A risk score based on real-world data to predict early death in acute promyelocytic leukemia

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Supplementary

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Supplementary Methods and References

Supplementary Methods

R packages and details of APL risk score development

All statistical analyses were performed using the computing environment R version 4.0.2 [1]. The packages compareGroups version 4.4.6 [2] and MASS version 7.3.53 [3] were applied for descriptive statistics, cohort comparisons and logistic regression analyses (Table 1-2, Supplementary Table 1-2). We applied backward stepwise selection minimizing the Akaike information criterion for removal of predictors for the final multivariable logistic regression model in Supplementary Table 2.

The package mice (version 3.12.0) [4] was used to impute missing data in the training cohort by predictive mean matching on 5 imputations with 50 iterations.

Multivariable penalized logistic regression analysis was performed by applying the package glmnet (version 4.1.1) [5] on the original dataset to obtain ridge regression coefficients. Ridge regression applies cross validation in order to maximize the predictive ability of a model and performs well with the availability of prespecified predictors [6].

The discriminative capability of the score was assessed based on the area under the receiver operating characteristic (AUROC) curve using pROC (version 1.16.2) [7].

No formal sample size calculations were performed since all available data was used to maximize the generalizability of the results. All statistical analyses were two-sided with $P < 0.05$ considered statistically significant. The risk score was developed in line with the Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis (TRIPOD) [8] statement with a completed checklist found on page 16 in this Supplementary.

Figures 1-2 and Supplementary Figure 4 were created using the package ggplot2 (version 3.3.2) [9]. Kaplan-Meier curves and log-rank P-values in Supplementary Figure 3 were obtained by the package survival (version 3.2.13) [10] and plotted by the package survminer (version 0.4.9) [11] for the different cut-off values for white blood cells at diagnosis with censoring of non-ED patients at 30 days. The package ggalluvial (version 0.12.3) [12] was used for Supplementary Figure 5.

The online calculator published at apl-early-death.shinyapps.io/risk-score was developed with the packages shiny (version 1.7.1) [13], shinythemes (version 1.2.0) [14] and shinydashboard (version 0.7.2) [15].

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Supplementary Tables

Supplementary Table 1. Demographic comparison of patients with complete and non-complete data in training cohort.

	Complete data (n = 275)	Non-complete data (n = 26)	P-value
Age (median, range)	55 (17 - 89)	46 (21 - 82)	0.34
Women (n, %)	134 (48.7)	17 (65.4)	0.16
WHO status (n, %)			0.20
0	63 (26.4)	7 (43.8)	
1	114 (47.7)	5 (31.2)	
2	43 (18.0)	2 (12.5)	
3	10 (4.2)	0 (0)	
4	9 (3.8)	2 (12.5)	
Time to early death, days (median, range)	6 (0 - 29)	2 (1 - 13)	0.36
Death within 7 d (n, %)	30 (10.9)	5 (19.2)	0.20
Death within 30 d (n, %)	53 (19.3)	6 (23.1)	0.84

Abbreviations: WHO: World Health Organization.

Supplementary Table 2. Multivariate logistic regression analyses for ED in the training cohort, n = 301.

	Odds ratio	95% CI
Age (continuous, increment of 10)	1.50	1.24 - 1.83
White blood cells, x10^9/L (continuous, increment of 5)	1.10	1.05 - 1.16
Thrombocytes, x10^9/L (continuous, increment of 10)	0.86	0.77 - 0.95

Footnotes: Hemoglobin was included as additional variable but was removed by backward selection.
Abbreviations: ED: Early death, i.e. death within 30 days from diagnosis; CI: Confidence interval.

Supplementary Table 3. Distribution of ED per risk score.

	Training cohort, n = 301				Validation cohort, n = 129			
Score	**Total (n)**	**Event (n)**	**No event (n)**	**% ED30**	**Total (n)**	**Event (n)**	**No event (n)**	**% ED30**
0	36	0	36	0 %	14	2	12	14 %
1	54	4	50	7 %	26	2	24	8 %
2	35	2	33	6 %	20	0	20	0 %
3	68	7	61	10 %	27	5	22	19 %
4	51	17	34	33 %	17	6	11	35 %
5	24	10	14	42 %	10	4	6	40 %
6	24	14	10	58 %	10	4	6	40 %
7	9	5	4	56 %	5	1	4	20 %
Total	301	59	242	**20 %**	129	24	105	**19 %**

Abbreviations: ED: Death within 30 days from diagnosis.

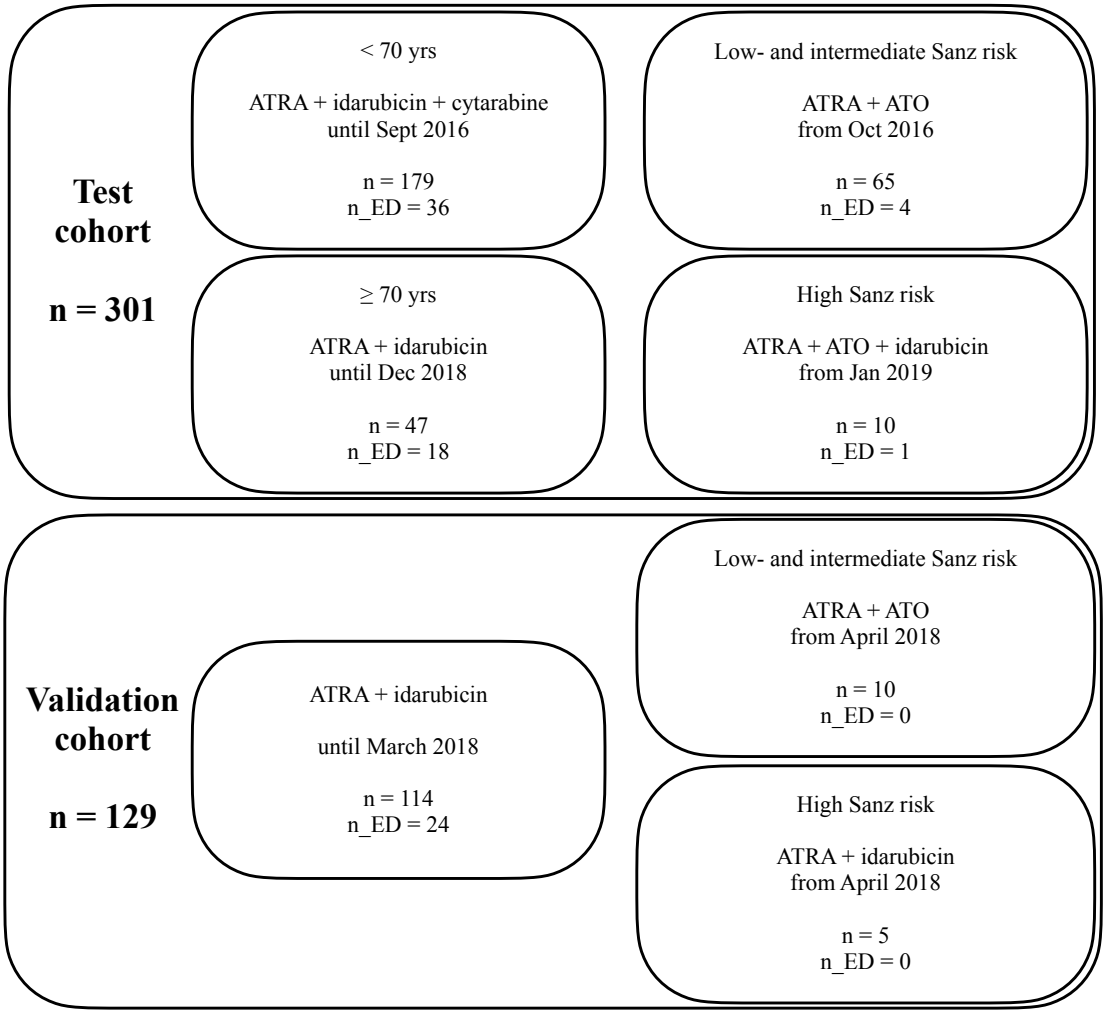
Supplementary Table 4. Reclassification table when comparing the proposed risk score to the Sanz risk score.

		ED (n = 83)			Reclassified, n (%)		
		Proposed risk score			Increased risk	Decreased risk	Net correctly reclassified
		LR	HR	Very HR			
Sanz risk	Low	7	7	2			
	Intermediate	3	13	9	18 (21.7)	18 (21.7)	0 (0)
	High	0	15	27			
	Total	10	35	38			
		No ED (n = 347)					
		Proposed risk score					
		LR	HR	Very HR			
Sanz risk	Low	73	36	2			
	Intermediate	102	50	6	44 (12.6)	144 (41.5)	100 (28.8)
	High	0	42	36			
	Total	175	128	44			
					62 (14.4)	162 (37.7)	100 (23.3)

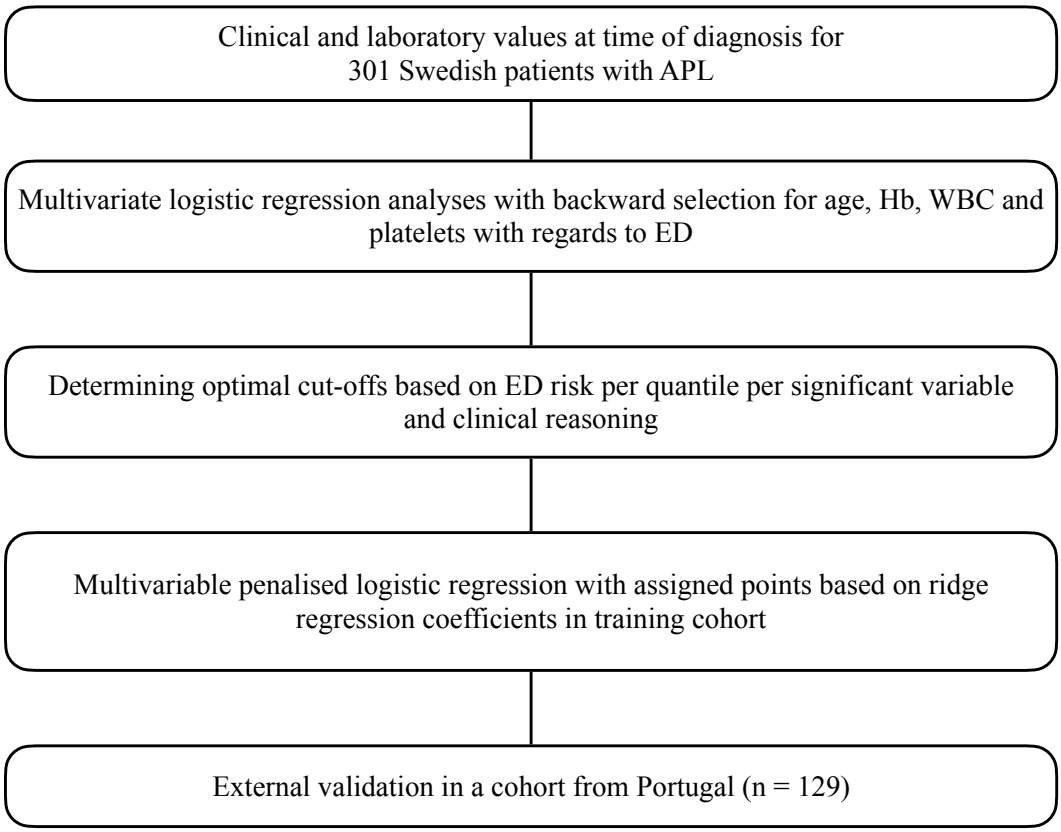
Abbreviations: ED: Early death, i.e. death within 30 days from diagnosis, LR: Low risk, HR: High risk.

Supplementary Figures

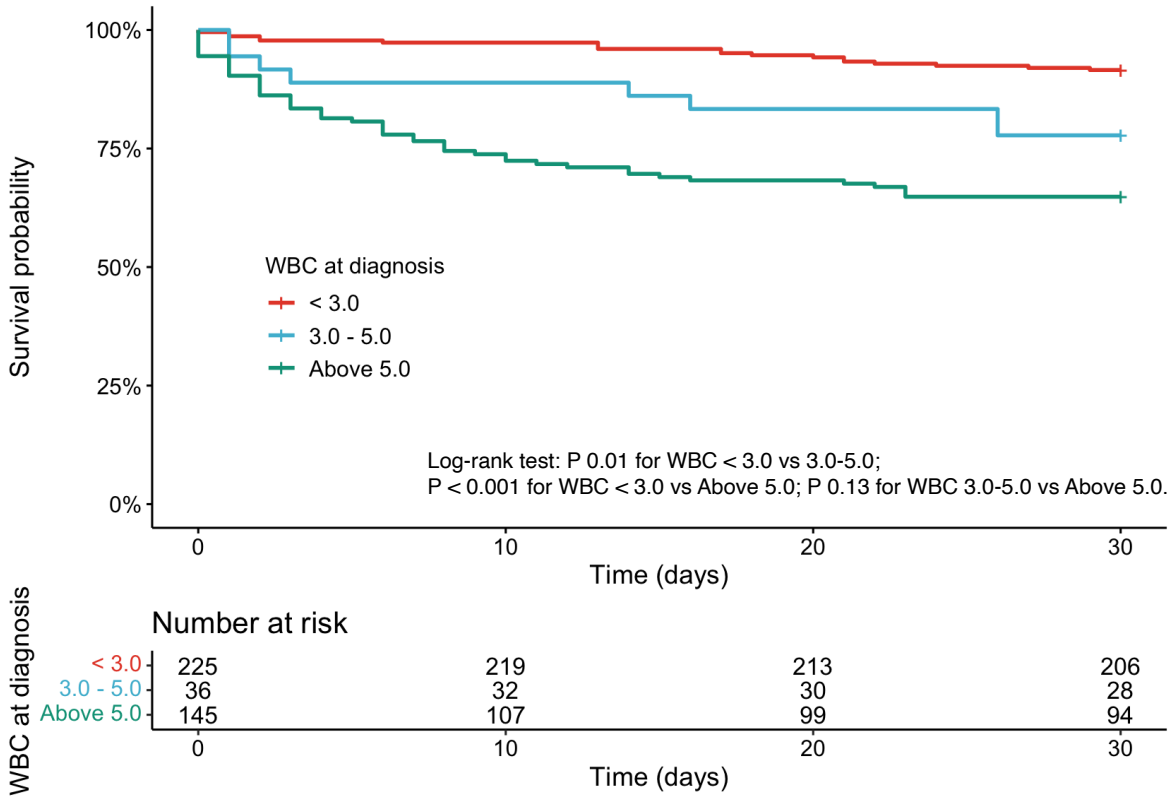
Supplementary Figure 1. Distribution of induction therapies.



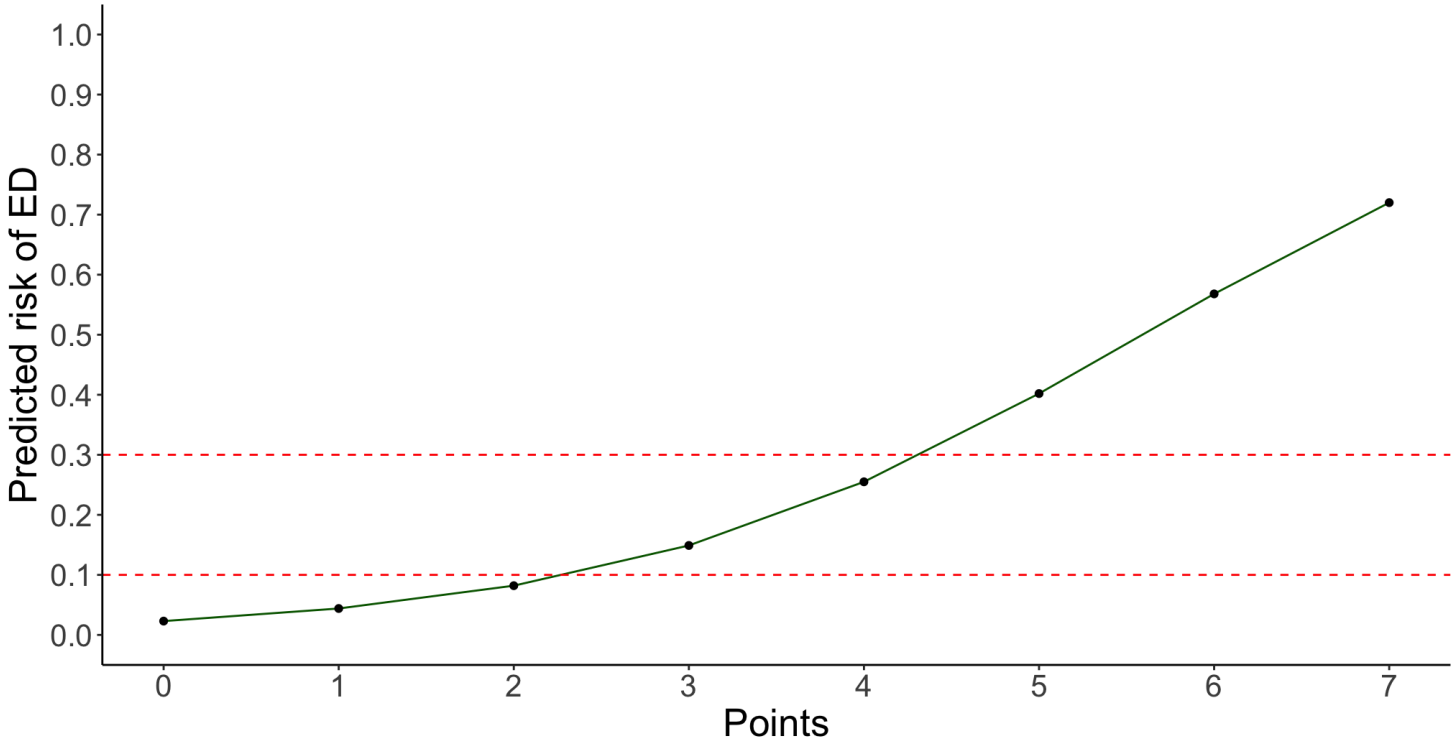
Supplementary Figure 2. Flow chart of score development.



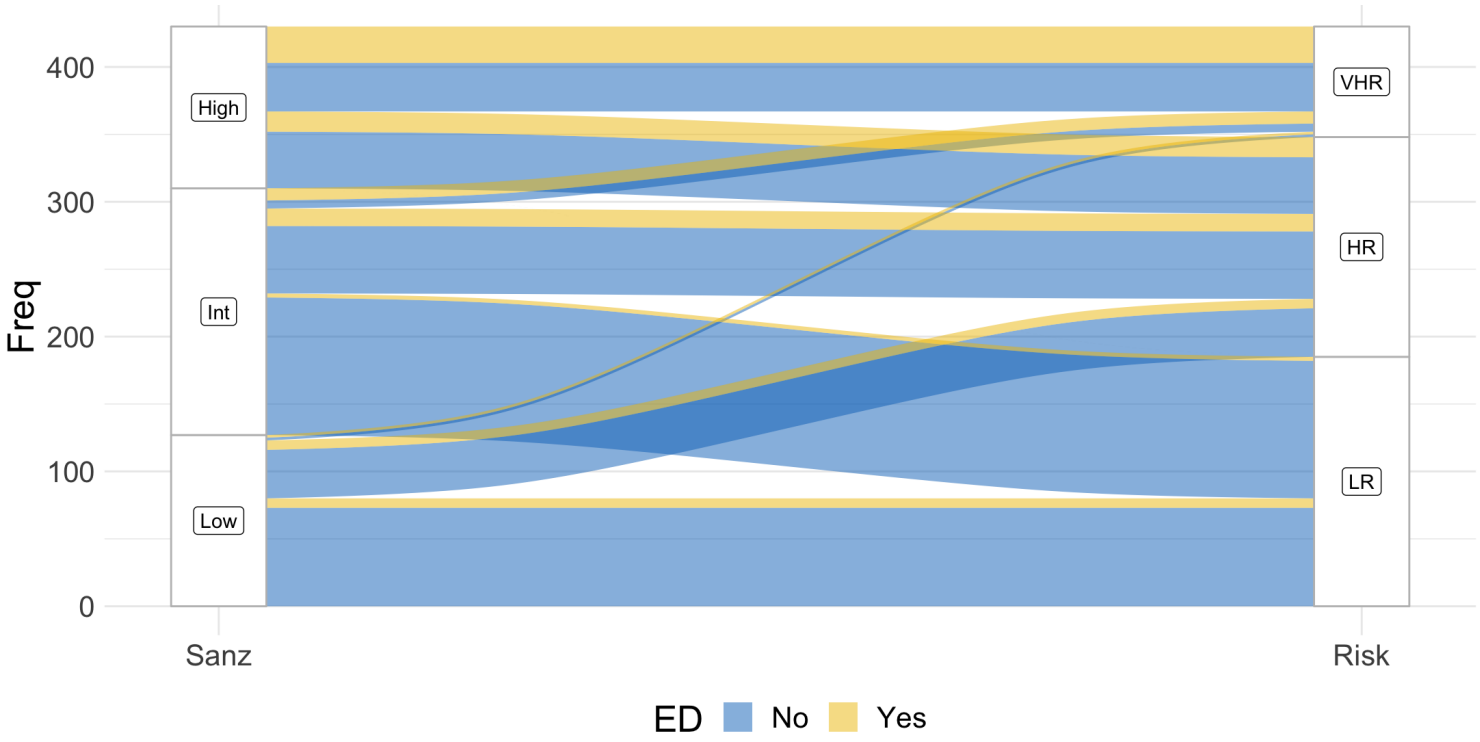
Supplementary Figure 3. Overall survival related to WBC at diagnosis.



Supplementary Figure 4. Predicted risk of ED per assigned point.



Supplementary Figure 5. Alluvial diagram for comparison of risk grouping using the proposed risk score to the Sanz risk score.



TRIPOD Checklist: Prediction Model Development and Validation

Section/Topic	Item		Checklist Item	Page
Title and abstract				
Title	1	D;V	Identify the study as developing and/or validating a multivariable prediction model, the target population, and the outcome to be predicted.	1
Abstract	2	D;V	Provide a summary of objectives, study design, setting, participants, sample size, predictors, outcome, statistical analysis, results, and conclusions.	2
Introduction				
Background and objectives	3a	D;V	Explain the medical context (including whether diagnostic or prognostic) and rationale for developing or validating the multivariable prediction model, including references to existing models.	3-4
	3b	D;V	Specify the objectives, including whether the study describes the development or validation of the model or both.	4
Methods				
Source of data	4a	D;V	Describe the study design or source of data (e.g., randomized trial, cohort, or registry data), separately for the development and validation data sets, if applicable.	4
	4b	D;V	Specify the key study dates, including start of accrual; end of accrual; and, if applicable, end of follow-up.	4
Participants	5a	D;V	Specify key elements of the study setting (e.g., primary care, secondary care, general population) including number and location of centres.	4-5
	5b	D;V	Describe eligibility criteria for participants.	4-5
	5c	D;V	Give details of treatments received, if relevant.	5
Outcome	6a	D;V	Clearly define the outcome that is predicted by the prediction model, including how and when assessed.	5
	6b	D;V	Report any actions to blind assessment of the outcome to be predicted.	NA
Predictors	7a	D;V	Clearly define all predictors used in developing or validating the multivariable prediction model, including how and when they were measured.	5-6
	7b	D;V	Report any actions to blind assessment of predictors for the outcome and other predictors.	NA
Sample size	8	D;V	Explain how the study size was arrived at.	Suppl.
Missing data	9	D;V	Describe how missing data were handled (e.g., complete-case analysis, single imputation, multiple imputation) with details of any imputation method.	Suppl.
Statistical analysis methods	10a	D	Describe how predictors were handled in the analyses.	5-6 Suppl.
	10b	D	Specify type of model, all model-building procedures (including any predictor selection), and method for internal validation.	5-6, Suppl.
	10c	V	For validation, describe how the predictions were calculated.	5-6, Suppl.
	10d	D;V	Specify all measures used to assess model performance and, if relevant, to compare multiple models.	Suppl.
	10e	V	Describe any model updating (e.g., recalibration) arising from the validation, if done.	NA
Risk groups	11	D;V	Provide details on how risk groups were created, if done.	8-9
Development vs. validation	12	V	For validation, identify any differences from the development data in setting, eligibility criteria, outcome, and predictors.	6-7
Results				
Participants	13a	D;V	Describe the flow of participants through the study, including the number of participants with and without the outcome and, if applicable, a summary of the follow-up time. A diagram may be helpful.	6-7
	13b	D;V	Describe the characteristics of the participants (basic demographics, clinical features, available predictors), including the number of participants with missing data for predictors and outcome.	6-7
	13c	V	For validation, show a comparison with the development data of the distribution of important variables (demographics, predictors and outcome).	Table 1
Model development	14a	D	Specify the number of participants and outcome events in each analysis.	6-7
	14b	D	If done, report the unadjusted association between each candidate predictor and outcome.	Table 2
Model specification	15a	D	Present the full prediction model to allow predictions for individuals (i.e., all regression coefficients, and model intercept or baseline survival at a given time point).	Table 3
	15b	D	Explain how to use the prediction model.	Table 3, Fig. 3
Model performance	16	D;V	Report performance measures (with CIs) for the prediction model.	9
Model-updating	17	V	If done, report the results from any model updating (i.e., model specification, model performance).	NA
Discussion				
Limitations	18	D;V	Discuss any limitations of the study (such as nonrepresentative sample, few events per predictor, missing data).	11-14
Interpretation	19a	V	For validation, discuss the results with reference to performance in the development data, and any other validation data.	11-14
	19b	D;V	Give an overall interpretation of the results, considering objectives, limitations, results from similar studies, and other relevant evidence.	11-14
Implications	20	D;V	Discuss the potential clinical use of the model and implications for future research.	11-14
Other information				
Supplementary information	21	D;V	Provide information about the availability of supplementary resources, such as study protocol, Web calculator, and data sets.	14
Funding	22	D;V	Give the source of funding and the role of the funders for the present study.	14-15

*Items relevant only to the development of a prediction model are denoted by D, items relating solely to a validation of a prediction model are denoted by V, and items relating to both are denoted D;V. We recommend using the TRIPOD Checklist in conjunction with the TRIPOD Explanation and Elaboration document.