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Comparison of Dynamic International Prognostic Scoring System and MYelofibrosis SECondary to PV and ET Prognostic Model for Prediction of Outcome in Polycythemia Vera and Essential Thrombocythemia Myelofibrosis after Allogeneic Stem Cell Transplantation

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A B S T R A C T

We aimed to validate the MYelofibrosis SECondary to PV and ET prognostic model (MYSEC-PM) in 159 patients with myelofibrosis secondary to polycythemia vera (PV) and essential thrombocythemia (ET) from the European Society for Blood and Marrow Transplantation registry undergoing transplantation from matched siblings or unrelated donors. Furthermore, we aimed to test its prognostic performance in comparison with the Dynamic International Prognostic Scoring System (DIPSS). Score performance was analyzed using the concordance index (C): the probability that a patient who experienced an event had a higher risk score than a patient who did not (C > .5

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Allogeneic stem cell transplantation

suggesting predictive ability). Median follow-up of the total cohort was 41 months (range, 34 to 54), 45 months in post-PV and 38 months in post-ET myelofibrosis. Survival at 1, 2, and 4 years was 70% (95% CI, 63% to 77%), 61% (95% CI, 53% to 69%), and 52% (95% CI, 43% to 61%) for the total cohort; 70% (95% CI, 59% to 80%), 61% (95% CI, 49% to 73%), and 51% (95% CI, 38% to 64%) for post-PV; and 71% (95% CI, 61% to 81%), 61% (95% CI, 50% to 72%), and 54% (95% CI, 42% to 66%) for post-ET myelofibrosis ($P = .78$). Overall, the DIPSS was not significantly predictive of outcome ($P = .28$). With respect to the MYSEC-PM, overall survival at 4 years was 69% for the low-risk, 55% for the intermediate 1-risk, 47% for the intermediate 2-risk, and 22% (0% to 45%) for the high-risk groups. The prognostic model was predictive of survival overall ($P = .05$), whereas groups with intermediate 2 and high risk showed no significant difference ($P = .44$). Assessment of prognostic utility yielded a C-index of .575 (95% CI, .502 to .648) for the DIPSS, whereas assessment of the MYSEC-PM resulted in a C-statistics of .636 (95% CI, .563 to .708), indicating improvement in prediction of post-transplant survival using the new MYSEC-PM. In addition, transplantations from an unrelated donor in comparison with an HLA-identical sibling showed worse outcome ($P = .04$), and transplant recipients seropositive for cytomegalovirus in comparison with seronegative recipients ($P = .01$) showed worse survival. In conclusion, incorporating transplant-specific and clinical and mutational information together with the MYSEC-PM may enhance risk stratification.

INTRODUCTION

In the last decade 3 clinical-derived prognostic models have been developed in patients with primary myelofibrosis [1-3]. Prognostication in myeloproliferative neoplasms, however, is moving toward integrated clinical-molecular models [4,5]. Therefore, more recently another prognostic system has been developed and validated by the MYSEC project (MYelofibrosis SECondary to PV and ET) specifically for myelofibrosis evolved from polycythemia vera (post-PV MF) and essential thrombocythemia (post-ET MF) [6,7]. The prognostic model by MYSEC (MYSEC-PM) included the presence of constitutional symptoms, platelets $< 150 \times 10^9$/L, hemoglobin < 11 g/dL, circulating blasts $\geq 3\%$, age, and a Calreticulin gene (CALR)-unmutated genotype resulting in improved prognostic ability compared with the International Prognostic Scoring System (IPSS). Collectively, all currently existing models have been developed in patients at diagnosis and were not applied to SMF patients undergoing allogeneic stem cell transplantation, which is still the only potentially curative treatment option [8,9].

We aimed to validate the MYSEC-PM in 159 patients with post-PV and post-ET MF from the European Society for Blood and Marrow Transplantation registry undergoing transplantation. Furthermore, we aimed to test its prognostic performance in comparison with the Dynamic IPSS (DIPSS), which includes 5 clinical prognostic variables (age > 65 years, hemoglobin < 10 g/dL, leukocyte count $> 25 \times 10^9$/L, circulating blasts $\geq 1\%$, and constitutional symptoms) and is currently used for risk stratification of patients with myelofibrosis undergoing transplantation.

METHODS

This study included 159 patients with post-PV (n = 76, 48%) and post-ET MF (n = 83, 52%) who received allogeneic stem cell transplantation from an HLA-identical sibling or unrelated donor with available data on driver mutation status between 2007 and 2015. Diagnoses of post-PV and post-ET MF were locally reviewed according to the International Working Group on Myeloproliferative Neoplasm Research and Treatment criteria [10]. Evolution to blast phase was defined when leukemic blast cells were >20%, according to the World Health Organization (WHO) criteria [11], and were thus excluded from the analysis.

Both the DIPSS and the MYSEC-PM were calculated at the time of transplantation. The DIPSS assigns 1 point to age > 65 years, WBC count $> 25 \times 10^9$/L, circulating blasts $\geq 1\%$, and presence of constitutional symptoms and 2 points to hemoglobin level < 10 g/dL, resulting in 4 risk categories: low (score of 0), intermediate 1 (score of 1 to 2), intermediate 2 (score of 3 to 4), and high (>4). The MYSEC-PM allocates 2 points to hemoglobin level < 11 g/dL, circulating blasts $\geq 3\%$, and CALR-unmutated genotype and 1 point to platelet count $< 150 \times 10^9$/L and the presence of constitutional symptoms. Age-related risk was rescaled accordingly, yielding approximately .15 points per year. Subsequently, MYSEC-PM is classified in 4 categories: low (score < 11), intermediate 1 (score of 11 to <14), intermediate 2 (score of 14 to <16), and high (≥ 16).

The primary objective was to validate DIPSS and MYSEC-PM regarding prediction of overall survival using Kaplan-Meier estimates, and the Cox proportional hazards model was used for regression [12,13]. The secondary endpoint was nonrelapse mortality assessed by the cumulative incidence method [14]. Score performance was analyzed using the concordance index (C): the probability that a patient who experienced an event had a higher risk score than a patient who did not ($C > .5$ suggesting predictive ability) [12]. Analyses were performed by using R package version 3.4.3 (The R Foundation, Vienna, Austria).

RESULTS

Median follow-up of the total cohort was 41 months (range, 34 to 54), 45 months in post-PV and 38 months in post-ET MF. The median time between diagnosis and transplant was 130 months for the total cohort, 140 months for post-PV, and 124 months for post-ET MF. Survival at 1, 2, and 4 years was 70% (63% to 77%), 61% (53% to 69%), and 52% (43% to 61%) for the total secondary myelofibrosis (SMF) cohort; 70% (59% to 80%), 61% (49% to 73%), and 51% (38% to 64%) for post-PV; and 71% (61% to 81%), 61% (50% to 72%), and 54% (42% to 66%) for post-ET MF ($P = .78$). To ascertain whether survival increased over calendar years, we performed a Cox regression including calendar year of transplantation, and no significant change in survival trend was found with a hazard ratio (HR) of 1.02 ($P = .75$). Nonrelapse mortality at 4 years was 34% (25% to 42%) for the overall series, 35% (22% to 48%) for post-PV, and 32% (21% to 43%) for post-ET MF ($P = .73$). Patient characteristics and the distribution of our patients into the risk groups of each prognostic model are shown in Table 1.

Figure 1 shows the survival curves of DIPSS and MYSEC-PM. Survival rates at 4 years according to each risk group of the DIPSS were 80% (59% to 100%) for the low-risk, 50% (35% to 65%) for the intermediate 1-risk, 51% (38% to 64%) for the intermediate 2-risk, and 41% (14% to 67%) for the high-risk groups (Figure 1A). Overall, the DIPSS was not significantly predictive of outcome ($P = .28$). Pairwise comparisons of intermediate 2 risk versus intermediate 1 and high risk were not significantly different ($P = .99$ and $P = .30$). With respect to the MYSEC-PM, overall survival at 4 years was 69% (51% to 87%) for the low-risk, 55% (40% to 69%) for the intermediate 1-risk, 47% (30% to 64%) for the intermediate 2-risk, and 22% (0% to 45%) for the high-risk groups (Figure 1B). The prognostic model was predictive of survival overall ($P = .05$), whereas groups with intermediate 2 and high risk showed no significant difference ($P = .44$) (Figure 1B).

Taking the DIPSS as reference, the MYSEC-PM reclassified 52 patients (33%) into a lower risk category and 33 (21%) into a higher risk one. Of note, 36 of 82 patients (44%) assigned to the intermediate 2- or high-risk categories by the DIPSS were downgraded into the low- or intermediate 1-risk groups by the MYSEC-PM. In contrast, only 14 of 75 patients (19%) in the low- or intermediate 1-risk groups by the DIPSS were upgraded to the intermediate 2- or high-risk groups by the MYSEC-PM.

Table 1
Patient Characteristics and Risk Distributions according to DIPSS and MYSEC-PM of the Total MF Cohort and of Patients with Post-PV and Post-ET MF Receiving Allogeneic Stem Cell Transplantation

	Total Cohort (N = 159)		Post-ET MF (n = 83)		Post-PV MF (n = 76)	
	n (or median)	% (or range)	n (or median)	% (or range)	n (or median)	% (or range)
Median age, yr (range)	59	(32.8-75)	57.1	(32.8-75)	60.3	(37.3-74.5)
Sex						
Female	72	45.3	39	47	33	43.4
Male	87	54.7	44	53	43	56.6
DIPSS						
High	14	8.8	9	10.8	5	6.6
Intermediate 1	59	37.1	25	30.1	34	44.7
Intermediate 2	70	44	42	50.6	28	36.8
Low	16	10.1	7	8.4	9	11.8
MYSEC-PM						
High	22	13.8	12	14.5	10	13.2
Intermediate 1	70	44	42	50.6	28	36.8
Intermediate 2	40	25.2	15	18.1	25	32.9
Low	27	17	14	16.9	13	17.1
Conditioning intensity						
Reduced	133	83.6	70	84.3	63	82.9
Myeloablative	26	16.4	13	15.7	13	17.1
Donor relation						
Identical sibling	59	37.1	27	32.5	32	42.1
Unrelated	100	62.9	56	67.5	44	57.9
Graft type						
Bone marrow	19	9.6	6	7.2	13	13.2
Peripheral blood	140	90.4	78	92.8	66	86.8
ATG use	115	72.3	57	68.7	58	76.3
Ruxolitinib pretransplant	36	22.6	19	22.9	15	19.7
Driver mutation						
CALR	27	17	22	26.5	5	6.6
JAK2 or MPL	126	79.2	59	71.1	67	88.2
Triple negative	6	3.8	2	2.4	4	5.3

ATG indicates antithymocyte globulin.

To quantify which prognostic system better fit survival, we calculated C-indices. As the prognostic capability of a system improves, the C-index will approach 1 and an estimate of .5 reflects outcome prediction by pure chance [15]. Assessment of prognostic utility yielded a C-index of .575 (.502 to .648) for the DIPSS, whereas assessment of the MYSEC-PM resulted in C-statistics of .636 (.563 to .708), indicating improvement in prediction of post-transplant survival using the new MYSEC-PM.

Because both scores were developed from multivariable models of disease- and patient-specific factors, we further evaluated the DIPSS and the MYSEC-PM according to each factor's impact on outcome after transplant. Regarding factors included in the DIPSS, none showed significant impact on outcome either in univariate or multivariate analysis. Univariate analysis of factors included in the MYSEC-PM showed survival rates for a CALR-unmutated genotype of 80% (63% to 96%) versus 46% (36% to 56%) for a CALR-mutated genotype (HR, 2.86; $P = .006$) and older age (HR, 1.28; $P = .02$), whereas platelet count $< 150 \times 10^9$/L, constitutional symptoms, blood blasts, and hemoglobin showed no significant impact on survival. In multivariate analysis only a CALR-unmutated genotype (HR, 3.02; 95% confidence interval [CI], 1.19 to 7.23; $P = .02$) and older age at transplantation (HR, 1.24; 95% CI, 1.01 to 1.52; $P = .04$) were significantly associated with worse survival (Table 2).

In addition, we investigated other factors related to transplantation that might influence prognosis. With regard to different conditioning intensities, reduced-intensity conditioning showed survival at 4 years of 61% (41% to 82%) versus 51% (41% to 61%) for myeloablative conditioning ($P = .13$). Hematopoietic cell transplant–specific comorbidity index of 0, 1 to 2, or >2 showed corresponding survival rates of 61%, 59%, and 63% ($P = .84$). Transplantations from an unrelated donor in comparison with an HLA-identical sibling showed worse overall survival at 4 years of 45% (34% to 57%) versus 63% (50% to 77%; $P = .04$). Transplant recipients seropositive for cytomegalovirus had worse survival of 43% (32% to 54%) in comparison with seronegative recipients showing rates of 68% (55% to 80%; $P = .01$).

In addition, splenectomy before transplantation showed 49% (26% to 71%) versus 53% (44% to 63%) of patients who did not receive a splenectomy ($P = .86$). *JAK2* inhibition before transplantation was received by 23% of all patients. However, outcome of pretransplant *JAK2* inhibition could not be evaluated in full detail because of a relatively short follow-up of patients receiving *JAK2* inhibition of 24 months compared with 49 months in patients without *JAK2* inhibition. Survival after 2 years did not differ between groups showing 59.

Last, we applied Cox proportional hazards regression adjusted for transplant-specific factors such as hematopoietic cell transplant–specific comorbidity index, donor relation, and cytomegalovirus serostatus to the MYSEC-PM. The HR for death (with the low-risk group as reference) was 2.91 (95% CI, 1.27 to

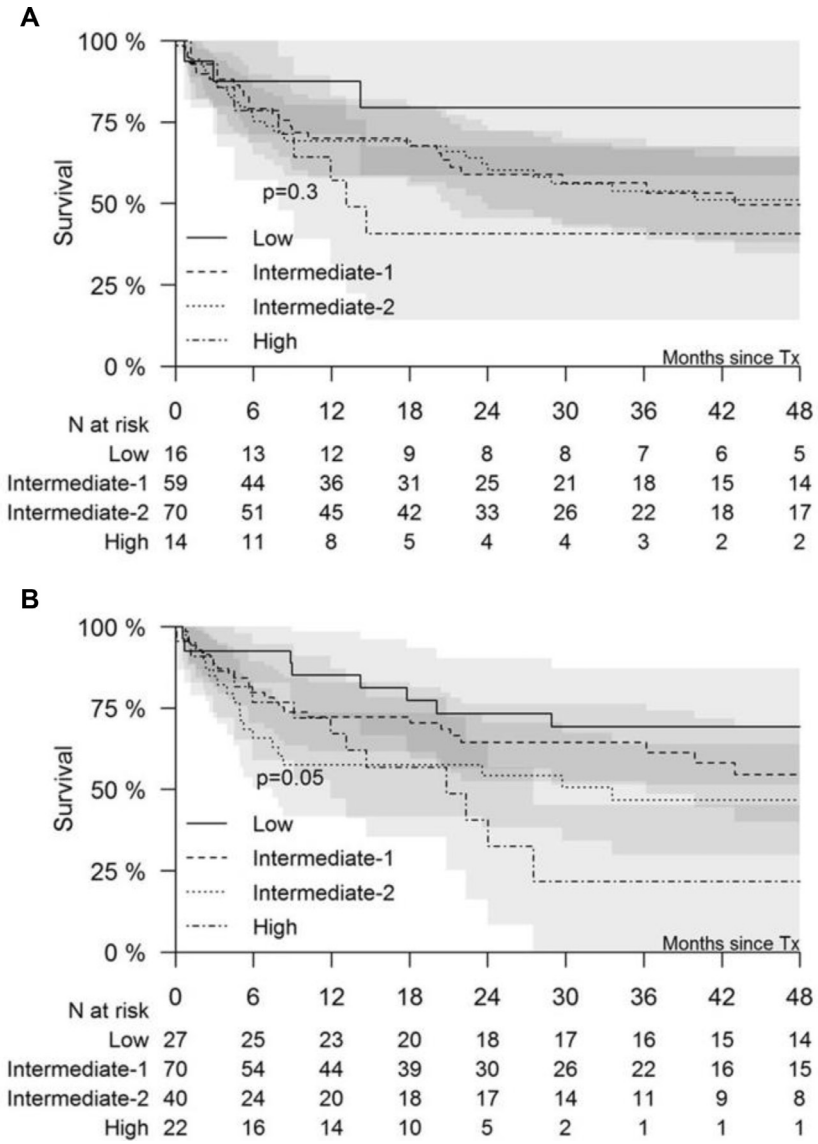

Figure 1. Overall survival according to each risk group of the prognostic model. (A) DIPSS. (B) MYSEC-PM.

Table 2
Multivariate Analysis Predictive Factors According to DIPSS and MYSEC-PM for the Outcome of Allogeneic Transplant in Post-PV and Post-ET MF

Clinical Variables	HR	95% CI	*P*
DIPSS			
Hemoglobin < 10 g/dL	1.05	.65-1.72	.84
WBC count > 25 × 109/L	1.58	.87-2.87	.14
Blood blasts > 0%	.83	.49-1.41	.50
Age > 65 yr	1.34	.70-2.54	.37
Constitutional symptoms	1.41	.84-2.39	.20
MYSEC-PM			
CALR-unmutated	3.02	1.19-7.63	.02
Blood blasts > 2%	1.34	.79-2.30	.28
Hemoglobin < 11 g/dL	.97	.54-1.76	.44
Platelets < 150 × 109/L	1.29	.76-2.18	.35
Constitutional symptoms	1.22	.73-2.02	.45
Age, yr	1.24	1.01-1.52	.04

6.66) for the intermediate 1-risk, 4.73 (95% CI, 2.01 to 11.11) for the intermediate 2-risk, and 6.68 (95% CI, 2.71 to 16.49) for the high-risk group, predicting post-transplant outcome even after transplant-related adjustment ($P < .001$). The overall survival model provided improved discriminatory power showing C-statistics of .675.

DISCUSSION

The present study including the largest population to date with MF secondary to PV and ET undergoing allogeneic stem cell transplantation from HLA-matched sibling or unrelated donors confirms that MYSEC-PM allows a more accurate prediction of survival than the DIPSS. However, clinicians must be aware of some relevant issues regarding the performance of the MYSEC-PM, specifically in MF patients undergoing transplantation. First, the prognostic capability of the prognostic model remains moderate (C-index = .636). Second, of all factors included in the model, only a CALR-unmutated genotype and age were independent factors for survival in multivariable analysis, suggesting that disease- and patient-related factors such as anemia or constitutional

symptoms may not carry predictive value in the transplant setting, whereas molecular characteristics maintain their effects during the disease course and its treatment. Third, incorporating transplant-related as well as clinical and mutational information [16] together with the MYSEC-PM may enhance risk stratification to properly select patients for allogeneic stem cell transplantation and to better counsel patients with respect to post-transplant outcomes specific to myelofibrosis patients post-PV and post-ET undergoing transplantation.

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