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Allogeneic – Adult

Predicting Survival after Allogeneic Hematopoietic Cell Transplantation in Myelofibrosis: Performance of the Myelofibrosis Transplant Scoring System (MTSS) and Development of a New Prognostic Model

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A B S T R A C T

Accurate prognostic tools are crucial to assess the risk/benefit ratio of allogeneic hematopoietic cell transplantation (allo-HCT) in patients with myelofibrosis (MF). We aimed to evaluate the performance of the Myelofibrosis Transplant Scoring System (MTSS) and identify risk factors for survival in a multicenter series of 197 patients with MF undergoing allo-HCT. After a median follow-up of 3.1 years, 47% of patients had died, and the estimated 5-year survival rate was 51%. Projected 5-year risk of nonrelapse mortality and relapse incidence was 30% and 20%, respectively. Factors independently associated with increased mortality were a hematopoietic cell transplantation-specific comorbidity index (HCT-CI) ≥3 and receiving a graft from an HLA-mismatched unrelated donor or cord blood, whereas post-transplant cyclophosphamide (PT-Cy) was associated with improved survival. Donor type was the only parameter included in the MTSS model with independent prognostic value for survival. According to the MTSS, 3-year survival was 62%, 66%, 37%, and 17% for low-, intermediate-, high-, and very high-risk

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groups, respectively. By pooling together the low- and intermediate-risk groups, as well as the high- and very high-risk groups, we pinpointed 2 categories: standard risk and high risk (25% of the series). Three-year survival was 62% in standard-risk and 25% in high-risk categories ($P < .001$).
We derived a risk score based on the 3 independent risk factors for survival in our series (donor type, HCT-CI, and PT-Cy). The corresponding 5-year survival for the low-, intermediate-, and high-risk categories was 79%, 55%, and 32%, respectively ($P < .001$).
In conclusion, the MTSS model failed to clearly delineate 4 prognostic groups in our series but may still be useful to identify a subset of patients with poor outcome. We provide a simple prognostic scoring system for risk/benefit considerations before transplantation in patients with MF.

INTRODUCTION

Myelofibrosis (MF) is a chronic myeloproliferative neoplasm with a highly heterogeneous but potentially aggressive clinical course. Median survival is around 6 years [1]. Allogeneic hematopoietic cell transplantation (allo-HCT) remains the only curative treatment, yet the advanced age of patients with MF and significant transplant-related mortality limit the applicability of this procedure [2].

The indications and optimal timing of allo-HCT in patients with MF are particularly challenging in daily clinical practice. Current recommendations indicate that patients with MF with expected survival of less than 5 years should be considered candidates for transplantation [3,4]. In order to identify such patients, a number of prognostic models [5-12] are available to accurately predict disease risk. However, only a minority of high-risk patients with MF actually undergo allo-HCT. In a Spanish nationwide series of 544 patients with MF aged ≤70 years followed up for a median of 3 years, only 17% of those in intermediate 2 or high-risk groups by the International Prognostic Scoring System [5] at diagnosis were subsequently allografted [13]. Factors such as patient comorbidities or poor performance status, lack of a suitable donor, or, particularly, patient or physician perceptions [14] regarding potential risks of transplantation may have precluded recommending curative treatment in most patients. It seems therefore essential to develop reliable prognostic tools that help appraise the risk/benefit ratio of HCT in patients with MF [3].

To this end, a clinical-molecular Myelofibrosis Transplant Scoring System (MTSS) integrating patient-, disease-, and transplant-specific factors has recently been proposed to estimate survival of patients with MF undergoing allo-HCT [15]. This prognostic scoring system was derived from a series of 205 patients with either primary MF or post-essential thrombocythemia or polycythemia vera MF from Hamburg and Paris. The MTSS model defines 4 risk categories (low, intermediate, high, and very high) based on 7 adverse prognostic factors evaluated at the time of transplantation (patient age ≥57 years, Karnofsky performance status [KPS] <90%, leukocytes >25 × 10^9/L, platelet counts <150 × 10^9/L, non-*CALR*/*MPL*driver mutation genotype status, *ASXL1* mutation, and HLA-mismatched unrelated donor). In an external validation cohort of 156 patients with MF from 2 German centers, 5-year survival was 83%, 64%, 37%, and 22% for the low-, intermediate-, high-, and very high-risk categories, respectively.

Although the MTSS may eventually prove useful in transplant decision making, any new prognostic model should be thoroughly tested for external validity and discrimination power before widespread use in daily clinical practice. Moreover, external testing can help fine-tune the model for enhanced clinical usefulness. Therefore, our primary goal was to evaluate the performance of the MTSS in a multicenter series of 197 transplanted patients with MF. In addition, we aimed to identify risk factors for survival that could improve prognostic assessment in this clinical setting.

METHODS

Study Population

This retrospective study included all adult patients who underwent first allo-HCT for MF between April 2003 and December 2019 in 19 Spanish hospitals. Patients who underwent transplantation after leukemic transformation were excluded. The study was approved by the Ethics Committee of Hospital Clínico Universitario of Valencia and registered by the AEMPS (Agencia Española de Medicamentos y Productos Sanitarios), with the reference number INC-TPH-2019-01. Informed consent for inclusion in the study was obtained in accordance with local ethics committee requirements.

Study Definitions and Variables

Assessment of hematologic recovery was performed only in patients who survived more than 28 days after graft infusion. Primary graft failure was defined as failing to reach neutrophil count >0.5 × 10^9/L within the first 28 days after stem cell infusion or documentation of autologous reconstitution by chimerism analysis in the absence of relapse [16]. Cases with relapse within 1 month of graft failure were classified as no graft failure [17]. Acute graft-versus-host disease (aGVHD) was graded according to Glucksberg et al. [18] and chronic graft-versus-host disease (cGVHD) according to Shulman et al. [19] criteria. Disease progression/relapse was defined as disease recurrence or persistence in patients who survived more than 28 days after transplantation [20]. In patients who died after disease relapse, this was considered the primary cause of failure, regardless of the immediate cause of death [21].

Variables investigated for prognostic significance were selected on the basis of their inclusion in the MTSS model and their clinical meaningfulness. They included year of transplantation (≤2009 versus later), patient sex, age ≥57 years, KPS <90%, hematopoietic cell transplantation-specific comorbidity index (HCT-CI) [22], MF subtype (primary versus secondary), prior splenectomy, spleen size, platelet count <150 × 10^9/L, leukocyte count >25 × 10^9/L, hemoglobin <10 g/dL, circulating blasts ≥5%, ferritin levels >1000 ng/mL, bone marrow osteosclerosis, Dynamic International Prognostic Scoring System risk category [6], transfusion dependence, driver mutations (*CALR*/*MPL* mutated versus others), additional somatic mutations (in *ASXL1*, *SRSF2*, *IDH1*, *IDH2*, or *U2AF1* genes), prior ruxolitinib treatment, intensity of conditioning regimen (myeloablative conditioning versus reduced-intensity conditioning), graft-versus-host disease (GVHD) prophylaxis, donor/patient cytomegalovirus serostatus, donor/patient sex (female donor to male recipient versus any other), donor type, donor/recipient HLA match, source of progenitor cells, and $CD34^+$ cell dose. The prognostic score according to the MTSS model was centrally calculated for each patient as previously described [15].

Outcome variables (graft failure, GVHD, disease progression/relapse) were considered only after the first transplant. For survival analysis, patients who received a second allo-HCT were not censored at the time of this transplant.

Statistical Methods

The primary study endpoint was survival. Secondary endpoints included nonrelapse mortality (NRM), graft failure, disease progression/relapse, aGVHD, and cGVHD. NRM was defined as death without evidence of relapse or disease progression. Survival was estimated by the Kaplan-Meier method and compared by log-rank test. Factors associated with overall survival at a significance level of $P \leq 0.1$ in univariable analysis were entered in a Cox proportional hazards model, using stepwise selection procedures to assess the independent effect of each covariate when controlled for the others. A weighted score was assigned to each significant variable for survival on the basis of the hazard ratios (HRs) obtained from multivariable analysis. A new prognostic scoring system was subsequently developed based on the sum of risk points to discriminate patient risk groups with significant differences in survival.

Median follow-up was determined using reverse Kaplan-Meier method. Risk of NRM, graft failure, disease progression/relapse, aGVHD, and cGVHD was evaluated in the context of competing risk and statistically compared by estimating the sub-hazard ratio (SHR) [23]. Death and relapse were taken as competing risks for acute and chronic GVHD. Continuous and count data were summarized as median and interquartile range. Categorical variables were represented as frequencies and percentages. The 95% confidence

Table 1
Baseline Characteristics in 197 Patients with Myelofibrosis Undergoing Allogeneic Hematopoietic Cell Transplantation

Characteristic	No. of Evaluable Cases	Value
Age, yr*	197	58 (52-62)
Male sex	197	116 (59)
Primary myelofibrosis	197	110 (56)
Palpable spleen ≥10 cm	153	42 (27.5)
Spleen size ≥22 cm by imaging	128	34 (27)
Blood levels*		
Hemoglobin, g/dL	193	8.9 (7.7-10.5)
Leukocytes, × 10^9/L	194	5.9 (3.2-11.2)
Platelets, × 10^9/L	194	113 (54-225)
Peripheral blasts	171	1 (0-3)
Ferritin levels, ng/mL*	164	612 (167-1359)
Bone marrow osteosclerosis	139	41 (29.5)
RBC transfusion dependence	195	111 (57)
KPS <90%	190	61 (32)
HCT-CI ≥3	183	47 (26)
Driver mutation		
JAK2	188	117 (62)
CALR	174	33 (19)
MPL	170	8 (5)
Triple negative	170	15 (9)
Additional somatic mutations		
ASXL1	71	26 (37)
SRSF2	60	6 (10)
IDH1	50	2 (4)
IDH2	49	3 (6)
U2AF1	49	4 (8)
DIPSS	179	
Low		3 (2)
Intermediate 1		43 (24)
Intermediate 2		95 (53)
High		38 (21)
Time to transplant, mo*	196	19 (9-43.5)
Year of transplant	197	
2000-2009		25 (13)
2010-2019		172 (87)
Female donor to male recipient	195	44 (23)
CMV serostatus patient/donor	187	
+/+		101 (54)
+/−		52 (28)
−/+		12 (6)
−/−		22 (12)
Myeloablative conditioning	197	64 (33)
PB as graft source	196	183 (93)
$CD34^+$ cell dose, × 10^6/kg*	193	5.4 (4.3-6.8)
Donor type	197	
HLA-matched related		85 (43)
HLA-matched unrelated		62 (31.5)
Single-allele mismatched related		2 (1)
Haploidentical related		18 (9)
HLA-mismatched unrelated		25 (13)
Cord blood		5 (2.5)
GVHD prophylaxis	191	
Cyclosporin based		103 (54)
Tacrolimus based		76 (40)
Rapamycin based		12 (6)
PT-Cy	197	55 (28)
ATG†	197	46 (23.5)
Splenectomy before transplant	197	13 (7)
JAK inhibitors before transplant	197	111 (56)

Data are given as frequency (%) unless otherwise specified. Percentages are calculated over the number of patients who had the data.
DIPSS indicates Dynamic International Prognostic Scoring System; CMV, cytomegalovirus; PB, peripheral blood; ATG, antihuman T-lymphocyte immunoglobulin.
* Median (interquartile range).
† One patient received alemtuzumab instead of ATG.

interval (CI) was used to inform about the precision of estimates. *P* values of less than or equal to .05 were considered statistically significant in all tests. All statistical analyses were performed with IBM SPSS 22.0 (SPSS, Inc., Chicago, IL) and Stata 11 (StataCorp, College Station, TX).

RESULTS

Patient Characteristics at Time of Transplant

Table 1 summarizes the main clinical and transplant-related characteristics of the series. Median age was 58 years, and 59% of patients were male. The majority of patients (56%) had been diagnosed with primary MF, and median time from MF diagnosis to transplant was 19 months. Most transplants (87%) were performed from 2010 to 2019. Compared with the original cohort of the MTSS, the present series included a higher proportion of transplants from HLA-matched related donors (43% versus 26%), haploidentical donors (9% versus 1%), and cord blood (2.5% versus 0%). In contrast, fewer patients received a graft from an HLA-mismatched unrelated donor in our series (13% versus 26%). A total of 55 patients (28%) received post-transplant cyclophosphamide (PT-Cy) as GVHD prophylaxis. Finally, 111 patients (56%) had received JAK inhibitors (mainly ruxolitinib) before allo-HCT.

Survival, Clinical Evolution, and Causes of Death

After a median follow-up of 3.1 years (95% CI, 2.5 to 3.5), 92 (47%) patients had died (8 within 28 days after graft infusion). Estimated survival rates at 1, 3, and 5 years were 60% (95% CI, 53% to 67%), 52% (95% CI, 45% to 59%), and 51% (95% CI, 43% to

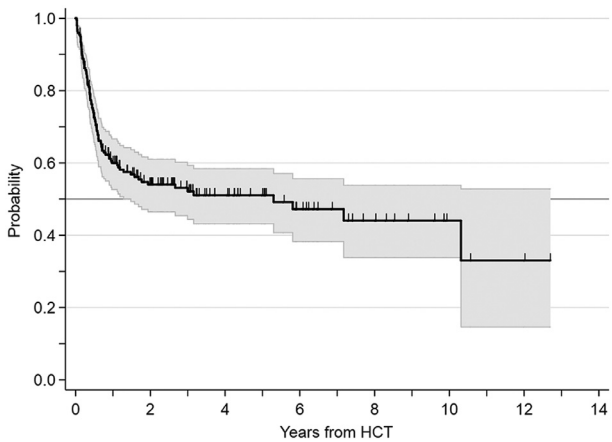

Figure 1. Projected survival of 197 patients with myelofibrosis undergoing allogeneic hematopoietic cell transplantation.

Table 2
Univariable Analysis of Factors Predicting Mortality in 197 Patients Undergoing Allo-HCT.

Factor	Univariable Analysis	
	HR (95% CI)	*P* Value
Age ≥57 yr	1.27 (0.84-1.94)	.26
Male sex	1.13 (0.74-1.72	.57
Myelofibrosis subtype	0.89 (0.59-1.34)	.56
Palpable spleen ≥10 cm	1.55 (0.94-2.54)	.083
Spleen size ≥22 cm by imaging	1.11 (0.61-2.0)	.74
Prior splenectomy	0.57 (0.23-1.42)	.23
KPS <90%	1.59 (1.03-2.45)	.037
HCT-CI ≥3	1.63 (1.02-2.61)	.041
Hemoglobin <10 g/dL	1.42 (0.88-2.27)	.15
Leukocyte counts >25 × 10^9/L	1.27 (0.62-2.64)	.51
Platelet counts <150 × 10^9/L	1.18 (0.78-1.80)	.44
Peripheral blasts ≥5%	1.45 (0.86-2.45)	.17
Ferritin level >1000 ng/mL	1.48 (0.92-2.37)	.10
Bone marrow osteosclerosis	1.0 (0.58-1.73)	.99
Transfusion dependency	1.38 (0.90-2.11)	.14
CALR or *MPL* unmutated	1.13 (0.62-2.07)	.69
ASXL1 mutated	1.08 (0.51-2.27)	.84
SRSF2 mutated	2.40 (0.81-7.12)	.12
IDH1 mutated	1.37 (0.18-10.43)	.76
IDH2 mutated	1.76 (0.40-7.71)	.45
U2AF1 mutated	1.51 (0.35-6.50)	.58
Intermediate 2/high-risk DIPSS	1.25 (0.73-2.14)	.41
Type of donor		
HLA-matched related	Reference	
HLA-matched unrelated	1.18 (0.71-1.94)	.52
Haploidentical related	0.92 (0.60-1.42)	.71
HLA-mismatched unrelated	1.21 (0.99-1.48)	.067
Cord blood	1.59 (1.25-2.03)	<.001
HLA-mismatched unrelated/cord blood	1.41 (1.10-1.80)	.007
Female donor/male recipient	1.25 (0.79-2.0)	.34
CMV serostatus patient/donor (+/−)	1.16 (0.73-1.86)	.52
Myeloablative conditioning	0.85 (0.54-1.33)	.47
CD34$^+$ cell dose ≥5 × 10^6/kg	0.74 (0.49-1.12)	.15
PT-Cy	0.49 (0.27-0.86)	.013
ATG use	1.74 (1.12-2.72)	.015
JAK inhibitors before transplant	0.76 (0.50-1.15)	.19
Transplant before year 2010	1.70 (1.01-2.87)	.046

59%), respectively (Figure 1). The projected risk of NRM at 1, 3, and 5 years was 27%, 29%, and 30%, respectively.

During follow-up, 108 (55%) patients were diagnosed with aGVHD (grade III to IV in 45, 23%) and 78 (40%) with cGVHD (extensive in 40, 20%). Cumulative incidence of grade II to IV aGVHD at 180 days was 40%. Cumulative incidence of any grade cGVHD and extensive cGVHD at 2 years was 33% and 24%, respectively.

Disease progression or relapse occurred in 35 (18%) patients and graft failure in 10 (5%). Cumulative incidence of relapse/progression at 1, 3, and 5 years was 16%, 19%, and 20%, respectively. A second transplant was performed in 11 (6%) patients. Supplementary Figure S1 shows the cumulative incidence of NRM and relapse/disease progression in the context of competing risks.

Causes of death were GVHD (n = 34, 37%), relapse/progression (n = 26, 28%), infection (n = 15, 16%), organ failure/toxicity (n = 8, 9%), graft failure (n = 6, 7%), and bleeding (n = 3, 3%).

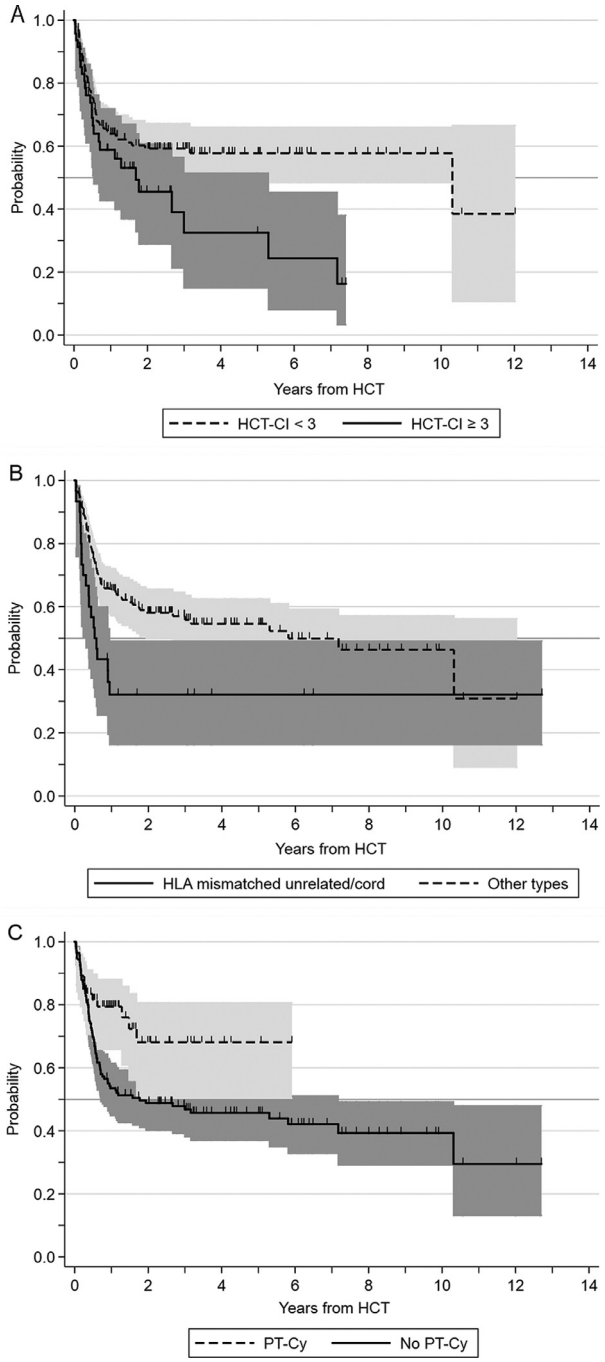

Figure 2. Unadjusted survival curves by risk factor in 197 patients with myelofibrosis who underwent transplantation: HCT-CI ≥3 (A), HLA-mismatched unrelated donor/cord blood (B), and use of post-transplant cyclophosphamide (C).

Prognostic Factors for Survival

Factors associated with survival are summarized in Table 2. In univariable analysis, the only 2 parameters included in the MTSS model that were significantly associated with survival were KPS <90% and receiving a graft from an HLA-mismatched unrelated donor or cord blood. Age ≥57 years, platelets <150 × 10^9/L, leukocytes >25 × 10^9/L, *ASXL1* mutations, and non-*CALR*/*MPL* driver mutation were not significantly correlated with survival. Six additional factors were included in multivariable analysis based on their association with survival

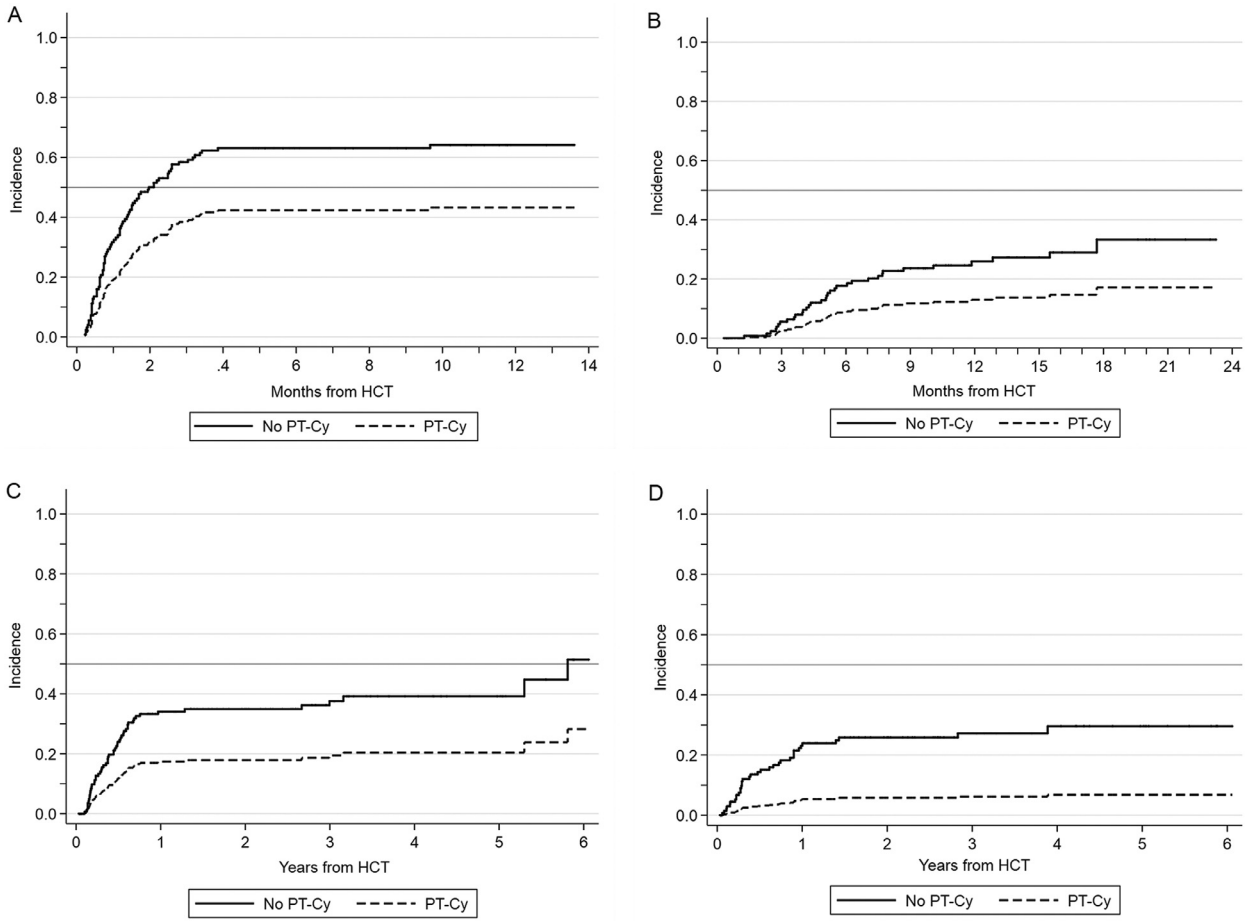

Figure 3. Cumulative incidence of grade II to IV aGVHD (A), extensive cGVHD (B), nonrelapse mortality (C), and disease relapse/progression with or without PT-Cy for GVHD prevention (D) in 197 patients with myelofibrosis who underwent transplantation. Death and relapse were competing events for aGVHD and cGVHD, whereas disease relapse/progression was competing with death without relapse.

($P \leq .1$): transplantation before the year 2010, HCT-CI ≥3, palpable spleen ≥10 cm below costal margin, ferritin >1000 ng/mL at transplant, use of antihuman T-lymphocyte immunoglobulin, and PT-Cy as GVHD prophylaxis.

Factors that remained independently associated with increased mortality after stepwise selection were HCT-CI ≥3 at time of transplant (HR, 1.68; 95% CI, 1.05 to 2.69; $P = .031$) and receiving a graft from an HLA-mismatched unrelated donor/cord blood (HR, 1.49; 95% CI, 1.13 to 1.97; $P = .005$), whereas PT-Cy for GVHD prevention was associated with improved survival (HR, 0.51; 95% CI, 0.28 to 0.90; $P = .022$). Figure 2 shows the unadjusted survival curves for the 3 independent prognostic factors. Figure 3 depicts the cumulative incidence of grade II to IV aGVHD, extensive cGVHD, disease relapse/progression, and NRM depending on whether or not PT-Cy was used for GVHD prevention. In univariable testing, PT-Cy was significantly associated with reduced risk of disease relapse/progression (SHR, 0.20; 95% CI, 0.06 to 0.64; $P = .007$), lower incidence of grade II to IV aGVHD (SHR, 0.55; 95% CI, 0.33 to 0.92; $P = .02$), and lower NRM (SHR, 0.46; 95% CI, 0.22 to 0.94; $P = .03$). With regard to extensive cGVHD, there was a nonsignificant trend for reduced incidence in patients who received PT-Cy (SHR, 0.46; 95% CI, 0.19 to 1.11; $P = .08$). Finally, Figure 4 shows the survival curves of the 55 patients undergoing allo-HCT with PT-Cy depending on the donor type: HLA-identical sibling/unrelated donor (n = 31, group A) or haploidentical/HLA-mismatched unrelated donor (n = 24, group B). As can be seen, no significant difference on survival was observed ($P = .78$).

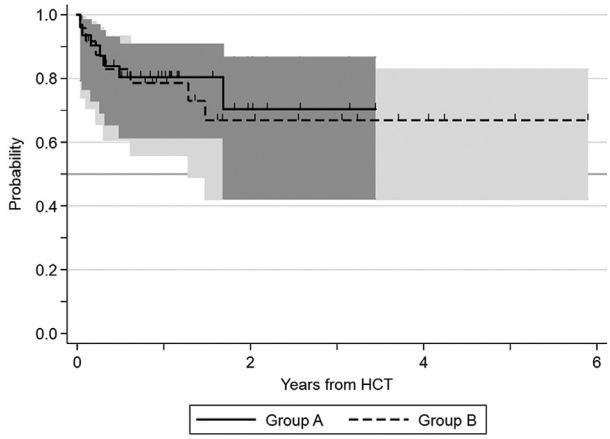

Figure 4. Survival curves of 55 patients with myelofibrosis undergoing allo-HCT with post-transplant cyclophosphamide depending on the donor type: HLA-identical sibling/unrelated donor (n = 31, group A) or haploidentical/HLA-mismatched unrelated donor (n = 24, group B).

Performance of MTSS Model

Among the 110 patients for whom information was sufficient to calculate MTSS category at transplant, 31 (28%), 51

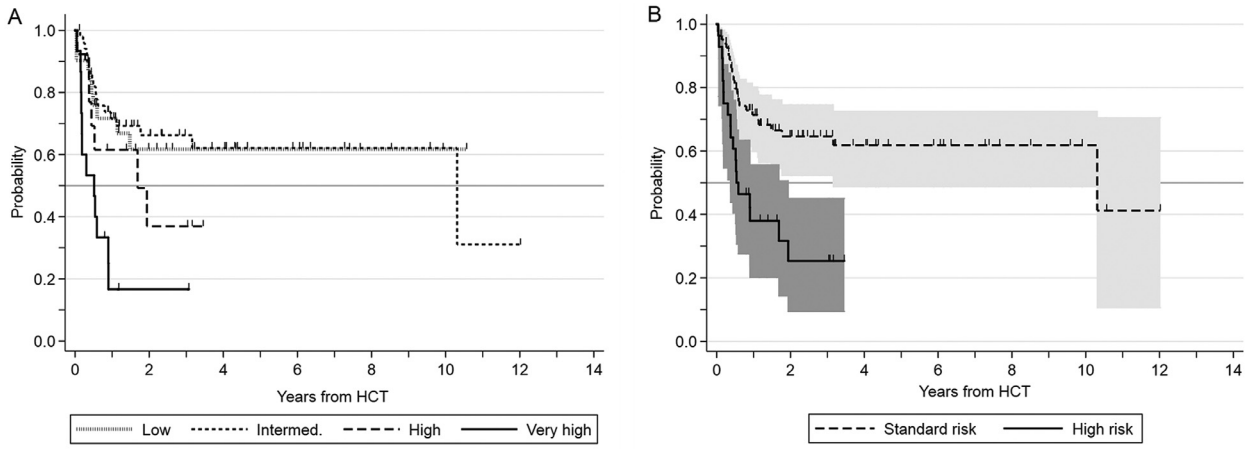

Figure 5. Survival curves of the different risk groups by the MTSS model (A) and after pooling together patients assigned to the low- and intermediate-risk groups, as well as those within the high- and very high-risk groups (B).

(46%), 13 (12%), and 15 (14%) cases were allocated to the low-, intermediate-, high-, and very high-risk groups, respectively. Overall, the proportion of patients assigned to each risk category was very similar to the original description of the MTSS. Estimated 3-year survival was 62% (95% CI, 43% to 81%), 66% (95% CI, 52% to 80%), 37% (95% CI, 6% to 68%), and 17% (95% CI, 0% to 37%) for low-, intermediate-, high-, and very high-risk groups, respectively (Figure 5A). As can be seen, the prognostic model was not able to discriminate 4 risk groups in our series. We then pooled together patients assigned to the low- and intermediate-risk groups, as well as those within the high- and very high-risk groups. On this basis, 2 categories could be identified: standard risk (n = 82) and high risk (n = 28, 25% of the series). Three-year overall survival was 62% (95% CI, 49% to 72%) in standard-risk and 25% (95% CI, 9% to 45%) in high-risk categories ($P < .001$) (Figure 5B).

Development of a New Prognostic Model

Based on the HRs of prognostic factors, we derived a risk score by adding 1 point to each HCT-CI ≥3 and transplant from HLA-mismatched unrelated donor/cord blood and subtracting 1 point for use of PT-Cy. Risk scores ranged from −1 to 2 and were grouped into 3 risk categories based on separation between adjacent prognostic classes with respect to HRs and overall survival. Low-risk category included score −1 (n = 35, 19%), intermediate-risk category included score 0 (n = 100, 55%), and high-risk category included scores 1 and 2 (n = 48, 26%). The corresponding 5-year overall survival for the low-, intermediate-, and high-risk groups was 79% (95% CI, 63% to 95%), 55% (95% CI, 45% to 65%), and 32% (95% CI, 17% to 47%), respectively ($P < .001$) (Figure 6). Cumulative incidence of NRM by risk group as defined by the MTSS and the Spanish risk score is shown in Supplementary Figure S2.

Table 3 summarizes the projected survival of patients belonging to each risk category in the MTSS and the new risk score, as well as the HRs when each category was compared with the immediately adjacent, lower risk one. As can be seen, the MTSS model failed to show significant differences in survival risk categories, whereas the new prognostic model defined 3 clearly separated risk groups.

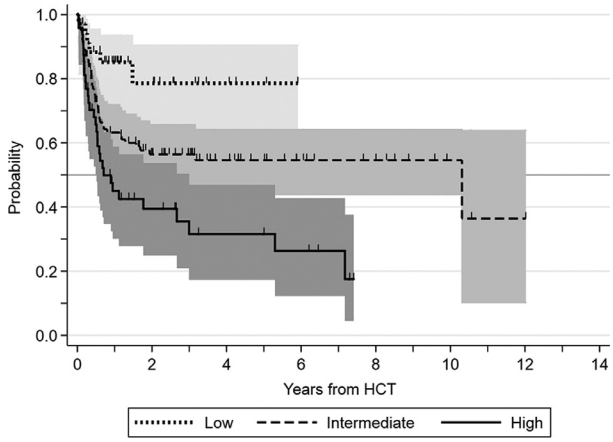

Figure 6. Survival curves of the different risk groups by the new prognostic model.

DISCUSSION

In the present study, we evaluated the MTSS scoring system and the risk factors associated with survival in a multicenter series of 197 patients with MF undergoing allo-HCT in Spain. The main independent factors predicting lower survival were an HCT-CI ≥3 at the time of transplantation and receiving a graft from an HLA-mismatched unrelated donor or cord blood, whereas PT-Cy for GVHD prevention was associated with improved survival. Of note, donor type was the only parameter included in the MTSS model with independent prognostic value for survival. KPS <90% was statistically significant in univariable analysis, but its independent prognostic value was not confirmed in the multivariable model. The original 4-group MTSS model did not fit our patients' survival, but its discrimination power increased substantially by collapsing the 4 groups into 2 risk categories. These findings indicate that the MTSS model has potential clinical utility but may require further refinement. Finally, we developed an easily implemented prognostic scoring system based on 3 independent risk factors. The resulting model divided patients into 3 risk categories with clearly distinct survival after transplant.

There are several potential explanations for the MTSS model's inability to discriminate 4-level risk stratification in our data set, the first being differences in MF populations or in transplant characteristics between both studies and possibly the smaller size of our series. Hematologic parameters at time of transplantation, particularly platelet counts at a threshold of 150×10^9/L, can vary depending on the treatment modality given just before transplantation and may not necessarily

Table 3
Projected Survival According to Risk Categories by Prognostic Scoring System in 197 Patients with Myelofibrosis Undergoing Transplantation

Risk Category	No. (%) of Patients	Survival, Median (95% CI), yr	Hazard Ratio* (95% CI)	*P* Value
MTSS				
Low	31 (28)	NR		
Intermediate	51 (46)	10.25	0.97 (0.45-2.10)	.94
High	13 (12)	1.7	1.81 (0.75-4.38)	0.19
Very high	15 (14)	0.5	2.36 (0.90-6.16)	0.079
New prognostic score				
Low	35 (19)	NR		
Intermediate	100 (55)	10.25	2.57 (1.09-6.04)	**.031**
High	48 (26)	0.8	1.80 (1.13-2.86)	**.013**

Numbers in bold are those with a significant *P* value on the statistical analysis ($P < .05$).
CI: confidence interval, NR: not reached.
* The hazard ratio compares a risk category with the immediate adjacent, lower risk one.

reflect disease biology. Moreover, healthy Mediterranean populations already have lower platelet counts than people from northern or central Europe [24]. It is worth noting here that previous studies have also observed the lack of prognostic significance of leukocytes $>25 \times 10^9$/L [25,26], mutational status of myeloproliferative neoplasm driver genes [27,28], or *ASXL1* mutations [27-29] in survival after allo-HCT.

In our view, although the MTSS model failed to discriminate 4 risk groups in the present series, it could still have value in clinical practice. Indeed, 2 risk categories can be delineated by pooling together patients assigned to the low- and intermediate-risk groups, as well as those within the high- and very high-risk groups: the "standard-risk" and the "high-risk" categories, with respective 3-year survival of 62% and 25%. Consequently, transplantation outcome in patients assigned to the "high-risk" category (25% of the series) is predicted to be poor, and this information will be useful for risk/benefit considerations before transplantation.

Survival after allo-HCT in our patients could be predicted by a prognostic scoring system based on 3 pretransplant factors: donor type, comorbidity index, and use of PT-Cy. It should be noted that the impact of patient comorbidities on survival was not evaluated in the original MTSS cohort [15] but has proven an important risk factor for mortality and NRM in other studies including patients with MF [26,30,31]. Notably, patients with significant comorbidities did not have a worse KPS at the time of transplantation (KPS <90% in 34% of patients with HCT-CI ≥3 versus 32% in those with HCT-CI <3). The weak correlation between HCT-CI scores and the KPS index has already been described [32], suggesting that both scales should be used to evaluate patient risk before transplantation. On the other hand, the beneficial effect on survival of PT-Cy was remarkable. PT-Cy is currently being used with promising results for GVHD prevention outside the haploidentical donor transplantation setting [33-35]. In line with this trend, PT-Cy was used after the year 2010 in all recipients of haploidentical donors (n = 18) but also in patients who underwent transplantation from HLA-identical siblings (n = 10) or unrelated donors (n = 21), as well as from HLA-mismatched unrelated donors (n = 6). Overall, patients receiving PT-Cy did not differ from the remaining ones in their main clinical characteristics (age, spleen size, KPS, comorbidity index, proportion of high-risk patients according to Dynamic International Prognostic Scoring System or MTSS) but had lower incidence of grade II to IV aGVHD, lower NRM, and less relapse/disease progression. Moreover, the use of PT-Cy was able to negate the potential adverse effect of HLA mismatching in the present series. Our prognostic model distinguished 3 risk groups with clearly distinct transplantation outcomes. Thus, the corresponding 5-year overall survival for the low-, intermediate-, and high-risk (26% of the series) groups was 79%, 55%, and 32%, respectively, indicating that transplant results in patients assigned to the high-risk category are suboptimal, and this treatment should be weighted up in each particular case against the predicted outcome without transplant.

In conclusion, the MTSS model failed to clearly delineate 4 prognostic groups in the present series. However, this prognostic model was still useful to identify a high-risk category of patients (about 25%) with poor outcomes in whom allo-HCT might not be the preferred treatment option. The favorable results achieved with PT-Cy in different transplant modalities merit further investigation in prospective clinical trials. Finally, we herein provide a simple prognostic scoring system that can help to assess the risk/benefit ratio of transplantation in potential candidates. Nevertheless, additional work is still needed to develop better prognostication models for transplant decision making in MF.

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SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.bbmt.2020.07.022.

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