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The EASIX score as a predictor of sinusoidal obstruction syndrome and nonrelapse mortality in paediatric patients receiving allogeneic haematopoietic stem cell transplantation

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The endothelial activation and stress index (EASIX) score, calculated as [lactate dehydrogenase (LDH; U/L) × serum creatinine (mg/dL)]/platelets (10e9/L)], has been shown to be predictive of nonrelapse mortality (NRM) and endothelial complications in adults receiving allogeneic stem cell transplantation (allo-HSCT); however, definitive results are lacking for children. We retrospectively evaluated consecutive paediatric allo-HSCT recipients and calculated the log2 EASIX score every day from admission to day +35. In 167 allo-HSCT recipients, the EASIX score increased from before conditioning (−0.79) to a maximum score on day +20 (2.23). In multivariate analysis, the EASIX score at day +7 was an independent predictor of sinusoidal obstruction syndrome/veno-occlusive disease (SOS/VOD) (OR 1.52; 95% CI, 1.08–2.13; $p = 0.017$) and NRM (OR 1.68; 95% CI 1.16–2.42; $p = 0.006$). At several time points between day +0 and day +14, the EASIX score was independently associated with NRM, with the strongest predictive power being observed on day +12 (OR 3.05; 95% CI, 1.53–6.10; $p = 0.002$). Age correlated linearly with the EASIX score at all analysed time points, but score prediction was confirmed even when age was added to the multivariate model, indicating that age was not a confounding factor in the observed associations. The EASIX score determined shortly after transplantation can be further explored as a predictor of SOS/VOD and NRM in paediatric allo-HSCT recipients.

Bone Marrow Transplantation; https://doi.org/10.1038/s41409-024-02489-8

INTRODUCTION

Endothelial injury after allogeneic haematopoietic stem cell transplantation (allo-HSCT) can lead to various complications, such as sinusoidal obstruction syndrome/veno-occlusive disease (SOS/VOD), jeopardizing the success of this procedure and contributing to nonrelapse mortality (NRM) [1–5]. Several factors, including conditioning regimens, immunosuppressive agents, microbial translocations, and alloreactivity, contribute to prolonged and extensive activation of the endothelial barrier, resulting in endothelial damage [6, 7]. The search for reliable and accessible biomarkers to monitor and predict this type of injury has remained elusive thus far [8]. The endothelial activation and stress index (EASIX) score, calculated as [lactate dehydrogenase (LDH; U/L) × serum creatinine (mg/dL)]/platelets (10e9/L), has been proposed to better assess the extent of endothelial dysfunction [9]. The EASIX score considers three routine laboratory parameters that are indicative of the severity of vascular damage, and in adult studies, the score significantly correlated with several HSCT outcomes, namely, acute graft-versus-host disease (aGvHD) [10], aGvHD-related mortality [9], sepsis [11], SOS/VOD [12], transplant-associated microangiopathy (TAM) [13], NRM and overall survival (OS) [10, 13–18]. Despite the growing evidence that suggests the role of the EASIX score as a valuable risk assessment tool for predicting and preventing HSCT complications and mortality, paediatric studies are lacking. The distinctive characteristics of HSCT in children, including the indications, conditioning regimens, and complications, require specific assessment of the validity of the EASIX score in predicting HSCT complications and mortality in paediatric patients. To date, only one cohort study including children was published by Luft et al. in 2020 [13], who analysed the predictive value of the EASIX score before conditioning in a population receiving allografts, mainly for nonmalignant diseases, with frequent use of reduced intensity conditioning (RIC); no correlation between the EASIX score and NRM was observed in the multivariate model, probably due to the confounding effect of age. Moreover, the risk and severity of SOS/VOD were not assessed [13].

Therefore, we conducted a retrospective analysis in a paediatric cohort undergoing allo-HSCT, aiming to provide a comprehensive evaluation of the role of the EASIX score in this setting and its validity in predicting transplant complications related to endothelial injury and NRM.

MATERIALS AND METHODS

Study population

This single-centre retrospective analysis included consecutive patients receiving allo-HSCT for any indication at the Pediatric Bone Marrow

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Received: 25 July 2024 Revised: 18 November 2024 Accepted: 26 November 2024
Published online: 10 December 2024

Transplant Unit of the IRCCS Azienda Ospedaliero-Universitaria di Bologna in Italy between January 2010 and March 2023. The study was approved by the Ethics Committee of CE-AVEC Emilia-Romagna, Italy. Written informed consent was obtained from all participants/legal guardians by the treating physicians. The study was conducted in accordance with the Declaration of Helsinki and European data protection regulations.

Clinical outcome evaluation

The EASIX score was calculated via the following formula: [LDH (U/L) × serum creatinine (mg/dL)]/platelets (10e9/L). The values obtained were normalized via log2 to reduce skewness according to the literature [13, 15]. Data were retrospectively collected from electronic clinical charts, and the EASIX score was calculated every day from admission, before the conditioning regimen, to day +35 after HSCT.

Definitions

The intensity of the conditioning regimen for myeloablative conditioning (MAC) or RIC was categorized according to Bacigalupo et al. [19]. SOS/VOD diagnosis and grading were established according to the new European Society for Blood and Marrow Transplantation (EBMT) criteria for paediatric SOS/VOD [20]. aGvHD was graded from 0 to IV according to the Glucksberg classification [21]. The occurrence of oral mucositis was determined by trained nurses and a physician and was graded according to the World Health Organization (WHO) criteria [22]. NRM was defined as death from transplant-related complications without the previous occurrence of relapse.

Procedures

For GvHD prophylaxis, in the case of a matched sibling donor (MSD), cyclosporine A and short-term methotrexate were administered. For matched unrelated donors (MUDs), antithymocyte globulin (ATG) was added to a standard cyclosporine A-methotrexate-based regimen. In haploidentical donors, posttransplant cyclophosphamide (PTCy) at a dose of 50 mg/kg on days +3 and +4 was employed; cyclosporine A and mycophenolate mofetil were started on day +5, and the latter was stopped on day +35. SOS/VOD prophylaxis was not administered in any patient. All the patients who developed SOS/VOD received defibrotide from the date of diagnosis for at least 21 days until the resolution of SOS/VOD signs and symptoms. The patients were treated in high-efficiency particulate air-filtered rooms to prevent infections. Antibiotic prophylaxis with levofloxacin was administered until January 2016, after which patients received no antibiotic prophylaxis.

Statistical analysis

Qualitative clinical variables are reported as the number and percentage of the total and were compared via Fisher's exact test. The Shapiro–Wilk test was used to test the normality of the data for continuous variables. Student's *t* test was used to compare the means of normally distributed data; otherwise, the Mann–Whitney test was used. The standard deviation and interquartile range (IQR) are reported for normally and nonnormally distributed data, respectively. Univariate and multivariate analyses were carried out via logistic regression, and only variables with a p value < 0.1 in the univariate analysis were entered into the multivariate analysis. To capture the dynamics of the EAXIS score during the HSCT course, scatter plots were constructed, and locally weighted scatterplot smoothing (LOWESS) lines were added to illustrate trends. The area under the curve (AUC) was calculated via the trapezoidal rule to quantify the overall variation. To assess the predictive accuracy of the EASIX score for clinical outcomes, receiver operating characteristic (ROC) curve analysis was employed. The optimal cut-off values were determined to maximize sensitivity and specificity, ensuring the best performance. The AUC value of the ROC curve was also calculated to assess the ability of the EASIX score to predict outcomes. A simple linear regression analysis was conducted to examine the correlation between the EASIX score and patient age. The probabilities of OS and NRM were calculated via the Kaplan–Meier method, and groups were compared via log-rank analysis. All *P* values were calculated via the two-sided method, and values lower than 0.05 were considered statistically significant. Analysis was performed via NCSS 12 Statistical Software (2018, NCSS, LLC. Kaysville, Utah, USA), GraphPad Prism version 10.0.0 for Mac OS (GraphPad Software, Boston, Massachusetts USA, www.graphpad.com), and JASP Team (2020, JASP (Version 0.12.2) [Computer software]).

RESULTS

Patient characteristics

A total of 167 allo-HSCT were included in this study. The median age at transplant was 9.3 years (range, 4 months–23 years). Among the included patients, 78% ($n = 130$) received an allograft for a malignant disease, mainly acute lymphoblastic leukaemia (39.5% of the whole cohort, $n = 66$). Regarding the type of donor, 61% ($n = 101$), 21% ($n = 34$) and 18% ($n = 18$) of the patients had MUDs, MSDs, and haploidentical donors, respectively. Regarding the stem cell sources, 80% ($n = 132$) of the patients received bone marrow stem cells, 15% ($n = 24$) received peripheral blood stem cells, and 5% ($n = 8$) received cord blood stem cells. A total of 92% of patients ($n = 154$) received MAC; among these patients, 63% ($n = 97$) received busulfan, and 15% ($n = 23$) received total body irradiation. Grade 2–4 aGvHD occurred in 31% of the patients ($n = 51$), whereas grade 3–4 aGvHD occurred in 11% ($n = 19$). The cumulative incidence of SOS/VOD was 16% ($n = 27$), with a median onset time of 11 days after HSCT (range 8–25). The one-year OS rate for the whole cohort was 76.1% (95% CI, 69.4% to 82.8%). The one-year cumulative incidence rate of NRM was 19.0% (95% CI, 13.9% to 26.2%) (Supplementary Fig. 1). The causes of one-year NRM are described in Supplementary Table 1. The detailed characteristics of the cohort are reported in Table 1.

EASIX score dynamics

The dynamics of the EASIX score from admission to day +35 after allo-HSCT are represented in Fig. 1. The median EASIX values increased from before conditioning (−0.79, IQR −1.60–0.42) to a maximum on day + 20 (2.23, IQR 0.57–3.1) and then slightly decreased, reaching a value of 1.20 (IQR −0.16–2.34) at day +35. The median EASIX values at days +7 and +14 for the whole cohort were 0.99 (IQR −0.36–1.89) and 1.20 (IQR 0.35–2.59), respectively.

No major differences were observed in EASIX score dynamics between patients receiving or not TBI-based or Busulfan-based conditioning regimens.

EASIX score dynamics and SOS/VOD

We then determined EASIX score dynamics via LOWESS analysis in patients who did and did not develop SOS/VOD, as shown in Fig. 1. The median values of the EASIX score were comparable at admission (−0.72 vs. −0.85; $p = 0.83$) but diverged significantly from day +7 to day +22, with the maximum difference being observed on day +18 (4.67 vs. 0.99; $p = 0.013$). Given that the earliest onset of SOS/VOD in our cohort occurred on day +8, we investigated whether EASIX scores obtained before this time point could serve as predictors for the subsequent development of SOS/VOD. On day +7, the median EASIX score was significantly greater in patients who later developed SOS/VOD (2.29 vs. 0.80; $p = 0.005$) (Fig. 2a). Univariate logistic regression revealed that the EASIX score at day +7 (EASIX + 7) was significantly correlated with the incidence of SOS/VOD (OR 1.41; 95% CI, 1.04–1.92; $p = 0.028$). To exclude the individual predictive value of each parameter comprising the EASIX + 7 in predicting SOS/VOD, we conducted univariate logistic regression analyses for each parameter. However, none of the parameters showed a significant association (data not shown). Multivariate analysis confirmed that the EASIX + 7 score was an independent predictor of SOS/VOD (OR 1.52; 95% CI, 1.08–2.13; $p = 0.017$) (Table 2). We then calculated the ROC curves for the prediction of SOS/VOD, and the optimal calculated cut-off value of the EASIX + 7 score was 1.93. The difference (Δ) between the EASIX + 7 score and the EASIX score at admission was not a predictor of subsequent SOS/VOD; however, we observed a trend towards statistical significance (OR 1.39; 95% CI, 1,00–1.95; $p = 0.053$). We calculated the AUC of the EASIX score until day +7 for patients who did and did not develop SOS/VOD. We observed significant differences between the groups (93.08 ± 6.45 vs. 75.43 ± 4.99, $p < 0.001$). Considering the low rate

Table 1. Clinical characteristic of allo-HCT procedures included in the study.

Patient characteristics	Study cohort ($N = 167$)
Age at HCT, years, median, (range)	9.3 (0.3–23.0)
Sex, male, *n* (%)	99 (60%)
Oncological disease, *n* (%)	130 (78%)
Indication, *n* (%)	
ALL	66 (40%)
AML	47 (28%)
MDS/JMML	10 (6%)
Lymphoma	7 (4%)
Non-Malignant	37 (22%)
Remission status at HCT for oncological disease, *n* (%)	
I CR	79 (60%)
≥ II CR	28 (22%)
Disease present	23 (18%)
Donor, *n* (%)	
MUD	101 (61%)
Haplo	30 (18%)
MSD	34 (21%)
Stem cell source, *n* (%)	
BM	132 (80%)
PBSC	24 (15%)
CB	8 (5%)
Conditioning regimen, *n* (%)	
MAC	154 (92%)
Busulfan-based	97 (63%)
TBI-based	23 (15%)
ATG, *n* (%)	107 (64%)
Neutrophils engraftment	
n (%)	154 (92%)
Days, median (range)	15 (10–29)
Mucositis 3-4, *n* (%)	30 (18%)
aGvHD	
aGvHD 2-4, *n* (%)	51 (31%)
aGvHD 3-4, *n* (%)	19 (11%)
BSI, *n* (%)	59 (35%)
SOS/VOD	
n (%)	27 (16%)
Day SOS/VOD, median (range)	11 (8–25)
SOS/VOD grading, *n* (%)	
Moderate	2 (7%)
Severe	20 (74%)
Very severe	5 (19%)

ALL acute lymphoblastic leukemia, *AML* acute myeloid leukemia, *ATG* anti-thymocyte globulin, *BM* bone marrow, *BSI* bloodstream infections, *CB* cord blood, *CR* complete remission, *aGvHD* acute graft versus host disease, *HCT* hematopoietic stem cell transplantation, *JMML* juvenile myelomonocytic leukemia, *MAC* myeloablative conditioning, *MDS* myelodysplastic syndrome, *MSD* matched sibling donor, *MUD* matched unrelated donor, *NRM* non-relapse mortality, *PBSC* peripheral blood stem cells, *SOS/VOD* sinusoidal obstruction syndrome/veno occlusive disease, *TBI* total body irradiation.

of SOS/VOD-related mortality (Supplementary Table 1), we did not observe any correlation between the SOS/VOD-related mortality rate and the EASIX + 7 score.

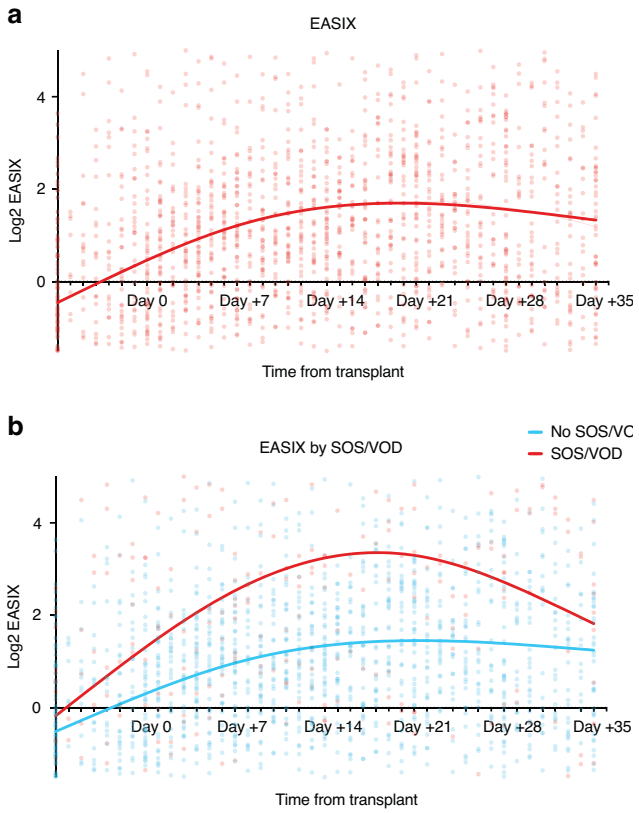

Fig. 1 Dynamics of EASIX score after allo-HCT. a EASIX score dynamics over time post allo-HCT for the whole cohort. **b** EASIX score dynamics in patients developing or not developing SOS/VOD. EASIX score was normalized using log2 and calculated every day. LOWESS lines were added in (**a**) to illustrate trends for the whole cohort (red line and red dots) and in (**b**) for patients developing (red line and red dots) or not developing (blue line and blue dots) SOS/VOD.

Median value of EASIX score at SOS/VOD diagnosis was 4.42, and no statistically significant associations were observed with SOS/VOD severity and outcome. All patients received defibrotide treatment from the day of diagnosis, and a statistically significant reduction was observed between EASIX score values at diagnosis and at day +35 (4.42 vs 1.87; $p = 0.023$).

EASIX score dynamics and NRM

EASIX score dynamics were different in patients who died from NRM or all-cause mortality (ACM) after allo-HSCT than in patients who survived after allo-HSCT. In both cases, the median values of the EASIX score were comparable at admission (NRM: 0.86 vs. 0.72; $p = 0.36$; ACM: 0.95 vs. 0.80; $p = 0.52$) but significantly diverged from day −1 to day +14, with the maximum difference being observed on day + 12 (NRM: 5.43 vs. 0.97; $p < 0.001$; ACM: 3.84 vs. 0.91; $p < 0.001$).

At the same time, as described previously, we analysed the predictive value of the EASIX score for mortality. The EASIX + 7 score was significantly correlated with NRM (OR 1.56; 95% CI, 1.13–2.13; $p = 0.006$) and ACM (OR 1.32; 95% CI, 1.01–1.71; $p = 0.041$). The median EASIX score was greater on day +7 in patients who subsequently died from NRM (1.92 vs. 0.80; $p = 0.035$) or ACM (1.78 vs. 0.66; $p = 0.03$) (Fig. 2B). The single parameters composing the EASIX + 7 score were not predictors of NRM or ACM (data not shown). The EASIX + 7 score remained an independent predictor of NRM in the multivariate model (OR 1.68; 95% CI 1.16–2.42; $p = 0.006$), as shown in Table 3. Conversely, the

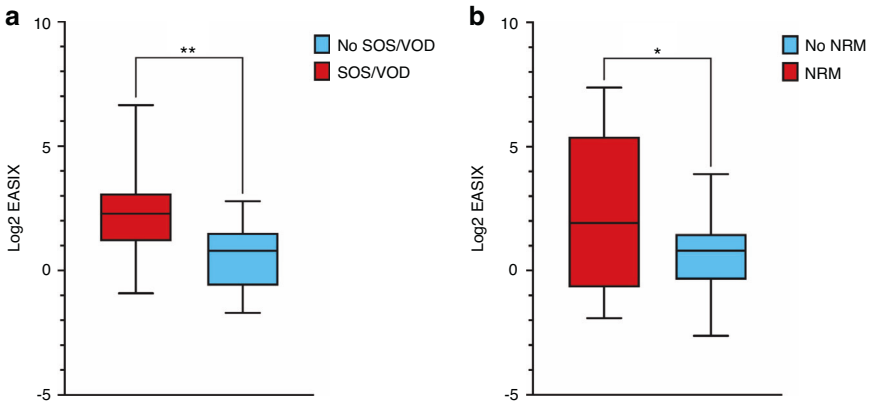

Fig. 2 Comparison of EASIX + 7 score across different outcomes. a Box plot comparison of EASIX + 7 in patients developing or not developing SOS/VOD. **b** Box plot comparison of EASIX + 7 in patients subsequently dying or not dying of NRM. Comparison made using the Mann–Whitney test: ***$P < 0.001$; **$P < 0.01$; *$P < 0.05$.

Table 2. Univariate and multivariate analysis on EASIX + 7 as a predictor of SOS/VOD.

	Univariate analysis on SOS/VOD		Multivariate analysis on SOS/VOD	
	OR (95% CI)	***P* value**	**OR (95% CI)**	***P* value**
EASIX + 7	1.41 (1.04–1.92)	0.028	1.52 (1.08–2.13)	**0.017**
Busulfan	2.90 (1.14–7.81)	0.027	3.3 (0.64–17.51)	0.15

OR odds ratio, *SOS/VOD* sinusoidal obstruction syndrome/veno occlusive disease.
Values in bold mean that the *p*-value is inferior to 0.05.

Table 3. Univariate and multivariate analysis on EASIX + 7 as a predictor of NRM.

	Univariate analysis on NRM		Multivariate analysis on NRM	
	OR (95% CI)	***P* value**	**OR (95% CI)**	***P* value**
EASIX + 7	1.56 (1.13–2.13)	0.006	1.68 (1.16–2.42)	**0.006**
Busulfan	1.87 (0.94–3.73)	0.072	1.63 (0.40–6.66)	0.15
Stem cell source	2.23 (1.01–4.95)	0.048	6.80 (1.57–29.41)	**0.01**
BSI	2.21 (1.11–4.42)	0.025	1.28 (0.30–5.44)	0.50

The stem cell source variable was considered binary (others vs BM).
BSI blood stream infections, *NRM* non-relapse mortality, *OR* odds ratio, *PBSC* peripheral blood stem cell.
Values in bold mean that the *p*-value is inferior to 0.05.

association was not confirmed for ACM in multivariate analysis (Supplementary Table 2). We performed ROC analysis to identify the EASIX + 7 score with the highest sensitivity and specificity for NRM, which was 1.77 (Supplementary Fig. 2). We then compared the cumulative incidence of NRM in patients stratified into two groups, namely, those with EASIX + 7 scores higher or lower than 1.77. Compared with the group with EASIX + 7 scores lower than 1.77, in the group with EASIX + 7 scores higher than 1.77, the rate of NRM was significantly increased, as shown in Fig. 3 (45.0%; 95% CI, 26.2% to 77.3% vs. 11.2%; 95% CI, 4.8% to 26.4%; $p = 0.002$) (Fig. 3A). The OS rate differed significantly between the two groups (55.1%; CI 95% 30.8% to 79.3% vs. 81.6%; CI 95% 69.7% to 93.5%; $p = 0.012$) (Fig. 3B). The Δ between the EASIX + 7 score and EASIX score at admission was significantly associated with NRM (OR 1.45; 95% CI, 1.05–2.00; $p = 0.023$) but not with ACM (OR 1.21; 95% CI, 0.92–1.59; $p = 0.18$). With respect to the association between the EASIX score and NRM, the EASIX + 0 score was also a significant predictor of NRM according to univariate (OR 1.79; 95% CI, 1.24–2.58; $p = 0.002$) and multivariate analyses (OR 1.79; 95% CI, 1.13–2.49; $p = 0.006$) (Supplementary Table 3). Moreover, the EASIX + 14 score was associated with subsequent NRM in univariate (OR 1.68; 95% CI, 1.23–2.28; $p = 0.001$) and multivariate analyses (OR 1.84; 95% CI, 1.28–2.63; $p = 0.002$) (Supplementary Table 4). For all the time points, day +12 (univariate OR 2.72; multivariate OR 3.05) showed the highest OR, with an AUC of the ROC curve of 0.891 (Supplementary Table 5).

EASIX score and age

Age correlated significantly with the EASIX score at all analysed time points. Specifically, there was a linear correlation between age and the EASIX + 7 score ($p < 0.001$), with the EASIX score increasing by 0.2064 units for each additional year of age (95% CI: 0.1413–0.2716) (Fig. 4). We then tried to assess whether the association between age and the EASIX score could be considered a confounder in the observed associations. However, the EASIX + 7 score was confirmed as an independent predictor of SOS/VOD and NRM even after age was added to the multivariate models (data not shown).

EASIX scores and other clinical outcomes

In our cohort, the EASIX + 7 score was not a predictor of TAM ($p = 0.88$) or posterior reversible encephalopathy syndrome (PRES)

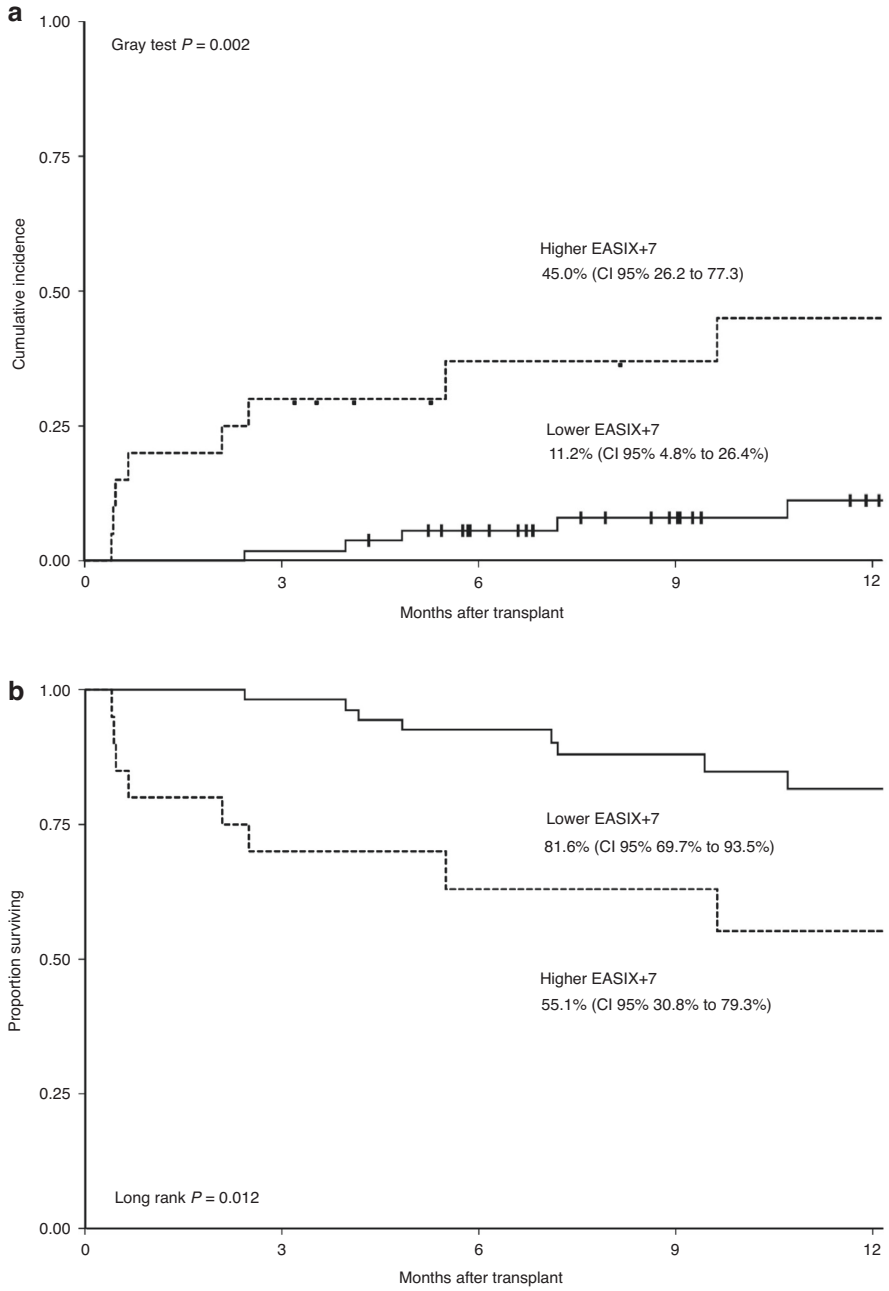

Fig. 3 Kaplan-Meier estimates for NRM and OS based on EASIX + 7 values. a NRM based on EASIX + 7. Patients were grouped by the EASIX + 7 value with the most sensitivity and specificity for NRM based on ROC analysis (1.77). **b** OS based on EASIX + 7. Patients were grouped by the same EASIX + 7 value calculated for NRM.

($p = 0.62$), two other complications considered secondarily to endothelial damage [23], as was the EASIX score at any other time point. The incidence of other known endothelial complications in our cohort was too low to perform any statistical analysis. Moreover, no correlations were found between the EASIX + 7 score and aGvHD, namely, any grade aGvHD, grade 2–4 aGvHD, grade 3–4 aGvHD, or steroid-resistant or steroid-dependent aGvHD. Conversely, the EASIX + 14 score was significantly associated with grade 3–4 aGvHD according to the univariate analysis (OR 1.39; 95% CI, 1.06–1.81; $p = 0.017$). Patients who developed severe aGvHD had higher EASIX scores at day +14 than patients who did not develop grade 3–4 aGvHD (2.80 vs. 1.06; $p = 0.013$) (Supplementary Fig. 3). Multivariate analysis confirmed the independent association between the EASIX + 14 score and grade 3–4 aGvHD (OR 1.57; 95% CI, 1.01–2.18; $p = 0.008$) (Supplementary Table 6).

DISCUSSION

In this study, we evaluated the predictive value of the EASIX score in a paediatric and adolescent cohort of allo-HSCT recipients. The EASIX + 7 score was an independent predictor of SOS/VOD and NRM in our patients, and the EASIX score measured at several other time points within two weeks after stem cell infusion was significantly correlated with subsequent NRM in univariate and multivariate analyses. Compared with the performance of the other 7 commonly applied scoring systems in adult allo-HSCT recipients, the EASIX score has been externally validated as one of

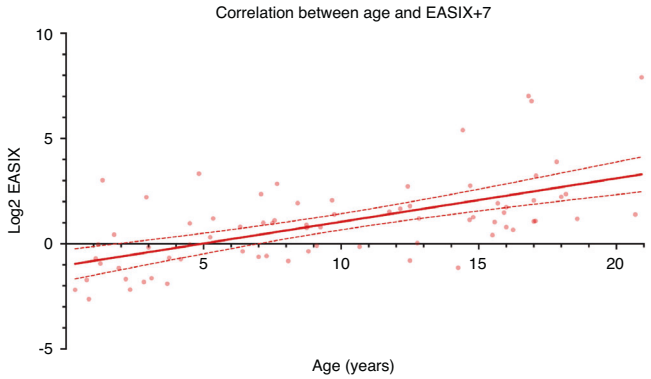

Fig. 4 Correlation between age and EASIX + 7 score. Linear correlation between EASIX + 7 and age. Each data point represents the EASIX + 7 value plotted against the corresponding patient age. The solid line represents the best-fit linear regression line, with the equation Y = 0.2064*X -1.021. The dotted lines represent the 95% confidence interval for the regression line. Age measured in years at HCT.

the strongest predictors of NRM, with the added value of incorporating only easy-to-access laboratory data [24]. The external validation of the score for the prediction of NRM and comparison with other prognostic scores is still lacking in children and should be precisely addressed. Furthermore, in our cohort, the EASIX score was shown to be an important biomarker for predicting the subsequent development of SOS/VOD. The EASIX + 7 score, in particular, may represent a tool for defining a subpopulation of allo-HSCT recipients at greater risk for SOS/VOD and may be beneficial for closer monitoring and/or prevention strategies [12, 25]. Another transplant-related complication in which endothelial cell dysfunction plays a pivotal role is aGvHD [26], and the EASIX score has already been shown to be a useful predictor in adult patients with aGvHD- and aGvHD-related mortality when measured on day +7 or at aGvHD onset, respectively [9, 10]. In our analysis of children who received bone marrow as the main graft source and MAC, the only time point that correlated with subsequent grade 3–4 aGvHD was day +14, possibly underlining a different biological process underpinning endothelial damage related to severe forms of aGvHD in this specific population.

Our results differ from those of another paediatric cohort study reported by Luft et al. [13], in which they analysed the predictive value of the EASIX score before conditioning in 262 patients with a median age of 7 years (range 0–33), allografted for a nonmalignant disease in more than 70% of all patients and in 46% of patients who received RIC. A higher EASIX score pre-HSCT was significantly associated with an increased incidence of TAM, a low OS rate and a high NRM rate in univariate analysis, although not in multivariate analyses, and the authors speculated that this may be due to the strong correlation between EASIX parameters and age in children. Conversely, in our study, allo-HSCT was performed for malignant disease in 78% of the patients, and MAC was employed in 92% of the patients. The two main distinctions, the EASIX time point and transplant characteristics, could explain the different results in these two cohorts. Compared with values obtained after HSCT, the EASIX score obtained before allo-HSCT may be a weaker predictor and be more influenced by patient age, as suggested in adult studies, in which post-HSCT EASIX scores seemed to be better predictors of NRM than pre-HCT scores [15]. Moreover, MAC and RIC exert different levels of endothelial injury [27], and the prognostic impact of the EASIX score has been shown to be dependent on the transplant source used [15], showing better predictive power within MAC cohorts [24]. Moreover, the EASIX score at all time points was linearly correlated with age in our patients, probably due to age-specific variations in LDH and serum creatine levels [13], but this did not impair the predictive role of the EASIX score after HSCT. Future studies should focus on the predictive value of the EASIX score in different groups, for example, comparing adults with children, to further disentangle the clinical implications of the EASIX score in different settings.

In this context, the pivotal challenges to better integrate the score into clinical practice are the choice of the best time point to assess the EASIX score to predict outcomes and which cut-off values should be used. To date, most studies on adult patients considered values obtained before conditioning [11, 13, 14, 16–18], but, as previously addressed, several other publications [9, 12, 15, 16, 18], including the present study, reported stronger correlations between post-HCT EASIX scores and clinical outcomes. As recently suggested, specific cut-off values for specific time points at which the EASIX score is evaluated should be calculated to improve the predictive value of the score compared with applying pretransplant optimal cut-off values [28]. In our dataset, an EASIX + 7 score of 1.77, which was calculated via ROC analysis at the day +7 time point, identified patients with an approximately 30% greater risk of subsequent NRM (Fig. 3a). In future studies, the specific time point at which an absolute cut-off valid for all cohorts could be applied, rather than one relative to individual cohorts, should be defined. Another issue to be considered is that the ideal time point for evaluating the EASIX score may differ on the basis of the clinical endpoints. In our cohort, the EASIX + 7 score was not correlated with aGvHD incidence, whereas the EASIX + 14 score was independently associated with subsequent severe aGvHD. The EASIX + 0 score was also not a predictor of SOS/VOD, whereas the EASIX + 7 score was. Moreover, several time points between day +0 and day +14 were independently associated with NRM, with the strongest association being observed on day +12 (Supplementary Table 4). This distinct predictive power of specific time points may reflect the different dynamics of endothelial damage associated with different complications, highlighting the need for further studies to better evaluate the ideal timing of EASIX score determination for translation into clinical practice.

Limitations of the present study include its retrospective design and the lack of external validation. The long period of inclusion resulted in the high rate of NRM observed in our cohort, considering that the incidence of NRM was 2.2 times higher in 2010–2016 than in 2017–2023 ($p = 0.002$). Further prospective multicentre studies are strongly needed to better define the potential of the EASIX score as a tool for predicting SOS/VOD, aGvHD and NRM in paediatric allo-HSCT recipients. Moreover, intrinsic limitations of the score, namely, the dependence of platelet and LDH values on transfusions and the age-related variations in serum creatinine levels, should be addressed and possibly overcome with slight variations in the formula, such as the modified EASIX score, which replaces the creatinine level with the C-reactive protein level and has already been explored in the setting of chimeric antigen receptor T-cell–related toxicities [29].

CONCLUSIONS

The EASIX score determined shortly after allo-HSCT is an independent predictor of NRM and endothelial complications in paediatric and adolescent patients. The EASIX sore is a readily available marker of endothelial dysfunction and could help in understanding the dynamics and biology of endothelial damage or be further studied as a prognostic factor in larger clinical studies. EASIX-based preventive strategies could also be possibly designed in the future to reduce the incidence of SOS/VOD and prevent NRM in children receiving allo-HSCT.

DATA AVAILABILITY

The datasets used and analyzed during the current study available from the corresponding author on reasonable request.

REFERENCES

1. Copelan EA, Chojecki A, Lazarus HM, Avalos BR. Allogeneic hematopoietic cell transplantation; the current renaissance. Blood Rev. 2019;34:34–44.
2. Masetti R, Muratore E, Gori D, Prete A, Locatelli F. Allogeneic hematopoietic stem cell transplantation for pediatric acute myeloid leukemia in first complete remission: a meta-analysis. Ann Hematol. 2022;101:2497–506.
3. Algeri M, Merli P, Locatelli F, Pagliara D. The role of allogeneic hematopoietic stem cell transplantation in pediatric leukemia. J Clin Med. 2021;10:3790.
4. Cordes S, Mokhtari Z, Bartosova M, Mertlitz S, Riesner K, Shi Y, et al. Endothelial damage and dysfunction in acute graft-versus-host disease. Haematologica. 2021;106:2147–60.
5. Dalle J-H, Giralt SA. Hepatic veno-occlusive disease after hematopoietic stem cell transplantation: risk factors and stratification, prophylaxis, and treatment. Biol Blood Marrow Transpl. 2016;22:400–9.
6. Milone G, Bellofiore C, Leotta S, Milone GA, Cupri A, Duminuco A, et al. Endothelial dysfunction after hematopoietic stem cell transplantation: a review based on physiopathology. J Clin Med. 2022;11:623.
7. Masetti R, Biagi E, Zama D, Muratore E, D'Amico F, Leardini D, et al. Early modifications of the gut microbiome in children with hepatic sinusoidal obstruction syndrome after hematopoietic stem cell transplantation. Sci Rep. 2021;11:1–11.
8. Farina M, Scaini MC, Facchinetti A, Leoni A, Bernardi S, Catoni C, et al. Evaluation of circulating endothelial cells as direct marker of endothelial damage in allotransplant recipients at high risk of hepatic veno-occlusive disease/sinusoidal obstruction syndrome. Transpl Cell Ther. 2024;30:580.e1–14.
9. Luft T, Benner A, Jodele S, Dandoy CE, Storb R, Gooley T, et al. EASIX in patients with acute graft-versus-host disease: a retrospective cohort analysis. Lancet Haematol. 2017;4:e414–23.
10. Pedraza A, Salas MQ, Rodríguez-Lobato LG, Escribano-Serrat S, Suárez-Lledo M, Martínez-Cebrian N, et al. Easix score correlates with endothelial dysfunction biomarkers and predicts risk of acute graft-versus-host disease after allogeneic transplantation. Transpl Cell Ther. 2024;30:187.e1–12.
11. Korell F, Schreck N, Müller-Tidow C, Dreger P, Luft T, the Taskforce allogeneic Stem Cell Transplantation, University Hospital Heidelberg. et al. Pre-transplant EASIX and sepsis after allogeneic stem cell transplantation. Intensive Care Med. 2022;48:753–5.
12. Jiang S, Penack O, Terzer T, Schult D, Majer-Lauterbach J, Radujkovic A, et al. Predicting sinusoidal obstruction syndrome after allogeneic stem cell transplantation with the EASIX biomarker panel. Haematologica. 2021;106:446–53.
13. Luft T, Benner A, Terzer T, Jodele S, Dandoy CE, Storb R, et al. EASIX and mortality after allogeneic stem cell transplantation. Bone Marrow Transpl. 2020;55:553–61.
14. Mariotti J, Magri F, Giordano L, De Philippis C, Sarina B, Mannina D, et al. EASIX predicts non-relapse mortality after haploidentical transplantation with post-transplant cyclophosphamide. Bone Marrow Transpl. 2023;58:247–56.
15. Nawas MT, Sanchez-Escamilla M, Devlin SM, Maloy MA, Ruiz JD, Sauter CS, et al. Dynamic EASIX scores closely predict nonrelapse mortality after allogeneic hematopoietic cell transplantation. Blood Adv. 2022;6:5898–907.
16. Sanchez-Escamilla M, Flynn J, Devlin S, Maloy M, Fatmi SA, Tomas AA, et al. EASIX score predicts inferior survival after allogeneic hematopoietic cell transplantation. Bone Marrow Transpl. 2023;58:498–505.
17. Peña M, Salas MQ, Mussetti A, Moreno-Gonzalez G, Bosch A, Patiño B, et al. Pretransplantation EASIX predicts intensive care unit admission in allogeneic hematopoietic cell transplantation. Blood Adv. 2021;5:3418–26.
18. Fujita S, Monna-Oiwa M, Kato S, Isobe M, Takahashi S, Nannya Y, et al. Pre-transplantation EASIX score predicts nonrelapse and overall mortality of adult patients undergoing single-unit unrelated cord blood transplantation. Transpl Cell Ther. 2023;29:580.e1–8.
19. Bacigalupo A, Ballen K, Rizzo D, Giralt S, Lazarus H, Ho V, et al. Defining the intensity of conditioning regimens: working definitions. Biol Blood Marrow Transplant. 2009;15:1628–33.
20. Corbacioglu S, Carreras E, Ansari M, Balduzzi A, Cesaro S, Dalle J-H, et al. Diagnosis and severity criteria for sinusoidal obstruction syndrome/veno-occlusive disease in pediatric patients: a new classification from the European Society for Blood and Marrow Transplantation. Bone Marrow Transpl. 2018;53:138–45.
21. Glucksberg H, Storb R, Fefer A, Buckner CD, Neiman PE, Clift RA, et al. Clinical manifestations of graft-versus-host disease in human recipients of marrow from HL-A-matched sibling donors. Transplantation. 1974;18:295–304.
22. Palmer MK. WHO handbook for reporting results of cancer treatment. Br J Cancer. 1982;45:484–5.
23. Carreras E, Diaz-Ricart M, Jodele S, Penack O, Vasu S. Early Complications of Endothelial Origin. In: Sureda A, Corbacioglu S, Greco R, Kröger N, Carreras E (eds). The EBMT Handbook: Hematopoietic Cell Transplantation and Cellular Therapies. Springer International Publishing: Cham, 2024, pp 373–83.
24. Shouval R, Fein JA, Shouval A, Danylesko I, Shem-Tov N, Zlotnik M, et al. External validation and comparison of multiple prognostic scores in allogeneic hematopoietic stem cell transplantation. Blood Adv. 2019;3:1881–90.
25. Mohty M, Malard F, Abecassis M, Aerts E, Alaskar AS, Aljurf M, et al. Sinusoidal obstruction syndrome/veno-occlusive disease: current situation and perspectives-a position statement from the European Society for Blood and Marrow Transplantation (EBMT). Bone Marrow Transpl. 2015;50:781–9.
26. Malard F, Holler E, Sandmaier BM, Huang H, Mohty M. Acute graft-versus-host disease. Nat Rev Dis Prim. 2023;9:27.
27. Strouse C, Zhang Y, Zhang M-J, DiGilio A, Pasquini M, Horowitz MM, et al. Risk score for the development of veno-occlusive disease after allogeneic hematopoietic cell transplant. Biol Blood Marrow Transpl. 2018;24:2072–80.
28. Escribano-Serrat S, Rodríguez-Lobato LG, Suárez-Lledó M, Pedraza A, Charry P, Cid J, et al. Improving the EASIX' predictive power for NRM in adults undergoing allogeneic hematopoietic cell transplantation. Bone Marrow Transplant. 2024. https://doi.org/10.1038/s41409-024-02267-6.
29. Pennisi M, Sanchez-Escamilla M, Flynn JR, Shouval R, Alarcon Tomas A, Silverberg ML, et al. Modified EASIX predicts severe cytokine release syndrome and neurotoxicity after chimeric antigen receptor T cells. Blood Adv. 2021;5:3397–406.

ACKNOWLEDGEMENTS

The work was in part supported by the Italian Ministry of Health, RC-2024-2790372 and by the Fondazione Cassa di Risparmio di Bologna (19431-2021.0082) (to RM).

AUTHOR CONTRIBUTIONS

EM and RM conceptualized the study. EM, LL, and GG collected the data. EM and DL performed the statistical analysis. DL and EM prepared the figures. EM, DL, and GG wrote the paper. FB, FV, FG, TB, AP, and RM critically reviewed the paper.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41409-024-02489-8.

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