Impact of genomic risk factors on outcome after hematopoietic stem cell transplantation for patients with chronic myeloid leukemia

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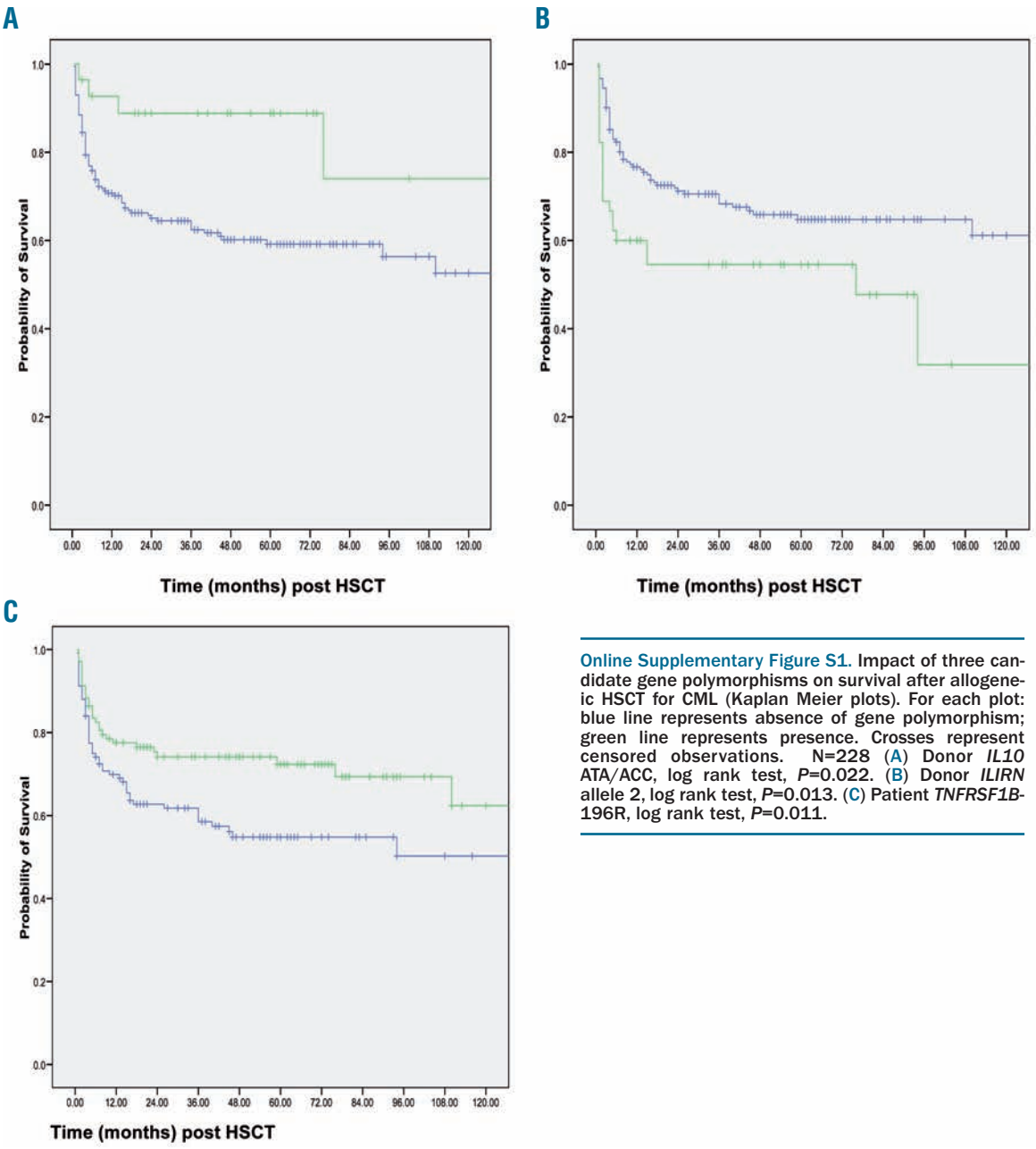
Supplementary Statistics Section

Goodness of fit and predictive value quantification

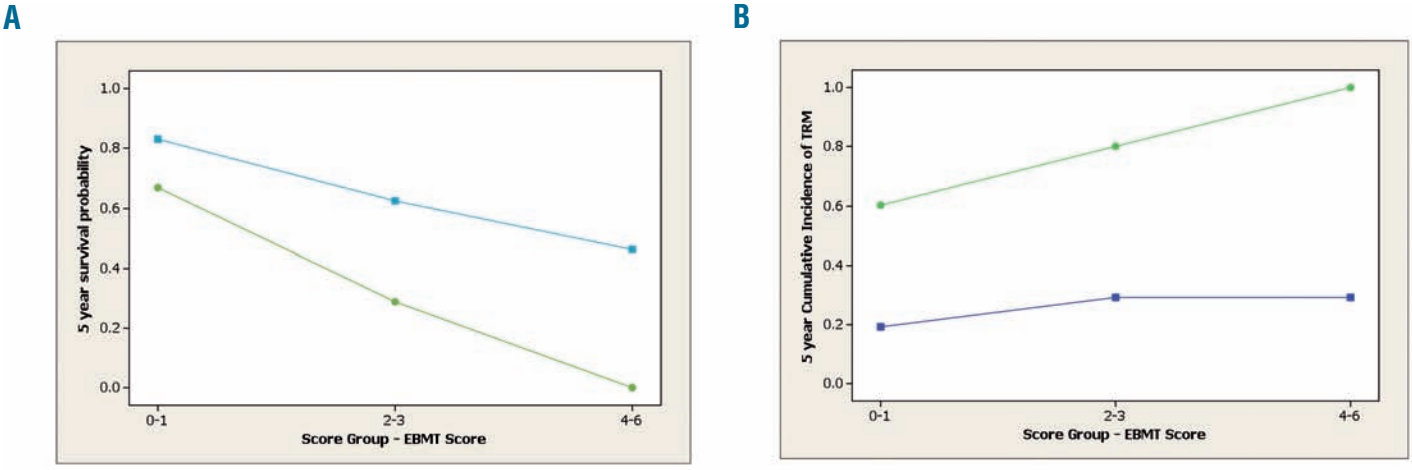
A likelihood ratio test for nested models was conducted. This compares a model with the single EBMT risk score variable and a model containing the single EBMT risk score and the three genotypes. The likelihood ratio test was significant ($P<0.0005$) and gave conclusive evidence that the genotypes improved the model i.e. the goodness of fit.

Predictive value quantification was first assessed using the c index. The c index measures the proportion of patient pairs for which the predicted and actual outcomes are concordant: a value of 0.5 means no discrimination by predictive groups, a value over 0.5 means higher predictive discrimination. Here the 'predicted outcomes' were prognostic groups derived from (i) the EBMT risk scores and (ii) the risk scores obtained from the modified model containing the EBMT risk score variable and the three genetic predictors. The index for the modified risk score groups is 0.67 and the index for the EBMT score groups is 0.64. Somer's Dxy rank correlation (2*c-1) for a censored response variable was also observed. The value of this correlation can lie between -1 and 1 (0 meaning no correlation); for this study the value was 0.34 for the modified risk score groups and 0.28 for the EBMT groups. An extension of the c index (ncorrp.cens in R) gave conclusive evidence that the modified risk score was more concordant than the EBMT score (U=3.82, $P<0.0005$).

Predictive value was also quantified using predictive error curves. These curves were formed utilizing bootstrap samples and allowed for the creation of training and test data. Basically, a training set containing our variables was used to calculate a model; predicted (fitted) values were then obtained using validation data and differences were found between actual and predicted responses. The generation of training and test data was repeated many times and essentially an average residual value was found. The same procedure was carried out for all available time points, producing a curve. A curve was produced for (i) the model containing EBMT risk score alone and (ii) for the model containing EBMT risk score and the three genotypes. The latter had a lower curve thus implying a model with better predictive ability.



Online Supplementary Figure S1. Impact of three candidate gene polymorphisms on survival after allogeneic HSCT for CML (Kaplan Meier plots). For each plot: blue line represents absence of gene polymorphism; green line represents presence. Crosses represent censored observations. N=228 (A) Donor *IL10* ATA/ACC, log rank test, *P*=0.022. (B) Donor *ILIRN* allele 2, log rank test, *P*=0.013. (C) Patient *TNFRSF1B*-196R, log rank test, *P*=0.011.



Online Supplementary Figure S2. (A) Survival probability at 5 years of 228 patients with an allogeneic HLA identical sibling HSCT for CML by EBMT risk score, with high risk (green line) and low risk (blue line) SNP profile. (B) Cumulative incidence of transplant-related mortality (TRM) at 5 years of patients with an allogeneic HLA identical sibling HSCT for CML by EBMT risk score, with high risk (green line) and low risk (blue line) SNP profile.

Online Supplementary Table S1. Probability of survival, cumulative incidence (CI) of transplant-related mortality (TRM) and relapse (together with 95% confidence interval in parentheses) for absence and presence of cytokine gene polymorphisms and low and high risk groups. N=228.

Donor *IL10* ATA/ACC	2 years			5 years		
	TRM CI (%)	Relapse CI (%)	Survival KM (%)	TRM CI (%)	Relapse CI (%)	Survival KM (%)
Absent	32 (25-41)	20 (14-28)	65 (58-71)	34 (27-43)	28 (21-37)	59 (51-66)
Present	14 (5-40)	14 (5-40)	89 (68-96)	14 (5-40)	14 (5-40)	89 (68-96)
	Gray's test for TRM P=0.13					
	Gray's test for relapse P=0.39					

Patient *TNFRSF1B*-196R	2 years			5 years		
	TRM CI (%)	Relapse CI (%)	Survival KM (%)	TRM CI (%)	Relapse CI (%)	Survival KM (%)
Absent	39(29-51)	15(9-26)	63(53-70)	41(32-54)	23(15-35)	55(44-63)
Present	20(13-32)	23(15-35)	74(64-81)	20(13-32)	29(20-42)	72(62-80)
	Gray's test for TRM P=0.003					
	Gray's test for relapse P=0.52					

Donor *IL1RN* allele 2	2 years			5 years		
	TRM CI (%)	Relapse CI (%)	Survival KM (%)	TRM CI (%)	Relapse CI (%)	Survival KM (%)
Absent	26 (20-35)	22 (16-30)	71(64-77)	28 (21-37)	26 (20-36)	65 (56-72)
Present	44 (29-67)	7 (2-27)	55 (37-67)	44 (29-67)	20 (9-45)	55 (37-67)
	Gray's test for TRM P=0.06					
	Gray's test for relapse P=0.38					

	TRM CI (%)	Relapse CI (%)	Survival KM	TRM CI (%)	Relapse CI (%)	Survival KM (%)
High risk	71 (52-96)	6 (0.88%-39%)	38 (15%-55%)	71 (52%-96%)	12 (3%-43%)	38 (15%-55%)
Low risk	25 (19-33)	21 (15-29)	72 (64-77)	26 (20-35)	27 (20-35)	66 (58-72)
	Gray's test for TRM P<0.0005					
	Gray's test for relapse P=0.13					

Online Supplementary Table S2. Hazard ratios for outcomes (survival and TRM) when one or two adverse genotypes are taken in addition to EBMT score in a Cox regression model.

	Outcome:Overall survival (Hazard Ratio i.e. hazard of death reported)	Outcome: TRM (Hazard Ratio i.e. hazard of TRM)
EBMT score alone	1.52	1.29
EBMT Score + Absent donor *IL10* ATA/ACC	1.55	1.32
EBMT Score + Present donor *IL1RN* allele 2	1.65	1.38
EBMT Score + Absent patient *TNFRSF1B* 196R	1.62	1.46
EBMT Score + Absent donor *IL10* ATA/ACC + present donor *IL1RN* allele 2	1.67	1.41
EBMT Score + Present donor *IL1RN* allele 2 + absent patient *TNFRSF1B* 196R	1.75	1.55
EBMT Score + Absent donor *IL10* ATA/ACC + absent patient *TNFRSF1B* 196R	1.63	1.47