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Original article

Scoring System Based on Post-Transplant Complications in Patients after Allogeneic Hematopoietic Cell Transplantation for Myelodysplastic Syndrome: A Study from the SFGM-TC

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ABSTRACT

Purpose: We developed a prognostic scoring system to evaluate the prognosis of myelodysplastic syndrome (MDS) patients surviving more than 100 days allogeneic hematopoietic cell transplantation after (allo-HCT).
Patients and methods: We performed a landmark analysis on a derivation cohort of 393 cases to identify prognostic factors for 3-year overall survival. Potential predictor variables included demographic and clinical data, transplantation modalities and early post-transplant complications. The scoring system was tested against a validation cohort which included 391 patients.
Results: Complications occurring before day 100 such as relapse [HR = 6.7; 95%CI, 4.5-10.0] (4 points), lack of platelet recovery [HR, 3.6; 95%CI, 2.2-5.8] (2 points), grade-II acute GVHD [HR = 1.7; 95%CI, 1.2-2.5] (1 point) and grade-III/IV [HR = 2.6; 95%CI, 1.8 -3.8] (2 points) were the only independent predictors of 3-year OS.
The 3-year OS associated with low (0), intermediate (1-3) and high (≥4) risk scores was respectively 70%, 46% and 6%. The model performed consistently in both cohorts, with good calibration.
Conclusion: This post-transplant scoring system is a powerful predictor of outcome after allo-HCT for

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MDS, and can provide useful guidance for clinicians. Additional studies are required to evaluate this scoring system for other hematologic malignancies.

INTRODUCTION

Allogeneic hematopoietic cell transplantation (allo-HCT) is a therapeutic option for high-risk hematological disorders including myelodysplastic syndrome (MDS) [1,2]. Nevertheless, this approach is still associated with potentially life-threatening complications such as conditioning-related toxicity, graft-versus-host disease (GVHD), poor graft function and relapse [3,4].

A key issue is managing patients with post-transplant complications. In addition, there is a need for a clinical tool that provides more cost-effective use of medical resources by streamlining the selection process of those patients who will truly benefit from curative care, including intensive care.

While most published scoring systems have focused on prognostic variables determined before allo-HCT [5–7], there are limited data regarding post-transplant prognostic evaluation, particularly within a specific disease type.

We hypothesized that a more complex model including early post-transplant events might be a more accurate predictor of. survival for those patients who have already been transplanted. Therefore, we developed a prognostic scoring system based on homogenous cohorts of transplanted MDS patients which takes into account disease characteristics and transplantation modalities as well as early post-transplant complications.

PATIENTS AND METHODS

This multicenter study was approved by the board of the Francophone Society of Bone Marrow Transplantation and Cellular Therapy (SFGM-TC), and was conducted in accordance with the Declaration of Helsinki. Written consent to use medically relevant data for research purposes was obtained from each patient and donor before transplant. To ensure confidentiality, each case was anonymized by assignment of a random identification number.

Data Source

The SFGM-TC database (ProMISe) was used to retrieve data from patients who underwent allo-HCT for MDS. In addition to an independent monitoring double-check, the quality of the data was controlled via a computerized search for discrepancy errors and vigorous on-site data verification of each file. HLA matching was cross-checked with the data of the French Bone Marrow Donor Registry as previously described [8,9].

Patient Selection

Two distinct cohorts of patients were used for this study, a derivation cohort and a validation cohort, with matching inclusion and exclusion criteria.

The derivation dataset came from the derivation cohort of patients (n = 461) treated for MDS with allo-HCT from January 1999 to December 2009.

Similarly, the validation dataset included all data from patients (n = 451) treated for MDS with allo-HCT from January 2010 to December 2013.

For inter-cohort homogeneity purposes, we only included patients who received a first allo-HCT. Stem cell sources were either bone marrow or peripheral blood stem cells (PBSC) from a sibling or HLA-matched (so-called 10/10) unrelated donor. Those who received allo-HCT from an HLA-mismatched or haploidentical donor were excluded. No patient received an ex-vivo T-cell depleted graft. Patients with chronic myelo-monocytic leukemia were also excluded.

To avoid the competing risk of early death, patients who died before day 100 were excluded from the derivation (n = 68, 14.8%) and validation (n = 60, 13.3%) cohorts.

STATISTICAL ANALYSIS

Patients and donor characteristics, transplantation modalities and early complications that occurred within 100 days post-transplant were taken into account. Inclusion of a variable in the predictive model was based on clinical relevance. The following variables were chosen: age at time of transplant; IPSS and cytogenetic score [10,11]; disease status at transplant (responder vs. non responder) according to IWG 2006 criteria [12]; bone marrow blast count at transplant (<5% vs. ≥ 5%), HLA matching (sibling vs. HLA-matched unrelated donor); sex mismatch defined as male patient receiving graft from a female; CMV positive status for donor and recipient; use of anti-thymocyte globulin (ATG); source of stem cells (bone marrow vs. PBSC); intensity of the conditioning regimen as defined by Bacigalupo et al [13]; grade of acute GVHD (0/I, II, III/IV) within 100 days post-transplant according to standard criteria [14]; early relapse before day 100 post-transplant; lack of platelet recovery [15]. The latter was defined by occurrence of transfusion-independent platelet count ≥20 G/L for the 7 consecutive days leading up to day 100 post-transplant even if platelet count may have then decreased at some point.

Quantitative variables are expressed as means (standard deviation) if the distribution was normal and as medians (interquartile range) if the distribution is otherwise. Categorical variables are expressed as frequencies and percentages. Normality of distribution was checked graphically and with use of the Shapiro–Wilk test. Using the Kaplan-Meier method, we estimated OS from 100 days after transplant, the landmark time point.

Before developing the multivariable prognostic model with Cox's proportional hazard regression model, the log-linearity assumption for age was assessed using Martingale residual plots and the restricted cubic spline functions [16]. Since no evidence of a non-log-linear relationship was shown, age was introduced as a linear term in the multivariable model. The proportional hazards assumption was assessed for each candidate predictor by plotting the Schoenfeld residuals against the rank of survival time [17].

Irrespective of their univariate association with OS, all variables were entered into the multivariable prognostic regression model. Missing data for individual variables ranged from 0 to 9.9% (1.7% of missing data points) leading to 86.0% of patients with no data missing data (ie. complete data) in the multivariable prognostic regression model. To prevent case deletion in multivariable analysis, missing data were imputed by simple imputation using a regression-switching approach (chained equations using all variables; death status and survival times introduced after logarithmic transformation) with predictive mean-matching method for the following: continuous variables; logistic regression model for binary variables; ordinal logistic regression for ordered categorical variables [18].

After a backward selection procedure, variables with low prognostic value ($P > 0.05$) were not kept in the final Cox model.

The results of significant predictors were reported as hazard ratios (HRs) and 95% confidence intervals (CI). The proportional hazard assumption was also assessed by plotting the Schoenfeld residuals for the prognostic index derived from the selected model against the rank of survival time. The performance of this model was assessed through its calibration and discrimination. In particular, calibration (i.e. the predicted-to-observed survival agreement) was evaluated by comparing the predicted mean survival curves to the

Table 1
Patient and disease characteristics at transplant and early post-transplant complications observed in derivation and validation cohorts.

	Derivation cohort ($n = 393$)	Validation cohort ($n = 391$)
Characteristics of the transplant		
Recipient age[a], years, mean ± SD	52.0 ± 10.8	56.6 ± 9.9
Recipient sex, n(%)	244 (62.1)	230 (58.8)
Male	149 (37.9)	161 (41.2)
Female		
Sex mismatch[a,b]	90 (22.9)	83 (21.2)
FAB/WHO category, n(%)	93 (23.7)	57 (14.6)
RA/RARS/RCMD	12 (3.1)	2 (0.5)
RAEB-1	253 (64.4)	285 (72.9)
RAEB-2	32 (8.1)	9 (2.3)
RAEB-t/AML	3 (0.7)	38 (9.7)
unclassified		
IPSS score[a], n(%)	204 (51.9)	138 (37.0)
Low/intermediate-1	189 (48.1)	235 (63.0)
Intermediate-2/high		
IPSS Cytogenetic risk score, n(%)	213 (55.3)	188 (48.8)
Favorable	90 (23.4)	81 (21.1)
Intermediate	82 (21.30)	116 (30.1)
High risk		
Pretransplantation therapy, n(%)	43 (12.0)	156 (39.9)
Hypomethylating agents only	154 (43.0)	89 (22.8)
Chemotherapy only	14 (3.9)	59 (15.1)
Both	147 (41.1)	87 (22.2)
None		
Disease status at transplant[a], n(%)	214 (54.5)	206 (52.7)
Responder	179 (45.5)	185 (47.3)
No responder		
Bone marrow blast count[a], (%)	156 (39.7)	119 (34.5)
<5%	237 (60.3)	226 (65.5)
≥5%		
HLA matching[a], n(%)	247 (62.8)	203 (51.9)
No	146 (37.2)	188 (48.1)
Yes		
Donor CMV status[a], n(%)	196 (49.9)	172 (44.3)
Positive	197 (50.1)	216 (55.7)
Negative		
Recipient CMV status[a], n(%)	213 (54.2)	199 (50.9)
Positive	180 (45.8)	192 (49.1)
Negative		
Use of anti-lymphocyte serum[a], n(%)	212 (53.9)	90 (23.0)
No	181 (46.1)	301 (77.0)
Yes		
Stem-cell source[a], n(%)	119 (30.3)	59 (15.1)
Marrow	274 (69.7)	332 (84.9)
PBSC		
Conditioning regimen[a], n(%)	145 (36.9)	109 (27.9)
RIC	248 (63.1)	282 (72.1)
MAC		
Total body irradiation, n(%)	254 (64.8)	326 (83.8)
No	129 (35.2)	63 (16.2)
Yes		
Early post-transplant complications		
Grade of acute GVHD[a], n(%)	243 (61.8)	293 (74.9)
0/I	92 (23.4)	60 (15.4)
II	58 (14.8)	38 (9.7)
III/IV		
Lack of platelet recovery before day 100[a], n(%)	368 (93.6)	365 (93.6)
No	25 (6.4)	25 (6.4)
Yes		
Relapse before day 100[a], n(%)	358 (91.1)	354 (90.8)
No	35 (8.9)	36 (9.2)
Yes		

Abbreviations: RA, refractory anemia; RARS, RA with ring siderobalsts; RCMD, Refractory cytopenia with multilineage dysplasia; RAEB, RA with excess of blasts; RAEB-t, REAB in transformation <30% of marrow blasts; HLA, human leukocyte antigen; CMV, cytomegalovirus; PBSC, peripheral blood stem cells; ATG, anti-thymocyte globulin; TBI, total body irradiation; GVHD, graft-versus-host disease; d100, day 100.

[a] Indicates selected variables for entrance into the multivariable prognostic regression model.

[b] Defined as male patient receiving graft from a female.

Kaplan-Meier survival curves of three specific risk groups which were determined by the prognostic index's distribution.

Discrimination was assessed via the Harrell's c-index of agreement [16], which indicates to what extent the model distinguishes between patients who will die from those who will survive. This c-statistic is expected to range from 0.60 to 0.85 for survival data [19]. The predicted overall survival probabilities were derived from the baseline survival estimates at the mean values of selected variables. To account for the reported overestimation of regression coefficients in prognosis models derived from multivariable regression analysis [16], we performed an internal validation by using bootstrap resampling with 200 repetitions to estimate the shrinkage factor and the c-statistic corrected for over-optimism.

For clinical purposes, a point-scoring model (e.g. a risk assessment tool) was created by assigning one point to the lowest hazard ratio (the constant factor that reflect 1 point in final point system) and by weighing every other one to the nearest approximation of the ratio of its HR with constant factor. The predictive accuracy of the point-scoring model was assessed by the previously mentioned method.

For the external validation, calibration and discrimination performances were assessed for continuous and discreet point-score models in the validation dataset. The predicted survival probabilities calculated within the validation dataset came from the coefficient estimates (after applying the shrinkage factor) and the baseline survival estimate from the derivation dataset.

Statistical testing was done at the two-tailed α level of 0.05. Data were analyzed using the SAS software package, release 9.4 (SAS Institute, Cary, NC).

RESULTS

Database

The derivation cohort included 393 patients and the validation cohort included 391 patients. The median follow-up from transplantation respectively for the derivation and validation cohort was 3.8 years (range, 0.3 to 11.8 years) and 2.9 years (range, 0.4 to 5.5 years). Table 1 reports baseline characteristics and early post-transplant complications of both cohorts. Mean recipient age was 52.0 ± 10.8 years in derivation cohort, and 56.6 ± 9.9 years in validation cohort. In the derivation and validation cohort, respectively 37.9% and 41.2% of recipients were female. Main differences were higher incidence of intermediate2/high IPSS score, broader use of ATG, increased pre-transplant treatment using hypomethylating agents, and less-intensive conditioning in the validation cohort. In the derivation cohort, 173 deaths occurred, and 145 deaths occurred in the validation cohort. Mean 3-year OS was 56% for the derivation cohort and 63% for the validation cohort.

Prognostic Scoring Model

Univariate associations of clinically relevant predictors with 3-year OS in the derivation cohort are available in Supplementary Table S1.

After a stepwise-backward selection procedure, the only independent risk factors of 3-year OS were the following:

1 Grade of acute GVHD (HR for grade II: 1.7; 95%CI: 1.2 - 2.5; HR for III/IV: 2.6; 95%CI: 1.8 to 3.8 using 0/I as reference).
2 Lack of platelet recovery before day 100 (HR: 3.6; 95%CI, 2.2 - 5.8).
3 Relapse before day 100 (HR: 6.7; 95%CI: 4.5 - 10.0).

See Table 1 for observed occurrence of these three complications among patients in both cohorts.

Internal validation

There was no deviation from proportional hazard assumptions for the prognostic index derived from the selected model. After correction for over optimism, the discrimination of the prognostic scoring model was 0.67 (95%CI: 0.63-0.71) with a shrinkage factor of 0.903. Calibration at 1 to 3 years from transplantation was good in all groups, implying that the predicted survival for each group were close to the observed ones (Fig. 1, Table 3, and Supplementary Table S2). Formulae and coefficients to estimate 1 to 3-year survival probability are detailed in the appendix.

External Validation

The discrimination value in the validation dataset was 0.65 (95% CI: 0.61-0.69). After the shrinkage of the coefficients, the calibration stayed satisfactory despite a slight underestimation observed in the highest risk group: 21.9 vs 9.7 for 3-year OS (see Supplementary Table S2).

Post-Transplant Scoring System (PTSS)

As shown in Table 2, grade of acute GVHD, lack of platelet recovery and relapse within 100 days after transplant were respectively assigned 1, 2 and 4 points. The point score model ranged from 0 - 8, discriminating low (0), intermediate (1 - 3), and high-risk (4 - 8) patients, according to survival prognosis. The observed 3-year OS after transplantation in patients with low, intermediate and high scores was accordingly 70% (95%CI: 63 - 76%), 46% (95%CI, 38 - 55%) and 6% (95%CI, 2 - 16%). In both datasets, discrimination and calibration were satisfactory (Table 3).

How to Use the PTSS: Proposal of an Algorithm

Patients requiring intense care due to early post-transplant complications are almost systematically transferred [15]. However,

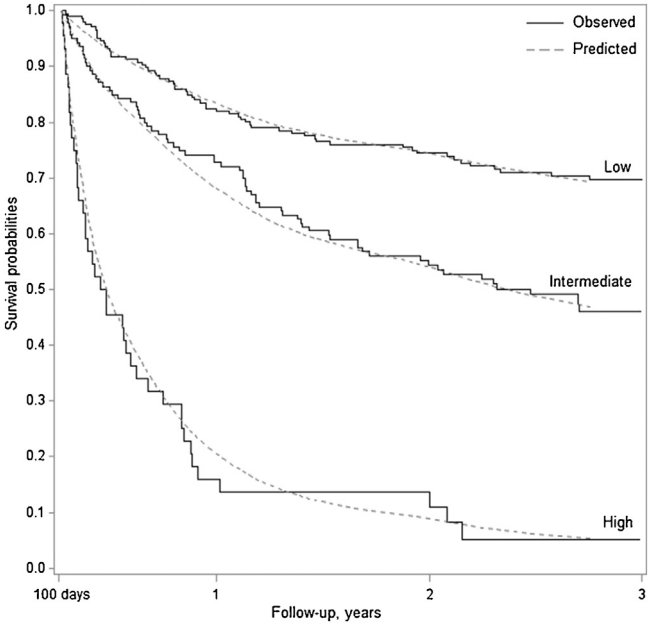

Fig. 1. Calibration of survival probabilities. The continuous prognostic model in the derivation cohort highlighted low (0 points), intermediate (1-3 points) and high (> 3 points) risk score according to corresponding survival probability. Origin of the landmark analysis is day 100.

Table 2
Scoring system of mortality risk according to early post-transplant complications.

Predictors	Points			
	0	1	2	4
Grade of acute GVHD	0/I	II	III/IV	-
Lack of platelet recovery before day 100	No	-	Yes	-
Relapse before day 100	No	-	-	Yes
Risk groups	**Score**[a]			
Low	0			
Intermediate	1-3			
High	4-8			

GVHD = graft-versus-host disease.
[a] Score: addition points of the 3 predictors described above.

the decision to transfer those developing complications after day 100 post-transplant is more difficult to make.

As shown in Fig. 2, the PTSS together with other scoring systems such as the Sepsis-Related Organ Failure Assessment (SOFA) [20] can facilitate the decision-making process before transferring a patient to the ICU. According to the expected 3-year survival observed with the PTSS, patients with a low score should be transferred regardless of their current complications, and those with a high score are less likely to benefit from intensive care. Prior to making a final decision regarding specific ICU care, patients with an intermediate PTSS score must undergo additional screening based on standard ICU scores [20–23]. Therefore, they can be transferred to the ICU if their SOFA score, for instance, is A, B or C (less than 10 points).

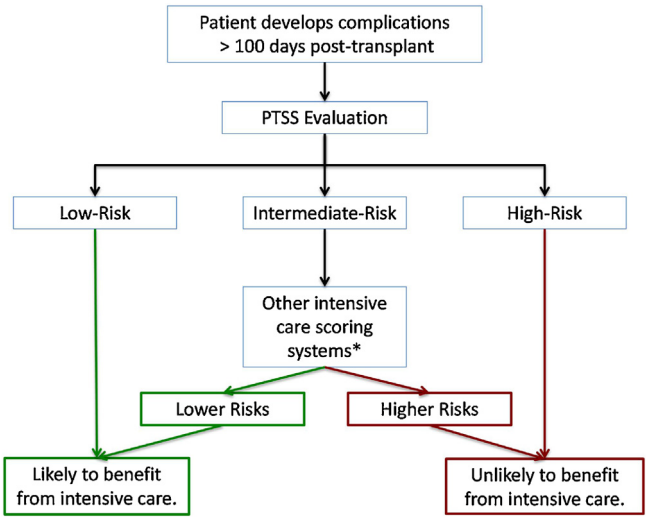

Fig. 2. Proposal of an algorithm for patients requiring transfer to ICU after day 100 post-transplant. (* examples of ICU scoring systems[20,24,25]).

DISCUSSION

To our knowledge, this is the first study to propose a clinical tool generated from variables evaluated after allo-HCT. This tool allows for early post-transplant prognostic assessment in patients with MDS.

Several approaches have been used to attempt to predict patient outcome after allo-HCT. One of these scoring approaches is to apply well-established disease-specific prognostic scores at the time of transplant [1,5,6], which poses significant limitations. By definition, patients eligible for allo-HCT are usually classified as "high-risk" per the given scoring system. While these scores are helpful for decision-making in terms of transplant, they overlook key transplant-related variables [6,7].

The main body of literature investigating prognostic factors assessed after hematopoietic cell transplant was published by the intensivist community. While of interest for patients admitted to the ICU, such studies fail to include key prognosticators such as disease characteristics and transplantation modalities [20,24–26]. For MDS in particular, other authors have combined disease-specific scores (R-IPSS) with other variables assessed at the time of transplant (HCT-CI) to assess prognosis after allo-HCT [5].

In this study, we computed a comprehensive set of data into a multivariable Cox model encompassing patient characteristics as well as detailed transplantation modalities. In contrast with previously reported models [7–11], we also included crucial early post-transplant complications using a landmark analysis at day 100. Notably, we considered IPSS score rather than IPSS-Revised score for baseline disease characteristics, as recommended by the European LeukemiaNet [27]. In addition, IPSS-R do not seem to

Table 3
Calibration and discrimination of point-score model.

	Derivation cohort			Validation cohort		
	Death/N	Observed	Predicted	Death/N	Observed	Predicted
1-year survival						
Risk group						
Low (0)	37/207	0.820	0.832	31/244	0.871	0.812
Intermediate (1 to 3)	38/142	0.727	0.686	36/109	0.669	0.655
High (4 to 8)	37/44	0.159	0.202	23/38	0.395	0.250
2-year survival						
Risk group						
Low (0)	52/207	0.744	0.745	61/244	0.738	0.715
Intermediate (1 to 3)	63/142	0.544	0.550	45/109	0.576	0.510
High (4 to 8)	39/44	0.109	0.087	27/38	0.283	0.114
3-year survival						
Risk group						
Low (0)	60/207	0.697	0.692	68/244	0.697	0.658
Intermediate (1 to 3)	72/142	0.463	0.475	48/109	0.537	0.434
High (4 to 8)	41/44	0.055	0.050	29/38	0.219	0.069
C-statistic (95%CI)	**0.67 (0.63-0.71)**[a]			**0.65 (0.61-0.69)**		

Observed values were calculated using Kaplan–Meier estimates.
In the derivation data set, predicted estimates in each risk group were calculated as the mean predicted probabilities by the Cox regression model (using score as continuous predictor). In the validation dataset, predicted estimates use shrinkage factor based on bootstrap validation in the derivation data set (see method and appendix for more information).
[a] C-statistic corrected for over-optimism.

change the outcome after allo-HCT compared to IPSS [28]. Interestingly, these post-transplant complications were found to be the only independent risk factors associated with decreased 3-year OS, whereas pre-transplant parameters were not found to be independent risk factors. Although pre-transplant factors such as disease characteristics and transplantation modalities play a major role in post-transplant survival, early post-transplant complications appeared to override the prognostic impact of pre-transplant parameters.

Strikingly, lack of platelet recovery at day 100 was a strong and independent predictor of low OS. The prognostic impact of impaired platelet recovery has already been described by others [29,30], but these studies observed heterogeneous cohorts in terms of disease type and transplant modalities. Therefore, this is the first clear report of the negative and independent impact of poor platelet recovery on long-term survival. Only a few patients who did not recover their platelet count before day 100 showed early relapse: 6/25 in derivation cohort; 4/25 in validation cohort. Regarding this, absence of durable platelet recovery could also reflect poor graft function, when not reflecting viral/bacterial infections or linked to GVHD [4,31,32]. Predictably, relapse before day 100 along with grade 2-4 acute GVHD adversely impacted survival in our model [33].

In light of the rising number of patients undergoing allo-HCT, the decision-making process of whether a patient should be treated with curative or palliative intent ought to be guided by robust statistical models. Despite the recent changes in allo-HCT management, expected and observed rates overlapped with our prognostic model when applied to a more recent cohort of patients (ie. validation cohort). In fact, older patients could still benefit from allo-HCT, with more severe disease highlighted by a higher-risk IPSS score. The recent growing use of PBSC as a transplant source and, therefore, the prophylactic use of ATG for GVHD [34] partly explain these differences. Interestingly, we observed that more patients received a myeloablative conditioning (MAC) regimen in the validation cohort, despite of increased age of transplantation.

For daily use, the PTSS, a clinical risk assessment tool was elaborated, stratifying patients with a score according to the following levels of mortality risk: low (0), moderate (1-3) and high ($\geq$4).

The PTSS score takes into account scores relative to the following variables: acute GVHD grade; lack of platelet recovery before day 100; relapse before day 100. This proposed clinical scoring tool could provide for a more cost-effective use of medical resources because it aims to more appropriately select those patients who will truly benefit from curative care, including intensive care.

Dramatically, early relapse systematically drives patient to the high-risk group as opposed to the occurrence of acute GvHD, which more weakly affects prognosis. Nevertheless, a prospective evaluation is needed to prove the cost-effectiveness of such a strategy.

According to recommendations from the SFGM-TC, patients requiring intensive care during the early post-transplant period should be transferred to the ICU regardless of their complication severity [15].

The PTSS can be helpful in making the decision to proceed to intensive care for patients surviving more than 100 days after allo-HCT. Indeed, it seems difficult to refuse to transfer a patient with a low PTSS-score (estimated 3-year OS of 70%). In contrast, with 6% of estimated 3-year OS, patients with a high score are less likely to benefit from ICU admission. Screening systems based on standard ICU scores[20,24,25] would be more helpful when it comes to patients with intermediate PTSS-score (estimated 3-year OS of 46%). Nevertheless, such hypothesis should be further validated in an independent prospective cohort of patients requiring treatment in intensive care settings.

One of the strengths of this study was the clear-cut definition of the predictor variables, which relevance are in line with previous studies. An additional strength is the simplicity of use of our prognostic assessment tool, suitable for clinical practice and bridging the gap between scores typically used by onco-hematologists and those applied in the ICU.

Due to prospective data collection in the ProMISe database, some variables were not included in the model, such as comorbidity evaluation, development of infection, acute kidney injury, or sinusoidal occlusion syndrome. However, occurrence of such complications and severe comorbidities were considered beforehand with regards to conditioning intensity, which was included in our multivariable model.

Finally, we would like to mention that an increasing amount of attention is being focused on molecular data in MDS. Due to the inclusion years, such data were not available in our database. If molecular data are suggested to improve the risk stratification of MDS patients [35], such an approach has yet to be prospectively validated in hematopoietic transplantation procedures. Given our aim to develop a simple and usable clinical score, adding such specific data did not appear relevant to us. Extending our prognostic score to patients who underwent allo-HCT for other hematological disorders, malignant or not, or other types of transplant is an encouraging potential next step that will ideally require prospective validation in homogenous cohorts.

CONCLUSION

In this study, we created and validated the first prognostic score based on early post-transplant complications to quickly and simply estimate the survival probability of myelodysplastic patients who survived more than 100 days after allo-HCT. Our findings support the robustness, the reliability and the reproducibility of this scoring system. The potential extension of our scoring system, to patients with other hematologic malignancies will be the next phase for the PTSS we propose. This next step will require further prospective evaluation.

Authors Contribution

AC, ED, AD and IYA designed the study, AC, ED, AD, IYA reviewed the data, analyzed results, and made the figures. All authors wrote and approved the manuscript.

Conflict of interest

All authors declare no competing financial interests.

This study was presented in part at the American Society of Hematology (San Diego, 2016).

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Appendix A. Calculating the 1, 2 and 3-year overall survival using the continuous prognostic model

Step 1: Calculate S

S = [-1.2706 * (Platelet recovery) + 0.5251 * (acute GVHD II) + 0.9592 * (acute GVHD III/IV) + 1.9011 * (Relapse)] * 0.9027

Where

(1) Platelet recovery =
   a 0.0636 if the patient recovers their platelet count before day 100
   b −0.9364 if the patient doesn't recover their platelet count before day 100
(2) Acute GVHD II =
   a 0.7659 if the patient has grade II acute GVHD
   b −0.2341 if the patient does not have grade II acute GVHD
(3) Acute GVHD III/IV =
   a 0.8524 if the patient has grade I/IV acute GVHD
   b −0.1476 if the patient does not have grade I/IV acute GVHD
(4) Relapse =
   a 0.9109 if the patient relapses before day 100
   b −0.0891 if the patient doesn't relapse before day 100
(5) −1.2706, 0.5251, 0.9592 and 1.9011 = regression coefficients estimated for the derivation dataset
(6) 0.9027 = the shrinkage factor estimated using bootstrap validation for the derivation dataset

Step 2: Calculate survival probability using S

1-year survival probability = $100 * 0.7374^{\exp(S)}$

2-year survival probability = $100 * 0.6130^{\exp(S)}$

3-year survival probability = $100 * 0.5426^{\exp(S)}$

Where 0.7374, 0.6130 and 0.5426 are the survival rate at the mean values of predictors in derivation dataset.

Example: a patient who recovers platelet count, relapses before 100 days and has grade 0 acute GVHD.

Step 1: Calculate S = [−1.2706 * (0.0636) + 0.5251 * (−0.2341) + 0.9592 * (−0.1476) + 1.9011 * (0.9109)] * 0.9027 = 1.2515

Step 2: Calculate survival probability using S

1-year survival probability = $100 * 0.7374^{\exp(1.2515)} = 34.5\%$

2-year survival probability = $100 * 0.6130^{\exp(1.2515)} = 18.1\%$

3-year survival probability = $100 * 0.5426^{\exp(1.2515)} = 11.8\%$

Appendix B. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.retram.2018.08.003.

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