensive induction chemotherapy. A total of 377 relapsing patients were identified with a median age at relapse of 69 years (range, 60-81) (Figure 5A). Sixty-two percent were classified as poor or very poor risk in the AML60+ classification at the time of diagnosis,[15] whereas 60% were adverse according to the 2022 ELN risk classification. Allo-HCT in CR1 was applied in 14% as postremission treatment (Figure 5A). A total of 97% of patients had at least 1 cytogenetic or molecular abnormality (median, 4), with 77% of patients having molecular mutations only, 1% having karyotype alterations only, and 21% having both. The most frequently mutated genes identified were *DNMT3A* (37%), *NPM1* (27%), and *ASXL1* (26%). *TP53* was mutated in 11% of patients. According to ELN 2022 criteria, the most common cytogenetic abnormality was a complex or monosomal karyotype (14%), whereas CBF abnormalities, specifically t(16;16)/inv(16) (1%) and t(8;21) (3%), were rare (Figure 5B). Median follow-up from relapse was 21 months for patients alive (range, 0-59 months; Figure 5A). OS rates at 1 and 4 years after first relapse year in the validation cohort were 30% ± 2% and 9% ± 2%, respectively. The 3 groups defined in the development cohort were used to classify the validation cohort: favorable (≤6 points; n = 137, 36%), intermediate (7 points; n = 85, 23%), and poor (≥8 points; n = 155, 41%), which were associated with distinct 1- and 4-year OS (1-year OS, 51% ± 4%, 26% ± 5%, and 14% ± 3%, respectively;

A

Predictor variable	HR	95% CI	*P*-value	Points
No CBF abnormalities	2.07	1.38-3.12	<.001	3
Mutated *TP53*	1.99	1.48-2.67	<.001	3
Relapse free interval ≤12 months	1.76	1.46-2.12	<.001	2
Previous allo-HCT	1.65	1.38-1.96	<.001	2
t(v;11q23)/KMT2A-rearranged	1.54	1.10-2.14	.01	2
Age at relapse ≥60 years	1.53	1.29-1.82	<.001	2
Complex karyotype (inc. MK)	1.40	1.08-1.82	.01	1
FLT3-ITD	1.37	1.11-1.69	.003	1
White blood cell count ≥10 ×10^9/L	1.27	1.07-1.52	.01	1

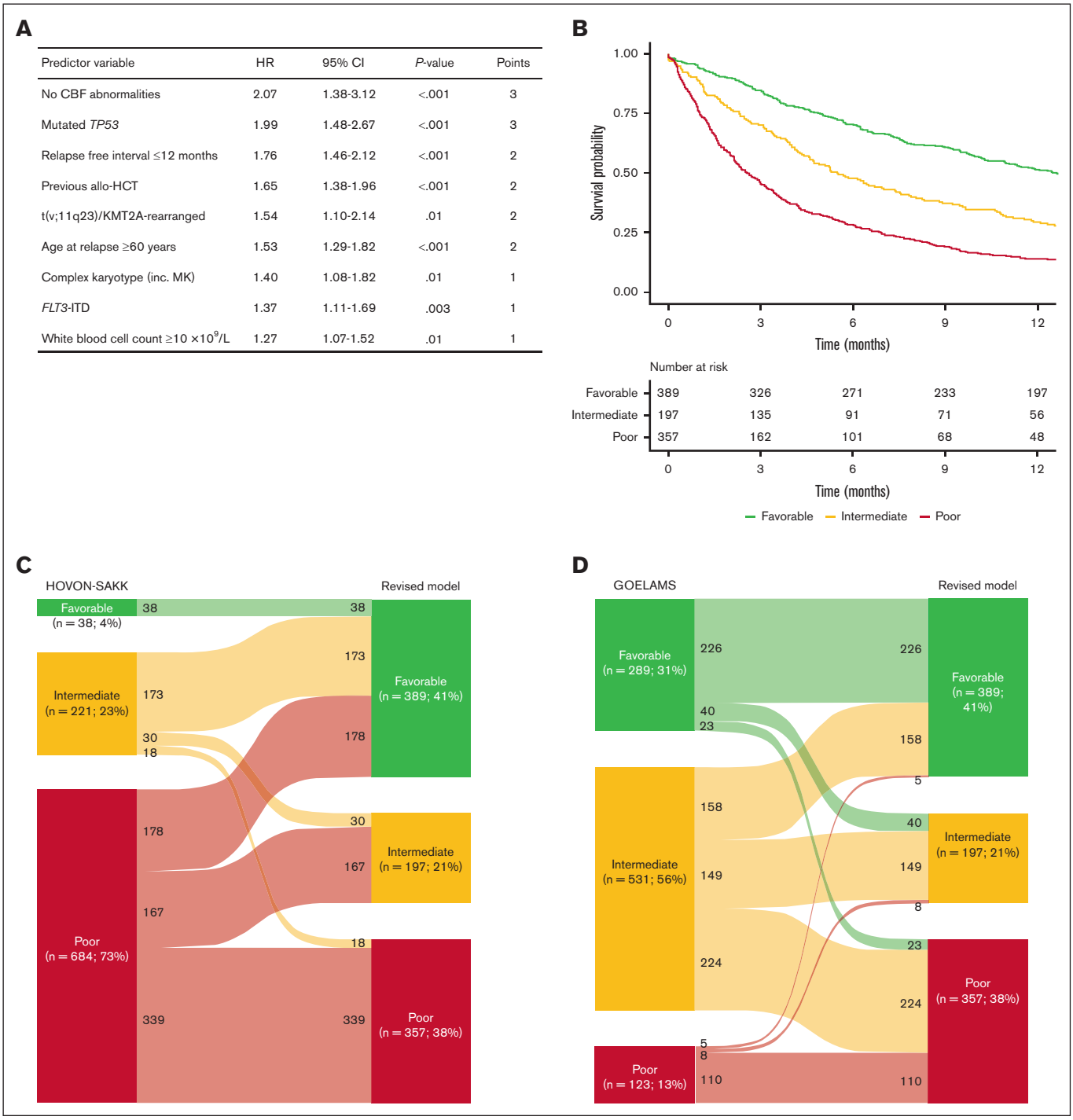

Figure 4. Revised prognostic model for AML after first relapse. HRs with 95% CI and *P* value of final model in the development cohort with points for a clinical prediction score (A) and OS after 1 year for patients in first relapse according to risk categories of the revised prognostic model in the development cohort (B). Supplemental Figure 9A shows the 4-year OS rates for patients from their first relapse, categorized by the revised prognostic model. Restratification of patients from HOVON-SAKK (C) and GOELAMS model (D) to the revised prognostic model in the development cohort. mk, monosomal karyotype; t, translocation of.

Figure 5C; supplemental Figure 9B). The performance of the revised prognostic model as measured by the C-index was 0.71 ± 0.028 with excellent calibration (supplemental Figure 10). The GOELAMS and HOVON-SAKK models had C-indices of 0.69 ± 0.027 and 0.62 ± 0.027 in the validation cohort, respectively. Similar to the development cohort, the

A

	Validation cohort (n = 377)
Age at relapse (median [range])	69.0 [60.0-81.0]
Sex	
Male	226 (59.9%)
Female	151 (40.1%)
WBC (at diagnosis;[×10^9/L]) (median [range])	6.4 [0-365]
ELN risk 2022 at diagnosis	
Favorable	58 (15.4%)
Intermediate	92 (24.4%)
Adverse	227 (60.2%)
AML60+ classification at diagnosis	
Favorable	25 (6.6%)
Intermediate	117 (31.0%)
Poor	178 (47.2%)
Very Poor	57 (15.1%)
Best response on protocol treatment	
CR	333 (88.3%)
CRi	44 (11.7%)
SCT in first CR(i)	
No	326 (86.5%)
Allogeneic	51 (13.5%)
Autologous	0 (0%)
Relapse free interval (months) (median [range])	12.1 [1-61]
Follow-up of patients alive after first relapse (months) (median [range])	21 [0-59]

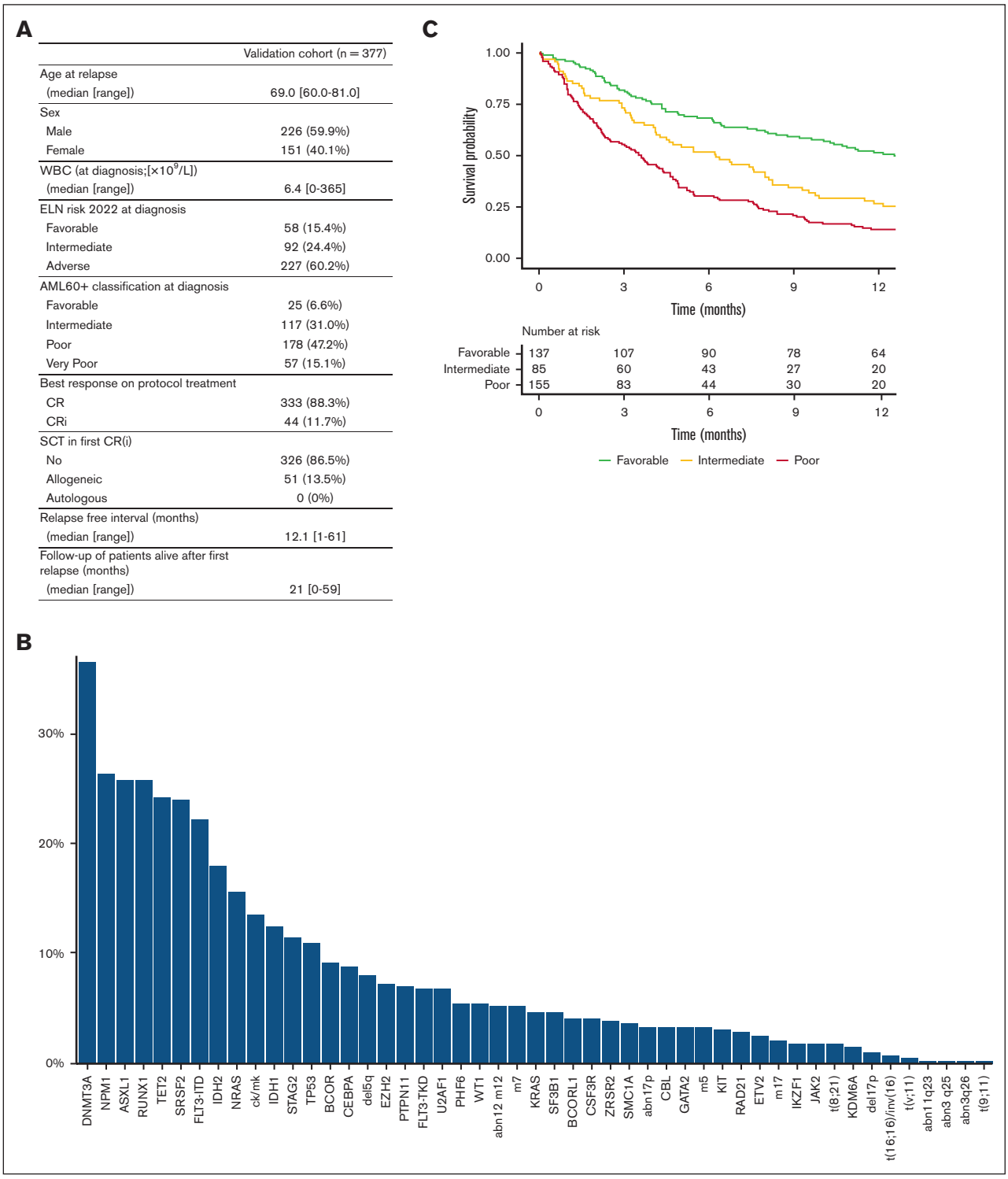

Figure 5. Validation of the revised prognostic model in the NCRI-AML18 trial. Patient characteristics (A) with the molecular and cytogenetic landscape at diagnosis of the validation cohort (B) and OS after 1 year for patients in first relapse according to risk categories of the revised prognostic model (C). Supplemental Figure 9B shows the 4-year OS rates for patients at their first relapse, categorized by the revised prognostic model. Restratification of patients from HOVON-SAKK (D) and GOELAMS model (E) to the revised prognostic model in the validation cohort. abn, abnormality in; ck, complex karyotype (annotated according to the 2022 ELN risk classification); CRi, CR with incomplete count recovery; del, deletion in; inv, inversion of; mk, monosomal karyotype; m, monosomy; t, translocation of.

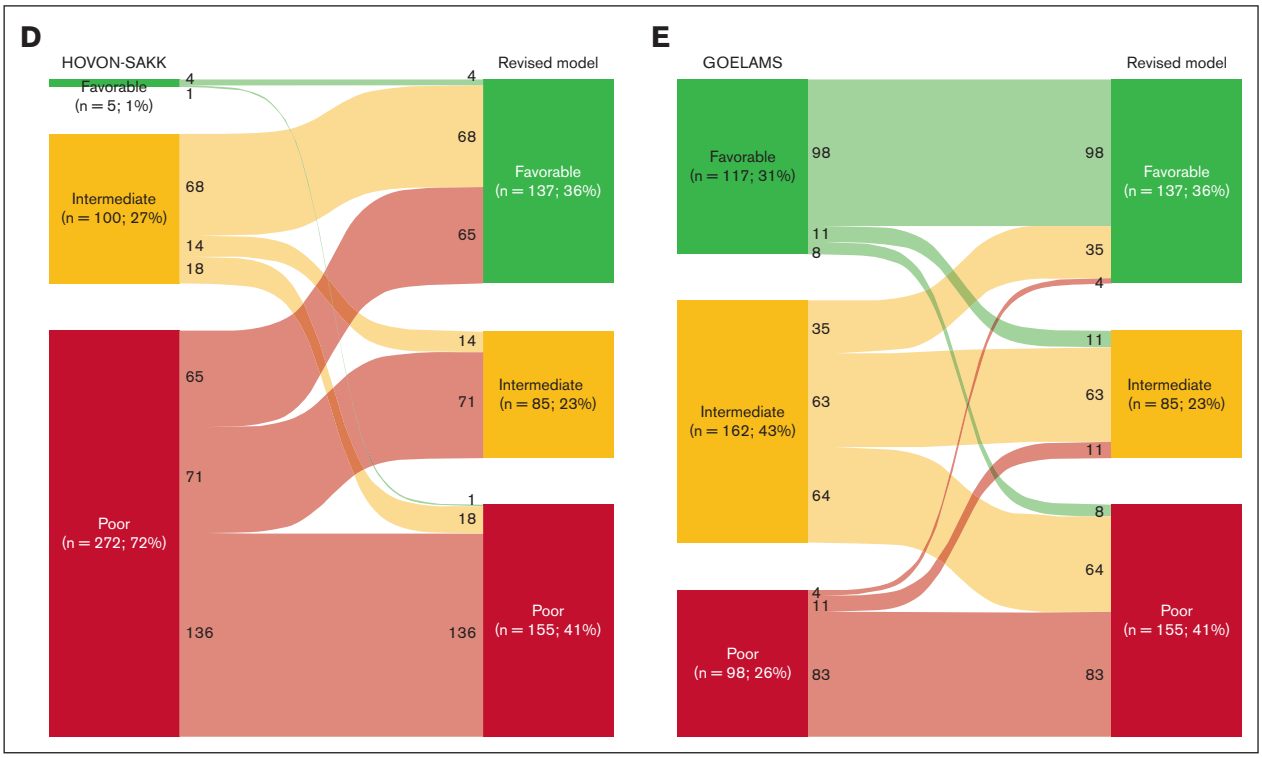

Figure 5 (continued)

revised model restratified 59% from the original HOVON-SAKK risk groups and 35% from the GOELAMS groups (Figure 5D-E). HOVON-SAKK poor-risk patients were considered favorable or intermediate in 24% and 26%, respectively, in the revised model.

Treatment after relapse

In the development cohort, reinduction treatment was used in 690 patients (73%), which resulted in a second CR (CR2) in 348 of patients (50%) (supplemental Figure 11; supplemental Table 2). Across subgroups, CR2 after reinduction treatment was obtained in 65% and 44% of the favorable- and intermediate-risk patients, respectively, which was higher than the poor-risk group (32%; C-index, 0.66; supplemental Tables 2 and 3). In addition, the revised model showed a distinct OS and event-free survival for patients who received reinduction treatment and relapse-free survival for patients in CR2 (supplemental Figure 12; supplemental Table 3). The revised model compared favorably in terms of accuracy to these outcomes with the previous risk stratification systems (supplemental Table 3). Allo-HCT was used as consolidation treatment of a CR2 in 159 patients (46%), and 38 (11%) received a donor lymphocyte infusion after CR2 (supplemental Figure 11; supplemental Table 2). A total of 342 patients (50%) did not achieve a CR2 despite reinduction treatment consisting of intensive chemotherapy (n = 279, 82%), upfront allo-HCT (n = 43, 13%), or donor lymphocyte infusion (n = 20, 6%) (supplemental Figure 11; supplemental Table 2).

A time-dependent analysis with allo-HCT as a time-varying covariate was performed for patients who had attained a CR2. OS was improved by allo-HCT compared with no allo-HCT (HR, 0.54; 95% CI, 0.37-0.79; P = .001; supplemental Figure 13), and cumulative incidence of relapse was lower after allo-HCT than no allo-HCT (HR, 0.58; 95% CI, 0.38-0.88; P = .011; supplemental Figure 13). In contrast, the cumulative incidence of NRM was higher in the allo-HCT group, although not significantly different (HR, 1.30; 95% CI, 0.61-2.80; P = .499; supplemental Figure 13). Low patient numbers precluded an analysis of the impact of allo-HCT per risk group.

Discussion

Relapse in AML is frequent with low response rates to reinduction treatment and dismal OS.[1-5,14] Recent prognostic models for patients with relapsed AML incorporating comprehensive genetic data are currently lacking. Therefore, it is necessary to reassess the prognostic value of clinical, cytogenetic, and molecular AML characteristics in patients with relapsed AML after intensive induction treatment. We analyzed the genomic landscape and clinical outcomes of 943 patients with AML with a first relapse aiming to develop a simple prognostic classification system. Using a machine-learning method for variable selection, 9 variables were identified, which were used to stratify patients into 3 risk groups. Although age, relapse-free interval, CBF abnormalities, *FLT3* ITD, and previous allo-HCT were confirmed from previous risk models,[1,2,14] we additionally found WBC count, mutated *TP53*, t(v;11q23)/*KMT2A* rearrangement, and complex/monosomal karyotype. The prognostic model was associated with highly distinct OS in 3 risk groups. The revised prognostic model was validated in an independent cohort of older patients with AML treated within the NCRI-AML18 trial indicating similar prognostic accuracy. It classifies patients into other risk groups allowing for better

discrimination of OS outcomes for patients with AML experiencing their first relapse than existing prognostic models, such as those from the HOVON-SAKK and GOELAMS groups.[1,2]

Salvage treatment for patients with relapse AML includes high-dose chemotherapy, hypomethylating agents, or targeted treatments for patients with specific mutations followed by allo-HCT as consolidation treatment in patients who obtain CR2.[10,11] High-dose chemotherapy regimens (eg, intermediate-dose cytarabine with or without anthracycline or the combination of fludarabine, cytarabine, idarubicin and G-CSF) are associated with remission rates of 20% to 65%, but also considerable toxicity and mortality (6%-22%).[28-33] Although the type and intensity of chemotherapy-based reinduction treatment strategies were not available in our data set, we observed a relatively high CR2 rate of 65% and 44% for favorable- and intermediate-risk patients, which was 32% for poor-risk patients. Alternative salvage treatment approaches might be considered such as targeted treatments with or without hypomethylating agents. Gilteritinib has been approved for patients with relapsed *FLT3* AML with CR rates of 34%.[8] Similarly, both ivosidenib (*IDH1* inhibitor) and enasidenib (*IDH2* inhibitor) offer 23%-33% CR rates in refractory or relapsed patients with *IDH*-mutated AML,[6,7] whereas menin inhibitors show a CR rate of 30% in *KMT2A*-rearranged or *NPM1* mutated leukemia.[9] Alternatively, combining venetoclax, a BCL2 inhibitor, with hypomethylating agents presents as a potential alternative to attain CR2, despite the absence of trial data in the relapsed setting.[34-37] Combination treatments of targeted drugs, hypomethylating agents, and venetoclax or high-dose chemotherapy with venetoclax are currently investigated, and early results have been encouraging.[38-41] Nevertheless, it remains largely unknown whether patient outcomes will significantly improve with these novel treatment modalities. These recent advancements may transform the therapeutic landscape of relapsed AML significantly in the next years, making it a necessity to further validate this prognostic index to reflect emerging treatment modalities in the future.

Historically, allo-HCT in CR2 has been the preferred approach for long-term survival. Our analysis confirms that allo-HCT in CR2 provides a survival benefit with reduced relapse incidence compared with non-allo-HCT treatments. Nonetheless, the benefit of allo-HCT in terms of relapse reduction can be compromised by NRM, particularly in older patients or those with underlying comorbidities.[42-44] Although the risk of a second failure without allo-HCT is high (85% in our study), it needs to be balanced against the risk of NRM as assessed by risk scores.[42-44] Ultimately, the decision to proceed with allo-HCT after AML relapse requires a personalized approach, depending on the specific characteristics of each patient and their disease. Of note, data from the recent ASAP trial suggested that immediate allo-HCT might be an alternative for fit patients with nonproliferative refractory/relapsed AML who have a stem cell donor available.[45] However, the small number of relapsing patients in this study precludes robust conclusions.

Our study has several limitations. The optimal external validation cohort may be debated, but Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis guidelines have recommended using a cohort that differs in key characteristics (eg, age), treatment approaches, or time period.[26] The revised model was validated in an independent cohort, in which patients received different intensive chemotherapy regimens and were older than the development cohort. The model was associated with strong performance across both cohort populations, without any limitations imposed by narrow age restrictions, highlighting broad applicability in patients with relapsing AML after first-line intensive treatment. Second, intensive chemotherapy and targeted therapies might exert a selective pressure to the clonal landscape of AML, leading to both treatment-sensitive and treatment-resistant cells. For example, RAS-pathway mutations that are acquired at relapse may confer a particularly therapy-resistant disease.[46,47] Leukemic transformation by RAS mutations exhibits resistance to the BCL2 inhibitor venetoclax, driving clinical resistance, relapse, and worse OS after relapse after venetoclax-based therapy.[37,46] This clonal evolution of the AML is not accounted for given that molecular and cytogenetic data were only available from the time of initial diagnosis. The predictive accuracy and discriminatory power of the model, as measured by the C-index, indicate that the model performs relatively good in distinguishing among patients with different risk levels. The C-index quantifies the risk classification performance based on the predicted risk, with values ranging from 0.5 (no better than random chance) to 1.0 (perfect discrimination). A higher C-index indicates better model performance in correctly identifying which patients are more likely to experience an event. The revised relapse model improved upon previous risk classification systems, and its predictive capability may be further enhanced by incorporating molecular and cytogenetic data at the time of relapse. In addition, the model was developed in cohort of patients who did not receive FLT3 inhibitors as part of the first-line induction regimen. Although 26% of patients (22 of 85) with *FLT3* ITD received quizartinib added to the intensive induction backbone in the validation cohort, the model needs further validation in the era of FLT3 targeted combination therapies. Finally, there is an inherent bias regarding treatment decision making in the patient population after first relapse. High-risk patients might not have received treatment because of their adverse risk factors (eg, mutated *TP53*, short relapse-free interval, older age, other adverse cytogenetics). For example, in the poor-risk group, only 215 patients (60%) received reinduction treatment. Among those, response rates were very low (32%), with only 20 patients proceeding to allo-HCT in CR2, suggesting that this is a particularly difficult AML population to treat.

In conclusion, the revised prognostic classification system for adult patients with AML in first relapse offers a useful and distinctive model for clinical practice. It identifies favorable- or intermediate-risk patients who may benefit from reinduction strategies and consolidation with allo-HCT taking into account the risk of NRM. Conversely, patients classified within the poor-risk group have dismal survival after first relapse and might be considered for novel treatment strategies, experimental treatments, or even best supportive care. To facilitate the integration of this prognostic tool into clinical practice, an online calculator has been developed.[48] Based on a patient-specific hematologic, cytogenetic, and molecular profile, the tool provides a personalized prediction score, assigns an associated risk group, and offers estimated OS projections. This tool may aid clinicians in evaluating the relative benefits of salvage and experimental treatments, balancing these against potential treatment-related risks.

Acknowledgments

This work was supported by a grant from the Erasmus Medical Center Foundation (D.d.H.).

Authorship

Contribution: N.G.v.d.M. and J.V. designed the study, analyzed the data, conceived of the statistical plan, performed the statistical analysis, had full access to all data, and wrote the manuscript; D.B., T.P., A.T., B.J.B., J.K., C.H.M.J.V.E., O.V., M.-C.V., C.G., J.M., S.K., M.D., S.F., I.T., G.H., C.C., P.V., N.R., G.O., and B.L. provided patient data; N.G.v.d.M., P.G., H.B.B., P.J.M.V., and J.V. collected and assembled clinical, laboratory, and genetic data; N.G.v.d.M., J.J.C., and J.V. interpreted data and contributed to research discussion; and all authors reviewed the manuscript and approved the submission.

Conflict-of-interest disclosure: The authors declare no competing financial interests.

ORCID profiles: N.G.v.d.M., 0009-0006-9751-8122; T.P., 0000-0002-6055-5257; P.G., 0000-0002-4620-9163; A.T., 0000-0002-8283-6762; B.J.B., 0000-0002-4426-5743; J.K., 0000-0002-3914-7806; C.G., 0000-0001-9236-3623; J.M., 0000-0003-4257-5980; S.K., 0000-0002-6405-4441; M.D., 0000-0002-2540-8673; S.F., 0000-0003-1869-180X; H.B.B., 0000-0003-2280-7617; C.C., 0000-0001-5041-6678; P.V., 0000-0003-3931-0914; B.L., 0000-0001-8982-5217; J.V., 0000-0003-2372-1663.

Correspondence: Jurjen Versluis, Department of Hematology, Erasmus Medical Center Cancer Institute, University of Rotterdam, Dr Molewaterplein 40, 3015GD Rotterdam, The Netherlands; email: j.versluis.1@erasmusmc.nl.

References

1. Breems DA, Van Putten WLJ, Huijgens PC, et al. Prognostic index for adult patients with acute myeloid leukemia in first relapse. *J Clin Oncol*. 2005;23(9):1969-1978.
2. Chevallier P, Labopin M, Turlure P, et al. A new Leukemia Prognostic Scoring System for refractory/relapsed adult acute myelogeneous leukaemia patients: a GOELAMS study. *Leukemia*. 2011;25(6):939-944.
3. Devillier R, Crocchiolo R, Etienne A, et al. Outcome of relapse after allogeneic stem cell transplant in patients with acute myeloid leukemia. *Leuk Lymphoma*. 2013;54(6):1228-1234.
4. Schmid C, de Wreede LC, van Biezen A, et al. Outcome after relapse of myelodysplastic syndrome and secondary acute myeloid leukemia following allogeneic stem cell transplantation: a retrospective registry analysis on 698 patients by the Chronic Malignancies Working Party of the European Society of Blood and Marrow Transplantation. *Haematologica*. 2018;103(2):237-245.
5. Ganzel C, Sun Z, Cripe LD, et al. Very poor long-term survival in past and more recent studies for relapsed AML patients: The ECOG-ACRIN experience. *Am J Hematol*. 2018;93(8):1074-1081.
6. Stein EM, DiNardo CD, Pollyea DA, et al. Enasidenib in mutant *IDH2* relapsed or refractory acute myeloid leukemia. *Blood*. 2017;130(6):722-731.
7. DiNardo CD, Stein EM, de Botton S, et al. Durable remissions with ivosidenib in IDH1-mutated relapsed or refractory AML. *N Engl J Med*. 2018;378(25):2386-2398.
8. Perl AE, Martinelli G, Cortes JE, et al. Gilteritinib or chemotherapy for relapsed or refractory -mutated AML. *N Engl J Med*. 2019;381(18):1728-1740.
9. Issa GC, Aldoss I, DiPersio J, et al. The menin inhibitor revumenib in KMT2A-rearranged or NPM1-mutant leukaemia. *Nature*. 2023;615(7954):920-924.
10. DeWolf S, Tallman MS. How I treat relapsed or refractory AML. *Blood*. 2020;136(9):1023-1032.
11. Döhner H, Wei AH, Appelbaum FR, et al. Diagnosis and management of AML in adults: 2022 recommendations from an international expert panel on behalf of the ELN. *Blood*. 2022;140(12):1345-1377.
12. Kantarjian HM, Keating MJ, Walters RS, McCredie KB, Freireich EJ. The characteristics and outcome of patients with late relapse acute myelogenous leukemia. *J Clin Oncol*. 1988;6(2):232-238.
13. Keating MJ, Kantarjian H, Smith TL, et al. Response to salvage therapy and survival after relapse in acute myelogenous leukemia. *J Clin Oncol*. 1989;7(8):1071-1080.
14. Craddock C, Versluis J, Labopin M, et al. Distinct factors determine the kinetics of disease relapse in adults transplanted for acute myeloid leukaemia. *J Intern Med*. 2018;283(4):371-379.
15. Versluis J, Metzner M, Wang A, et al. Risk stratification in older intensively treated patients with AML. *J Clin Oncol*. 2024;42(34):4084-4094.
16. Löwenberg B, van Putten W, Theobald M, et al. Effect of priming with granulocyte colony-stimulating factor on the outcome of chemotherapy for acute myeloid leukemia. *N Engl J Med*. 2003;349(8):743-752.
17. Löwenberg B, Beck J, Graux C, et al. Gemtuzumab ozogamicin as postremission treatment in AML at 60 years of age or more: results of a multicenter phase 3 study. *Blood*. 2010;115(13):2586-2591.
18. Löwenberg B, Pabst T, Vellenga E, et al. Cytarabine dose for acute myeloid leukemia. *N Engl J Med*. 2011;364(11):1027-1036.
19. Terwijn M, van Putten WLJ, Kelder A, et al. High prognostic impact of flow cytometric minimal residual disease detection in acute myeloid leukemia: data from the HOVON/SAKK AML 42A study. *J Clin Oncol*. 2013;31(31):3889-3897.

20. Löwenberg B, Pabst T, Maertens J, et al. Therapeutic value of clofarabine in younger and middle-aged (18-65 years) adults with newly diagnosed AML. *Blood*. 2017;129(12):1636-1645.
21. Ossenkoppele GJ, Breems DA, Stuessi G, et al. Lenalidomide added to standard intensive treatment for older patients with AML and high-risk MDS. *Leukemia*. 2020;34(7):1751-1759.
22. Löwenberg B, Pabst T, Maertens J, et al. Addition of lenalidomide to intensive treatment in younger and middle-aged adults with newly diagnosed AML: the HOVON-SAKK-132 trial. *Blood Adv*. 2021;5(4):1110-1121.
23. Janssen JJWM, Löwenberg B, Manz M, et al. Addition of the nuclear export inhibitor selinexor to standard intensive treatment for elderly patients with acute myeloid leukemia and high risk myelodysplastic syndrome. *Leukemia*. 2022;36(9):2189-2195.
24. Döhner H, Estey E, Grimwade D, et al. Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. *Blood*. 2017;129(4):424-447.
25. Freeman SD, Thomas A, Thomas I, et al. Fractionated vs single-dose gemtuzumab ozogamicin with determinants of benefit in older patients with AML: the UK NCRI AML18 trial. *Blood*. 2023;142(20):1697-1707.
26. Moons KGM, Altman DG, Reitsma JB, et al. Transparent Reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD): explanation and elaboration. *Ann Intern Med*. 2015;162(1):W1-W73.
27. Papaemmanuil E, Gerstung M, Bullinger L, et al. Genomic classification and prognosis in acute myeloid leukemia. *N Engl J Med*. 2016;374(23):2209-2221.
28. Herzig RH, Lazarus HM, Wolff SN, Phillips GL, Herzig GP. High-dose cytosine arabinoside therapy with and without anthracycline antibiotics for remission reinduction of acute nonlymphoblastic leukemia. *J Clin Oncol*. 1985;3(7):992-997.
29. Amadori S, Arcese W, Isacchi G, et al. Mitoxantrone, etoposide, and intermediate-dose cytarabine: an effective and tolerable regimen for the treatment of refractory acute myeloid leukemia. *J Clin Oncol*. 1991;9(7):1210-1214.
30. Vogler WR, McCarley DL, Stagg M, et al. A phase III trial of high-dose cytosine arabinoside with or without etoposide in relapsed and refractory acute myelogenous leukemia. A Southeastern Cancer Study Group trial. *Leukemia*. 1994;8(11):1847-1853.
31. Parker JE, Pagliuca A, Mijovic A, et al. Fludarabine, cytarabine, G-CSF and idarubicin (FLAG-IDA) for the treatment of poor-risk myelodysplastic syndromes and acute myeloid leukaemia. *Br J Haematol*. 1997;99(4):939-944.
32. Litzow MR, Wang XV, Carroll MP, et al. A randomized trial of three novel regimens for recurrent acute myeloid leukemia demonstrates the continuing challenge of treating this difficult disease. *Am J Hematol*. 2019;94(1):111-117.
33. Mühleck R, Scholl S, Hilgendorf I, et al. Outcome of patients with relapsed or refractory acute myeloid leukemia treated with Mito-FLAG salvage chemotherapy. *J Cancer Res Clin Oncol*. 2021;148(9):2539-2548.
34. Brancati S, Gozzo L, Romano GL, et al. Venetoclax in relapsed/refractory acute myeloid leukemia: are supporting evidences enough? *Cancers*. 2021;14(1):22.
35. Kwag D, Cho B-S, Bang S-Y, et al. Venetoclax with decitabine versus decitabine monotherapy in elderly acute myeloid leukemia: a propensity score-matched analysis. *Blood Cancer J*. 2022;12:169.
36. Angotzi F, Lessi F, Leoncin M, et al. Efficacy and safety of venetoclax plus hypomethylating agents in relapsed/refractory acute myeloid leukemia: a multicenter real-life experience. *Front Oncol*. 2024;14:1370405.
37. Stahl M, Menghrajani K, Derkach A, et al. Clinical and molecular predictors of response and survival following venetoclax therapy in relapsed/refractory AML. *Blood Adv*. 2021;5:1552-1564.
38. Atluri H. *Phase Ib/2 study of oral decitabine/cedazuridine (ASTX727) and venetoclax in combination with the targeted mutant IDH1 inhibitor ivosidenib or the targeted mutant IDH2 inhibitor enasidenib: 2023 update. Paper presented at*. 65th ASH Annual Meeting & Exposition; 2023/12/11.
39. Briski R. *A phase I/II study of combination of ASTX727, gilteritinib and venetoclax in patients with relapsed/refractory FLT3- mutated acute myeloid leukemia (AML). Paper presented at*. 65th ASH Annual Meeting & Exposition; 2023/12/10.
40. Yilmaz M. *Phase I/II study of quizartinib, venetoclax, and decitabine triple combination in FLT3-ITD mutated AML. Paper presented at*. 65th ASH Annual Meeting & Exposition; 2023/12/9.
41. Al-Shaibani E. *FLAG-IDA plus venetoclax in high-risk newly diagnosed and relapsed or refractory acute myeloid leukemia: the Princess Margaret Cancer Center experience. Paper presented at*. 66th ASH Annual Meeting & Exposition; 2024.
42. Cornelissen JJ, Gratwohl A, Schlenk RF, et al. The European LeukemiaNet AML Working Party consensus statement on allogeneic HSCT for patients with AML in remission: an integrated-risk adapted approach. *Nat Rev Clin Oncol*. 2012;9(10):579-590.
43. Versluis J, Labopin M, Niederwieser D, et al. Prediction of non-relapse mortality in recipients of reduced intensity conditioning allogeneic stem cell transplantation with AML in first complete remission. *Leukemia*. 2015;29(1):51-57.
44. Hermans SJF, Versluis J, Labopin M, et al. Prediction of nonrelapse mortality in patients with acute myeloid leukemia and acute lymphoblastic leukemia receiving allogeneic stem cell transplantation with posttransplantation cyclophosphamide-based graft versus host disease prophylaxis. *HemaSphere*. 2023;7(3):e846.
45. Stelljes M, Middeke JM, Bug G, et al. Remission induction versus immediate allogeneic haematopoietic stem cell transplantation for patients with relapsed or poor responsive acute myeloid leukaemia (ASAP): a randomised, open-label, phase 3, non-inferiority trial. *Lancet Haematol*. 2024;11(5):e324-e335.

46. Sango J, Carcamo S, Sirenko M, et al. RAS-mutant leukaemia stem cells drive clinical resistance to venetoclax. *Nature*. 2024;636(8041):241-250.

47. McMahon CM, Ferng T, Canaani J, et al. Clonal selection with RAS pathway activation mediates secondary clinical resistance to selective FLT3 inhibition in acute myeloid leukemia. *Cancer Discov*. 2019;9(8):1050-1063.

48. HOVON. Survival prediction for patients with AML and first relapse. 2024. Accessed 25 June 2025. https://hovon-aml.shinyapps.io/AML_Relapse_Score/