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Pretransplantation EASIX predicts intensive care unit admission in allogeneic hematopoietic cell transplantation

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Key Points

- EASIX-PRE identifies a cohort of patients undergoing alloHCT at increased risk of ICU admission during posttransplantation follow-up.
- EASIX-PRE predicts OS and NRM in those undergoing alloHCT.

The Endothelial Activation and Stress Index (EASIX) is a laboratory-based prognosis index defined as creatinine × lactate dehydrogenase/platelets. When measured at pretransplantation evaluation (EASIX-PRE), it predicts allogeneic hematopoietic cell transplantation (alloHCT) mortality. This study explores its ability to predict intensive care unit (ICU) admission and validates EASIX-PRE predictive power for overall survival (OS) and nonrelapse mortality (NRM) in 167 consecutive patients undergoing alloHCT. EASIX-PRE was calculated retrospectively in all patients and transformed into $\log_2$ values ($\log_2$-EASIX-PRE). Log_2-EASIX-PRE predicted ICU admission (hazard ratio [HR], 1.41; $P < .001$), OS (HR, 1.19; $P = .011$), and NRM (HR, 1.28; $P = .004$). The most discriminating EASIX-PRE cutoff value for risk of ICU admission was the 75th percentile (2.795); for OS and NRM, it was the median value (1.703). Patients with EASIX-PRE >2.795 had higher incidence of ICU admission in comparison with patients with lower EASIX-PRE values (day +180, 35.8% vs 12.8%; HR, 2.28; $P = .010$). Additionally, patients with EASIX-PRE >1.073 had lower OS (2 years, 57.7% vs 68.7%; HR, 1.98; $P = .006$) and higher NRM (2 years, 38.7% vs 18.5%; HR, 2.92; $P = .001$) than patients with lower EASIX-PRE results. Log_2-EASIX-PRE was not associated with incidence of transplantation-associated microangiopathy, sinusoidal obstruction syndrome, or acute graft-versus-host disease. This study proposes EASIX-PRE as a prognostic tool to identify patients undergoing alloHCT at increased risk of severe organ dysfunction and who would therefore require ICU admission. Early identification of patients at high risk of severe events could contribute to personalized intervention design. Additionally, it validates the association between EASIX-PRE and OS and NRM in those undergoing alloHCT.

Introduction

Allogeneic hematopoietic cell transplantation (alloHCT) is a curative therapy for patients with high-risk hematologic disorders.[1] However, alloHCT is associated with a significant mortality risk and a relevant impact on patients' quality of life.[1–3]

Estimation of the mortality risk is a key part of a candidate's evaluation for alloHCT; it is essential for patient counseling. The most integrated prognostic indices in daily clinical practice include the Hematopoetic Cell Transplantation–Specific Comorbidity Index (HCT-CI),[4] the European Group for Blood and Marrow Transplantation risk score,[5] and the Disease Risk Index.[6] AlloHCT has evolved during the last 2 decades to result

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The full-text version of this article contains a data supplement.

in more refined transplantation techniques, donor selection, and supportive care.[7] These developments have led to an ongoing need to update risk indices aimed at improving risk stratification of patients undergoing alloHCT.[8–10]

Endothelial-origin syndromes such as transplantation-associated microangiopathy (TAM), sinusoidal obstruction syndrome (SOS), and acute graft-versus-host disease (GVHD) comprise some early transplantation complications that can significantly contribute to transplantation-related mortality.[11] The Endothelial Activation and Stress Index (EASIX) is a biomarker-based laboratory formula defined as creatinine (mg/dL) × lactate dehydrogenase (LDH; U/L)/platelets (× 10^9/L), which was originally designed to predict mortality in patients with acute GVHD.[12] The utility of EASIX has successfully been extended to a general prediction of mortality when evaluated before alloHCT (EASIX-PRE).[13,14] Furthermore, it has been used to predict transplantation complications when evaluated at different time points after alloHCT.[15–17]

Because endothelial syndromes can lead to organ dysfunction and a subsequent need for advanced support measures, we hypothesized that EASIX-PRE could predict the probability of clinically relevant complications that would require intensive care unit (ICU)–specific treatments. Therefore, the goal of the present study was to validate the predictive power of EASIX-PRE for overall survival (OS) and nonrelapse mortality (NRM) in a cohort of adults undergoing alloHCT and explore the ability of the score to predict relevant transplantation-related complications such as ICU admission.

Methods

Patient selection

Between January 2015 and June 2020, 167 consecutive adults aged between 18 and 65 years underwent alloHCT at the Institut Català d'Oncologia-Hospitalet in Barcelona, Spain. Eligibility criteria for alloHCT and main definitions are detailed in the data supplement. Data were collected through retrospective reviews of medical records and updated in November 2020. The study was approved by the ethics committee of the Institut Català d'Oncologia and conducted in accordance with standards set forth by the Declaration of Helsinki.

EASIX application

The EASIX-PRE variable was defined as creatinine (mg/dL) × LDH (U/L)/platelets (×10^9/L). Information on individual variables was collected based on results obtained from blood work done during pretransplantation assessments (between days −30 and −7 before alloHCT). Following standard practices in literature,[12,14] the original value of the index was converted to a logarithm with base 2 value (log_2-EASIX-PRE). Patients were stratified into 4 risk groups according to quartile values of the log_2-EASIX-PRE and divided into 2 groups according to an optimal survival curve cutoff value obtained as part of the study.

Statistical methods

Main outcomes included OS, NRM, and cumulative incidence of ICU admission, and the main variable of interest was log_2-EASIX-PRE. Secondary outcomes were the cumulative incidences of TAM, SOS, and acute GVHD. Impact of the main variable on outcomes was explored using log_2-EASIX-PRE as a continuous variable and distribution quartiles as categorical variables. A statistically optimal cutoff value of log_2-EASIX-PRE was established based on the binary partitioning method. The association between high and low EASIX-PRE values and patient baseline characteristics was explored using a multivariate logistic regression analysis.

Descriptive variables are presented as counts and percentages. Continuous variables are presented as medians and ranges. Time to event was calculated as date of transplantation to date of the event or last follow-up. OS and relapse-free survival rates were calculated using the Kaplan-Meier estimator method. NRM and cumulative incidence of relapse were estimated using the Gray test cumulative incidence method and considering relapse as a competing event for NRM and NRM for cumulative incidence of relapse. The cumulative incidences of ICU admission, TAM, and SOS were estimated considering death as a competing event. The cumulative incidence of acute GVHD was estimated considering death and relapse as competing events. The impact of the explanatory variable and other risk factors on the main outcome variables were analyzed using univariate and multivariate Cox and Fine-Gray regression models. Variables found to be significant in the univariate analysis and/or those considered clinically relevant for the study were included in the multivariate analysis. To evaluate the prediction accuracy of our prognostic model, EASIX-PRE prediction error estimation was calculated for the probability of ICU admission using a multivariate time-dependent adaption of the Brier score method. The multivariate model was adjusted by the following confounders: patient age, HCT-CI score (≥3 vs <3), donor selection (10/10 HLA-matched related donor vs other), and intensity of the conditioning regimen (reduced-intensity conditioning [RIC] vs myeloablative conditioning [MAC]). These variables were selected according to the degree of statistical significance found in the univariate analysis for the prediction of ICU admission or considered clinically relevant. All P values were 2 sided. For statistical analyses, $P < .05$ was considered to indicate a statistically significant result. Statistical analysis was performed using EZR software (version 1.54).[18]

Results

Patient information

Patient baseline characteristics are summarized in Table 1. The median age was 53 years (range, 18-65 years), and 93 (55.7%) patients were men. Acute myeloid leukemia and myelodysplastic syndromes were the most prevalent baseline diagnoses (n = 74 [44.3%]), followed by lymphoproliferative disorders (n = 60 [35.9%]). One hundred twenty-nine patients (77.2%) underwent RIC transplantation, and 64 (38.3%) received haploidentical donor grafts.

EASIX value and distribution

EASIX-PRE was calculated for all patients. The median EASIX-PRE and log_2-EASIX-PRE values were 1.073 (interquartile range [IQR], 0.719-2.795) and 0.102 (IQR, −0.474 to 1.483), respectively. Patients age >60 years (odds ratio, 2.78; 95% confidence interval [CI], 1.14-6.74; $P = .024$) and with a high/very high Disease Risk Index before alloHCT (odds ratio, 2.56; 95% CI, 1.13-5.55; $P = .022$) were more likely to have an EASIX-PRE higher than the median value of the variable (1.073). Patient sex, HCT-CI score, and European Group for Blood and Marrow Transplantation risk score were not associated with the probability of EASIX-PRE >1.073 (supplemental Table 1).

Table 1. Patient characteristics

	Overall (N = 167)
Age, y	
Median	53
Range	18-65
Sex	
Male	93 (55.7)
Baseline diagnosis	
AML, MDS	74 (44.3)
MPN	4 (2.4)
ALL	10 (6.0)
Lymphoproliferative disease/CLL	60 (35.9)
MM	9 (5.4)
Other	10 (6.0)
Disease Risk Index	
Low/moderate	122 (73)
High/very high	39 (23.4)
Not applicable*	6 (3.6)
HCT-CI score	
<3	135 (80.8)
≥3	32 (19.2)
EBMT score	
<5	153 (91.6)
≥5	14 (8.4)
Conditioning regimen intensity	
MAC	38 (22.8)
RIC	129 (77.2)
GVHD prophylaxis	
ATG based	22 (13.2)
PTCY based	75 (44.9)
Sirolimus-tacrolimus	19 (11.4)
MTX-CNI	51 (30.5)
Donor type	
10/10 MRD	53 (31.7)
10/10 and 9/10 MUD	45 (26.9)
Haploidentical	64 (38.3)
Dual (haploidentical + cord blood)	5 (3)
Stem cell source	
Peripheral blood	155 (92.8)
Bone marrow	12 (7.2)
Follow-up in survivors, mo	
Median	21.1
Range	3.8-70.8
EASIX result	
EASIX-PRE	
Median	1.073
Range	0.142-78.600
25th percentile	0.719
75th percentile	2.795
Log_2-EASIX-PRE	
Median	0.102
Range	−2.814 to 6.296
25th percentile	−0.474
75th percentile	1.483

Data are presented as n (%) unless otherwise indicated.

ALL, Acute lymphoblastic leukemia; AML, acute myeloid leukemia; ATG, antithymocyte globulin; CLL, chronic lymphoid leukemia; CNI, calcineurin inhibitor; EBMT, European Group for Blood and Marrow Transplantation; MDS, myelodysplastic syndrome; MM, multiple myeloma; MPN, myeloproliferative neoplasm; MRD, matched related donor; MTX, methotrexate; MUD, matched unrelated donor; PTCY, posttransplantation cyclophosphamide.

*Disease Risk Index not calculated in 6 patients because they had nonmalignant disease.

Correlation between EASIX-PRE and ICU admission

Of the 167 patients included in the study, 42 were admitted to the ICU, with a day +180 cumulative incidence of ICU admission of 18.6% (95% CI, 13.1%-24.9%). The median time between stem cell infusion and ICU admission was 46 days (range, 2-1175 days). The most discriminating cutoff value of log_2-EASIX-PRE for the cumulative incidence of ICU admission was the 75th percentile (1.483). This corresponds to a value of the original variable (pre–logarithmic-transformed EASIX-PRE) of 2.795. Patients with EASIX-PRE >2.795 had a higher probability of ICU admission during posttransplantation follow-up compared with patients with EASIX-PRE ≤2.795 (day +180, 35.8% vs 12.8%; $P = .010$; Figure 1). The multivariate analysis confirmed that patients with EASIX-PRE >2.795 had a higher probability of ICU admission during posttransplantation follow-up than patients with EASIX-PRE ≤2.795 (hazard ratio [HR], 2.26; 95% CI, 1.22-4.1; $P = .009$; Table 2). Figure 2 summarizes the prediction error of EASIX-PRE for the estimation of the probability of ICU admission. The lower prediction error curve found in the model that included EASIX-PRE (red curve) supports the usefulness of EASIX-PRE for predicting prognosis.

The median time between stem cell infusion and ICU admission was 46 days (range, 2-1175 days). Causes of ICU admission were sepsis (n = 18), respiratory failure (n = 11), altered level of consciousness (n = 5), alveolar hemorrhage (n = 2), endothelial complications (n = 5 [TAM, n = 3; SOS, n = 2]), and hepatic failure (n = 1). The median time of ICU stay was 6.5 days (range, 0-38 days), and the mortality rate in these patients was 47.6%. Log_2-EASIX-PRE did not predict length of ICU stay ($P = .597$), mortality after ICU admission ($P = .727$), or hospital mortality after ICU admission ($P = .547$). EASIX-PRE median values were comparable between the 21 patients who were successfully discharged from the ICU and the 21 patients who died during ICU admission (1.59 vs 1.44; $P = .862$). Additionally, 14 of the 21 patients discharged from the ICU died during follow-up; the median EASIX-PRE value for these patients was 3.04, and for the 7 patients who survived, it was 0.98 ($P = .322$; supplemental Table 2).

Validation of EASIX-PRE predictive power for OS and NRM

With a median follow-up among survivors of 21.1 months (range, 3.8-70.8 months), 2-year OS and NRM rates were 55.4% (95%

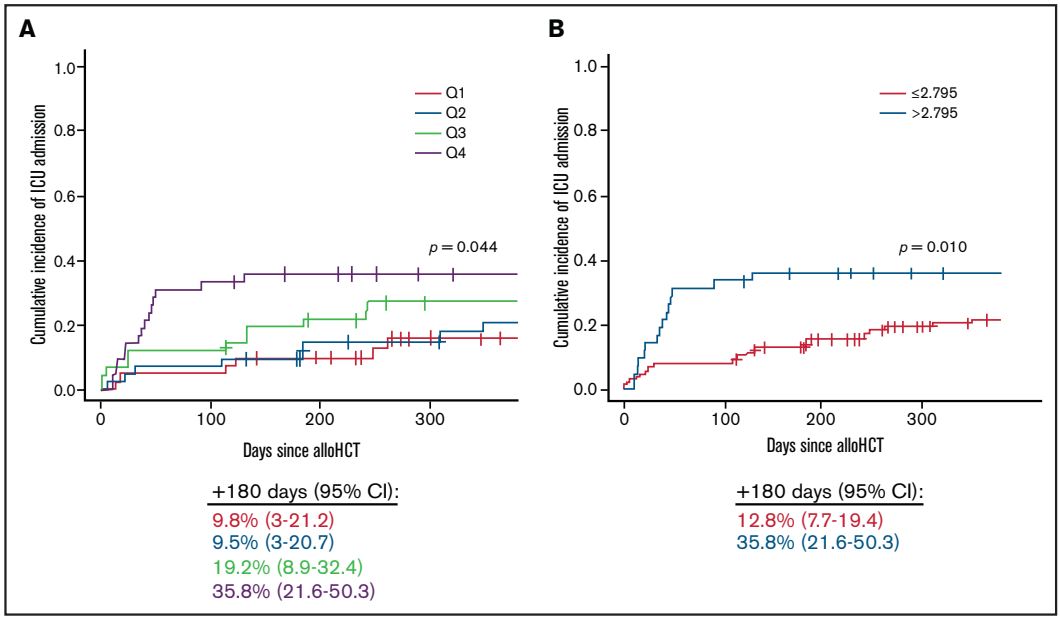

Figure 1. Visualization of the univariate outcome analysis. EASIX-PRE quartiles (Qs) (A) and 75th percentile (2.795) (B).

Table 2. Association between EASIX-PRE and ICU admission

	Cumulative incidence of ICU admission	
	HR (95% CI)	*P*
Univariate analysis		
EASIX-PRE		
75th percentile value 2.795 (vs ≤2.795)	2.28 (1.21-4.28)	.010
Age, y		
Continuous variable	1.03 (0.98-1.07)	.140
Disease Risk Index		
High/very high (vs low/moderate)	0.99 (0.50-1.99)	1
HCT-CI		
≥3 (vs <3)	1.66 (0.83-3.30)	.150
EBMT score		
≥5 (vs <5)	0.87 (0.44-1.71)	.700
Conditioning regimen intensity		
RIC (vs MAC)	0.58 (0.29-1.13)	.110
Donor selection		
10/10 HLA MRD (vs other)	0.32 (0.13-0.77)	.010
Transplantation period		
2018-2020 (vs 2015-2017)	0.97 (0.52-1.80)	.940
Multivariate analysis		
EASIX-PRE		
75th percentile value 2.795 (vs ≤2.795)	2.26 (1.22-4.18)	.009
Age, y		
Continuous variable	1.02 (0.98-1.07)	.180
HCT-CI		
≥3 (vs <3)	1.18 (0.95-1.48)	.120
Donor selection		
10/10 HLA MRD (vs other)	0.36 (0.15-0.87)	.024
Intensity of the conditioning regimen		
RIC (vs MAC)	0.66 (0.33-1.32)	.250

EBMT, European Group for Blood and Marrow Transplantation; MRD, matched related donor.

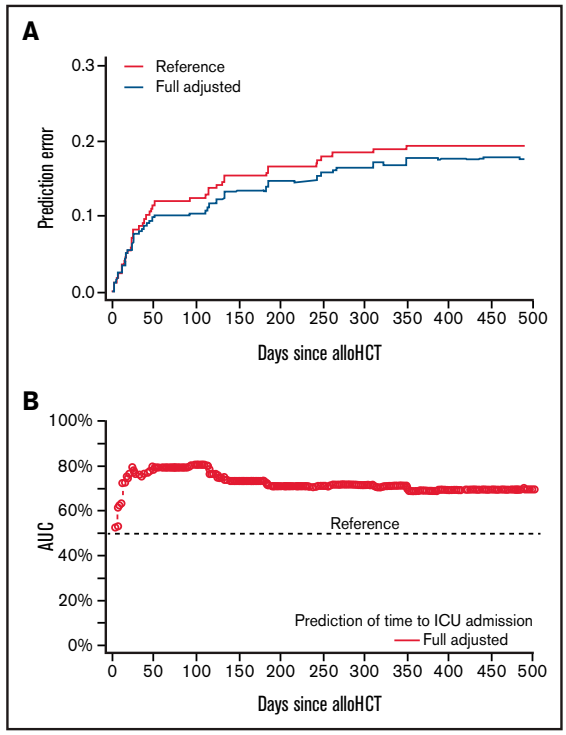

Figure 2. Model validation of EASIX-PRE as predictor of ICU admission. (A) Multivariate model. The prediction error of EASIX-PRE (red curve) developed in the study cohort was computed for the entire follow-up and compared with the prediction error of the reference value (black curve). A lower prediction error curve in the model including EASIX (red curve) supports the usefulness of EASIX for predicting prognosis. (B) Time-dependent concordance indices for ICU admission. The highest concordance index is found in the model that includes EASIX-PRE (red; multivariable). A concordance index of 0.5 (dotted line) implies random concordance. A concordance index >0.6 is regarded as acceptable. The concordance index found in our analysis was >0.7. AUC, area under the curve.

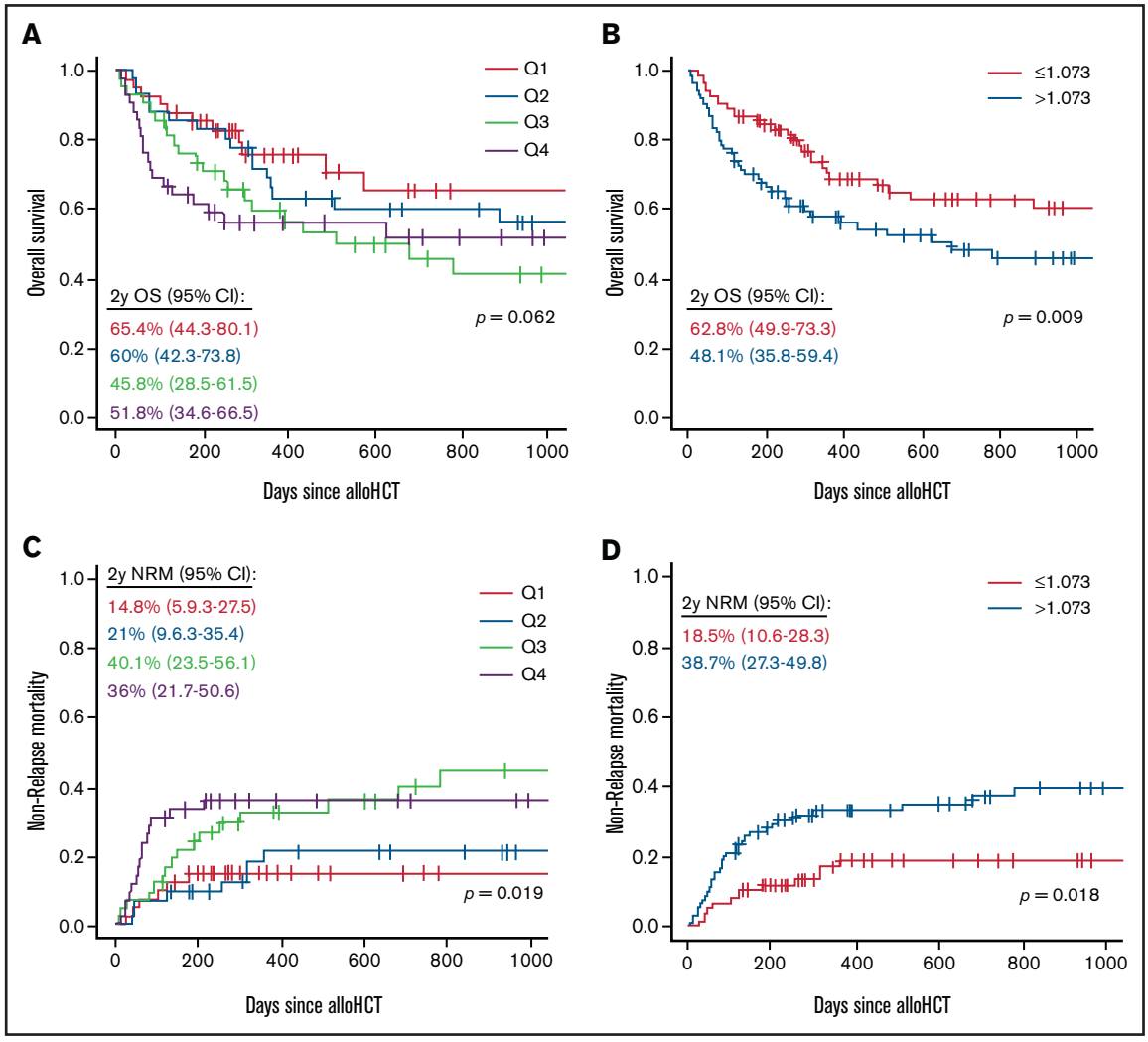

Figure 3. Visualization of the univariate outcome analysis. OS (A-B) by EASIX-PRE quartile (Q) (A,C) and NRM (C-D) by optimal cutoff value (1.073) (B,D).

CI, 46.6%-63.4%) and 28.7% (95% CI, 21.5%-36.2%), respectively (Table 3). Forty-seven patients died without relapse: 5 of 47 secondary to endothelial complications, and 13 of 47 secondary to steroid-refractory acute (n = 10) or chronic (n = 3) GVHD.

Figure 3 shows the association between $\log_2$-EASIX-PRE and OS and NRM. Results provided by the univariate and multivariate analyses are shown in supplemental Table 3 (univariate) and Table 4 (multivariate). Log_2-EASIX-PRE predicted OS (HR, 1.19; 95% CI, 1.04-1.37; $P = .011$) and NRM (HR, 1.28; 95% CI, 1.08-1.53; $P = .004$) in our series. The most discriminating $\log_2$-EASIX-PRE cutoff value for OS and NRM was the median value (0.102). This implies an EASIX-PRE value equal to 1.073. Patients with EASIX-PRE >1.073 had lower OS (2 years, 48.1% vs 62.8%; $P = .009$) and higher NRM (2 years, 38.7% vs 18.5%; $P = .0018$) in comparison with patients with EASIX-PRE ≤1.073. The multivariate analysis confirmed that patients with EASIX-PRE >1.073 had worse OS (HR, 1.98; 95% CI, 1.21-3.24; $P = .006$) and higher NRM (HR, 2.92; 95% CI, 1.50-5.68; $P = .001$) than patients with EASIX-PRE ≤1.073. Age at transplantation and HCT-CI score ≥3 were found to be additional risk factors for OS, and HCT-CI score ≥3 was found to be a predictor for higher NRM in the multivariate analysis.

Correlation between EASIX-PRE and engraftment information, posttransplantation endothelial complications, and GVHD

The main results are summarized in Table 3. Overall, 166 patients (99.4%) underwent engraftment, with a median time from stem cell infusion to neutrophil and platelet engraftment of 16 (range, 8-52) and 14 days (range, 0-104 days), respectively. Graft failure was documented in 3 patients (1.7%; primary, n = 1; secondary, n = 2). Day +28 cumulative incidence of SOS and day +180 cumulative incidence of TAM were 7.2% (95% CI, 3.9%-11.8%) and 11.4% (95% CI, 7.1%-16.7%), respectively, with a median time of onset of 11 (IQR, 8-14) and 34 days (IQR, 13-48 days). The cumulative incidences of grade II to IV and grade III to IV acute GVHD at day +100 were 18.8% (95% CI, 13.2%-25.1%) and 10.3% (95% CI, 6.2%-15.5%), respectively. The cumulative incidence of moderate/severe chronic GVHD at 1 year was 22.1% (95% CI, 15.1%-29.9%).

Table 3. Descriptive information and association between log_2-EASIX-PRE and posttransplantation complications

	Descriptive Information % (95% CI)	Association HR (95% CI)	*P*
Association between EASIX-PRE and posttransplantation outcomes			
OS		1.19 (1.04-1.37)	.011
1 y	63.1 (54.8-70.3)		
2 y	55.4 (44.6-62.4)		
NRM		1.28 (1.08-1.53)	.004
1 y	26.6 (19.8-32.7)		
2 y	28.7 (21.5-32.7)		
PFS		1.102 (0.89-1.35)	.360
1 y	56.0 (47.5-63.7)		
2 y	51.8 (42.9-59.9)		
CIR		1.12 (0.82-1.54)	.450
1 y	18.9 (13.0-25.8)		
2 y	22.9 (16.1-30.4)		
Association between EASIX-PRE and cumulative incidences			
ICU admission*			
Day +180	18.6 (13.1-24.9)	1.28 (1.08-1.53)	.004
SOS*			
Day +28	7.2 (3.9-11.8)	0.79 (0.42-1.46)	.460
TAM*			
Day +180	11.4 (7.1-16.7)	1.17 (0.90-1.51)	.230
Graft failure			
Day +180	1.2 (0.1-4.0)	1.01 (0.51-2.26)	.841
GVHD†			
Grade II-IV acute GVHD at day +100	18.8 (13.2-25.1)	0.99 (0.82-1.18)	.920
Grade III-IV acute GVHD at day +100	10.3 (6.2-15.5)	0.99 (0.79-1.25)	.970
Moderate/severe chronic GVHD at 1 y	22.1 (15-1-29.9)	0.89 (0.72-1.11)	.320

CIR, cumulative incidence of relapse; PFS, progression-free survival.
*Cumulative incidence analysis considering death as competing event.
†Cumulative Incidence analysis considering death and relapse as competing events.

Table 4. Association between EASIX-PRE and OS and NRM

	OS		NRM	
	HR (95% CI)	*P*	HR (95% CI)	*P*
Univariate analysis				
EASIX-PRE median cutoff value >1.073 (vs ≤ median [1.073])	1.88 (1.16-3.04)	.010	2.60 (1.39-4.86)	.002
Multivariate analysis				
EASIX-PRE				
Median cutoff value >1.073 (vs ≤ median [1.073])	1.98 (1.21-3.24)	.006	2.92 (1.50-5.68)	.001
Age, y				
Continuous variable	1.03 (1.01-1.06)	.007	1.03 (0.99-1.07)	.110
HCT-CI				
≥3 (vs <3)	2.08 (1.18-3.66)	.011	1.32 (1.05-1.67)	.016
Donor selection				
10/10 HLA MRD (vs other)	0.79 (0.47-1.34)	.389	0.74 (0.39-1.41)	.370
Intensity of conditioning regimen				
RIC (vs MAC)	0.84 (0.48-1.46)	.542	0.64 (0.34-1.20)	.170

MRD, matched related donor.

In our series, no statistically significant associations were observed between log_2-EASIX-PRE and the appearance of SOS (HR, 0.79; 95% CI, 0.42-1.46; $P = .46$) or TAM (HR, 1.17; 95% CI, 0.90-1.51; $P = .23$). Log_2-EASIX-PRE did not predict the probability of neutrophil engraftment (HR, 0.90; 95% CI, 0.82-1.01; $P = .052$), platelet engraftment (HR, 0.91; 95% CI, 0.83-1.01; $P = .099$), or graft failure (HR, 1.01; 95% CI, 0.51-2.26; $P = .84$). Additionally, log_2-EASIX-PRE did not predict the probability of grade II to IV (HR, 0.99; 95% CI, 0.82-1.18; $P = .92$) or grade III to IV acute GVHD (HR, 0.99; 95% CI, 0.79-1.25; $P = .97$) or moderate/severe chronic GVHD (HR, 0.89; 95% CI, 0.72-1.11; $P = .32$).

Discussion

This study proposes EASIX-PRE as a predictor of ICU admission in alloHCT recipients and supports EASIX-PRE as a predictor of mortality in adult patients undergoing alloHCT. The EASIX score comprises 3 biomarkers of endothelial dysfunction (LDH, creatinine, and platelets) and, when evaluated before alloHCT (EASIX-PRE), predicts OS and NRM.[12,14,17] Endothelial dysfunction is a common pathologic mechanism of many severe infectious and noninfectious alloHCT-related complications.[14] Because the endothelium plays a major role in a patient's systemic response to infection and organ failure onset,[19] we hypothesized that EASIX-PRE could predict the development of severe organ dysfunction that would require specific support in the ICU. The main finding conferred by this study is that EASIX-PRE could allow clinicians to identify a cohort of patients with an increased risk of ICU admission during posttransplantation follow-up. Patients with an EASIX-PRE value above the 75th percentile (2.795) were 2.31 times more likely to require ICU admission.

Different prognostic scores are used in daily clinical practice to predict outcomes of critically ill patients at ICU admission (SOFA, SAPSII, PICAT, APACHE II, and APACHE IV). Of them, the APACHE II score has shown superiority in predicting ICU mortality in patients undergoing alloHCT.[10,20] Nevertheless, no specific indices have been defined for the prediction of ICU admission in alloHCT patients before the procedure. Despite recent improvements made in intensive care support, survival of alloHCT patients admitted to the ICU remains dismal; it depends on the number of organ injuries, time between first organ injury and ICU admission, the need for mechanical ventilation, and the presence of GVHD.[21,22] Given the significant increase in alloHCT-attributed mortality in ICU-transferred patients, early identification of patients with a high risk of organ failure who will require intensive care is of utmost importance. Importantly, the association between EASIX-PRE and ICU admission found in the present study was independent of the cause of organ failure. This fact reinforces the potential utility of this index within regular clinical practice. Further analysis is, however, required to externally validate the results provided by this analysis.

This study additionally validates the applicability of EASIX-PRE as a predictor of OS and NRM in a cohort of consecutive patients undergoing transplantation in Spain. The cohort of patients selected for this study included adults with malignant and nonmalignant disorders undergoing transplantation using a MAC or RIC regimen, and in comparison with those in related publications,[13] this cohort included a larger proportion of patients receiving transplants from haploidentical donors (38.3%).[14] Furthermore, this study proposes an optimal cutoff value to identify patients with a higher risk of mortality and therefore increase the applicability of this index in clinical practice. The optimal cutoff value capable of stratifying the study cohort into 2 statistically independent risk groups was the median value of log_2-EASIX-PRE (0.102), corresponding to a value of the original (pre–logarithmic-transformed) variable EASIX-PRE (1.073). Patients with EASIX-PRE higher than the median value had an almost twofold increased likelihood of lower OS and a threefold increased likelihood of higher NRM than patients with EASIX-PRE <1.073. Secondary to the heterogeneity of the study cohort, the proposed cutoff may be applicable in other transplantation centers.

Risk assessment for posttransplantation complications using the EASIX score at different time points before and after alloHCT has been explored by various research groups. EASIX has shown predictive potential for TAM when calculated during pretransplantation evaluation,[14] for SOS when calculated at the time of stem cell infusion (EASIX day 0),[15] and for fluid overload when calculated at the time of admission.[16] Additionally, a higher EASIX score at days +30 and +100 post–RIC alloHCT has been associated with grade II to IV acute GVHD, higher NRM, and poorer OS.[17] No association was observed between EASIX-PRE and the probability of TAM, SOS, or acute GVHD onset during the posttransplantation phase. The association between EASIX-PRE and increased risk of TAM was reported in a large cohort of 755 adults treated with alloHCT.[14] However, this association was not reproduced in our analysis. This difference could be attributed to variances in baseline clinical information, donor type, and conditioning platforms between the 2 cohorts. Additionally, in the 167 patients included in our study, severe TAM was only diagnosed in 3 patients. We hypothesize that this low number of patients with clinically relevant TAM may have mitigated the predictive capacity of EASIX-PRE for this complication in our study. EASIX, assessed at day 0, was associated with the incidence of SOS in adults undergoing alloHCT.[15] Nevertheless, no association between EASIX-PRE and SOS was found in our analysis. The lack of association found in our study could be attributed to the calculation of EASIX before start of the preparative regimen. The pathophysiology of SOS is characterized by endothelial injury caused by an association between pretransplantation damage and toxicity secondary to the conditioning regimen. We suggest that the combination of both effects may potentially modify the value of the index, increasing its capacity of predicting SOS when measured on the day of stem cell infusion. Platelet count was found to be a predictor of engraftment in a retrospective analysis conducted in 197 patients undergoing transplantation using a MAC or RIC preparative regimen.[23] Given that platelet count is included in the EASIX formula, a potential association between EASIX-PRE and the probability of engraftment and the incidence of graft failure was explored in our analysis. However, the differences found between these associations were not statistically significant. The dynamics of the EASIX score were recently monitored at continual time points after alloHCT. The EASIX value rapidly increased from its baseline value, peaked on day +8, abruptly decreased until day +40, and had lower values from then on, while nonetheless remaining above the baseline value during the first year after alloHCT.[24] EASIX predicts different posttransplantation complications when measured at various reference points before and after alloHCT. This capacity enhances the utility of this promising index as a prognostic tool during the entire alloHCT process. EASIX evaluated at the time of ICU admission could potentially predict patient outcomes. However, this study focused on the association between EASIX-PRE and posttransplantation complications, and no calculation of EASIX was made at any other time point after alloHCT.

EASIX-PRE was calculated in all patients included in the study, secondary to accessibility to laboratory parameters. Using cutoff values allows clinicians to quickly stratify patients with a higher risk of mortality and severe clinical complications requiring ICU admission. Such implementation enhances integration of this numeric index in daily clinical practice. More importantly, the EASIX score may be used to improve organization of transplantation unit admission when restricted access to the ICU is expected, as in exceptional situations like pandemics. It furthermore may help clinicians conceive individualized interventions for patients at higher risk of severe events and ICU admission. The results reported in this study and in other related publications raise the question of whether EASIX could also predict severe acute complications and mortality in patients diagnosed with other hematologic disorders and candidates for intense therapies. Additional studies, however, will be needed to address this research question in the future.

This study did have some limitations, including the retrospective design and absence of a validation cohort. Additionally, the likelihood of ICU admission varies from center to center; published series have reported a wide range of admission rates, from 9% to 57%.[21] Prospective analyses should be conducted to validate the predictive power of EASIX and the risk of ICU admission in patients undergoing alloHCT.

In conclusion, this study validates the utility of EASIX-PRE in the prediction of OS and NRM in a heterogeneous cohort of adults undergoing alloHCT. EASIX, when determined at pretransplantation evaluation, identified a group of patients with an increased risk of severe organ dysfunction who would require ICU admission during posttransplantation follow-up. EASIX is easily applicable, and these findings support use of this score as a potential resource for clinicians when designing prospective and personalized interventions for patients at high risk of severe events and ICU admission.

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Authorship

Contribution: M.P. and M.Q.S. designed the study, performed the statistical analysis, created the figures, and wrote the paper. M.P. and M.K. collected the data; and A.M., G.M.-G., A.B., B.P., L.J., R.P., and A.S. provided valuable input during the study and reviewed the manuscript.

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