



## OPEN ACCESS

## EDITED BY

Kris Michael Mahadeo,  
Duke University, United States

## REVIEWED BY

Katrine Kielsen,  
Rigshospitalet, University of Copenhagen,  
Denmark  
Mirko Farina,  
Civil Hospital of Brescia, Italy

## \*CORRESPONDENCE

Saad Ghafoor

✉ lama.elbahlawan@stjude.org

Lama Elbahlawan

✉ saad.ghafoor@stjude.org

RECEIVED 09 November 2025

REVISED 12 January 2026

ACCEPTED 20 January 2026

PUBLISHED 11 February 2026

## CITATION

Ghafoor S, Uchida K, McArthur J, Avent Y,  
Hsu C-W, Pan H and Elbahlawan L (2026)  
Detecting Endothelial Compromise  
Objectively through Dynamic EASIX scoring  
(DECODE) - predictive utility of EASIX and  
modified EASIX scores for endothelial  
complications post hematopoietic cell  
transplant.

*Front. Oncol.* 16:1742467.

doi: 10.3389/fonc.2026.1742467

## COPYRIGHT

© 2026 Ghafoor, Uchida, McArthur, Avent, Hsu,  
Pan and Elbahlawan. This is an open-access  
article distributed under the terms of the  
[Creative Commons Attribution License \(CC BY\)](https://creativecommons.org/licenses/by/4.0/).  
The use, distribution or reproduction in other  
forums is permitted, provided the original  
author(s) and the copyright owner(s) are  
credited and that the original publication in  
this journal is cited, in accordance with  
accepted academic practice. No use,  
distribution or reproduction is permitted  
which does not comply with these terms.

# Detecting Endothelial Compromise Objectively through Dynamic EASIX scoring (DECODE) - predictive utility of EASIX and modified EASIX scores for endothelial complications post hematopoietic cell transplant

Saad Ghafoor<sup>1,2\*</sup>, Kimberly Uchida<sup>1,2,3</sup>, Jennifer McArthur<sup>1,2</sup>,  
Yvonne Avent<sup>1</sup>, Chia-Wei Hsu<sup>4</sup>, Haitao Pan<sup>4</sup>  
and Lama Elbahlawan<sup>1\*</sup>

<sup>1</sup>Department of Pediatric Medicine, Division of Critical Care Medicine, St. Jude Children's Research Hospital, Memphis, TN, United States, <sup>2</sup>Department of Pediatrics, Division of Pediatric Critical Care, University of Tennessee Health Science Center, Memphis, TN, United States, <sup>3</sup>Department of Pediatrics, Division of Pediatric Critical Care, University of Utah, Salt Lake City, UT, United States, <sup>4</sup>Department of Biostatistics, St. Jude Children's Research Hospital, Memphis, TN, United States

**Introduction:** Endothelial injury is a major contributor to morbidity and mortality in pediatric patients undergoing hematopoietic cell transplantation (HCT). It appears as sinusoidal obstruction syndrome (SOS) or transplant-associated thrombotic microangiopathy (TMA), among other conditions. Composite indices like the Endothelial Activation and Stress Index (EASIX) and its modified version (m-EASIX) may serve as accessible biomarkers for early identification. However, their utility in pediatric populations is unestablished. We aimed to explore whether EASIX and m-EASIX can help identify endothelial complications in this setting.

**Methods:** We conducted a prospective, single-center observational cohort study of 31 children and young adults undergoing HCT. Serial measurements of EASIX and m-EASIX scores, based on standard laboratory parameters, were collected at baseline and at multiple post-HCT time points (Days 0, 7, 14, 21, 28, and 100).

**Results:** Within 100 days after HCT, SOS and/or TMA developed in six patients. At Day 21, EASIX and m-EASIX scores were significantly higher in children with endothelial complications than in controls. The m-EASIX score also showed predictive value at Day 14. Receiver operating characteristic analysis showed discrimination at Day 21 for both scores (AUCs of 0.807 for EASIX and 0.865 for m-EASIX). Changes from baseline to Day 21 further improved accuracy, with thresholds achieving high sensitivity for screening patients at increased risk of SOS and/or TMA. The Day 21 landmark is most relevant for identifying patients at

risk of later-onset or persistent endothelial injury, which remains clinically significant.

**Conclusions:** Our findings suggest that EASIX and m-EASIX may serve as practical and dynamic biomarkers for detecting endothelial injury in pediatric HCT recipients. The observation that Day 21 scores and their changes from baseline correlate with later complications highlights a potential window for risk stratification. However, these results should be interpreted cautiously, given the single-center design and limited sample size. Further research is needed to confirm whether these indices can reliably guide clinical decisions across diverse settings. Exploring their use in populations where reduced-intensity conditioning (RIC) and alternative donors are standard could provide important insights. Multicenter studies will be essential to validate these preliminary observations and refine biomarker-based strategies for post-HCT care.

#### KEYWORDS

EASIX score, endothelial injury, endotheliopathy, hematopoietic cell transplantation, modified EASIX score, pediatric, sinusoidal obstruction syndrome, transplant-associated thrombotic microangiopathy

## 1 Introduction

Endothelial injury is a key contributor to morbidity and mortality after pediatric hematopoietic cell transplantation (HCT). The endothelium is a dynamic interface between circulating blood and tissue. It plays a crucial role in regulating vascular tone, coagulation, and immune function, and it maintains barrier integrity. In the post-HCT setting, the endothelium is often disrupted by cytotoxic conditioning regimens, immunosuppressive agents, infections, and immune reconstitution, resulting in endothelial dysfunction syndromes, such as sinusoidal occlusive syndrome (SOS) and transplant-associated thrombotic microangiopathy (TMA) (1–3).

The underlying mechanisms of endothelial injury include pro-inflammatory cytokine activation, complement system dysregulation, and direct endothelial cytotoxicity. SOS and TMA represent severe, persistent forms of endothelial injury: SOS is characterized by hepatic sinusoidal blockage, and TMA is characterized by widespread microvascular thrombosis. Both syndromes lead to significant organ damage and adverse outcomes (4, 5). Pediatric patients are particularly vulnerable due to their smaller vascular volumes, immature immune systems, and limited physiological reserves. Endothelial dysfunction in this population increases the need for intensive care, extends hospitalizations, and contributes to long-term organ complications (6–8).

Despite its clinical significance, identifying evolving endothelial injury early remains challenging. Traditional diagnostic methods, which rely on clinical symptoms and isolated laboratory findings, often lack adequate sensitivity and specificity. Invasive procedures, such as biopsies and advanced imaging, are seldom feasible in children. This diagnosis underscores the need for accessible, reliable

biomarkers that can identify endothelial stress before irreversible damage occurs. Composite scores derived from routine laboratory values offer a pragmatic solution. The Endothelial Activation and Stress Index (EASIX), calculated from lactate dehydrogenase (LDH), creatinine, and platelet count, reflects systemic endothelial stress and organ dysfunction and can be monitored serially at the bedside (9).

The ease of use and reproducibility of EASIX are particularly beneficial in pediatric settings, where frequent assessments are required (10). Recent evidence suggests that a modified EASIX (m-EASIX) score, which substitutes C-reactive protein (CRP) for Creatinine, enhances the predictive value for severe, persistent endothelial complications, such as SOS and TMA (11). The EASIX and m-EASIX scores are strongly correlated with clinical outcomes, including nonrelapse mortality, intensive care unit (ICU) admission, and organ failure. Significantly, they facilitate risk stratification at critical time points before transplantation, during conditioning, and in the early post-HCT phase. This enables clinicians to identify patients at increased risk before their overt clinical decline (12).

Whether EASIX and m-EASIX scores can predict endothelial injury in pediatric HCT recipients remains insufficiently characterized. To address this gap, we prospectively studied the relations between the EASIX and m-EASIX scores and the development of SOS and/or TMA in children undergoing HCT. We hypothesized that elevated EASIX and m-EASIX values at specific post-HCT time points would be associated with the onset of these complications. Additionally, we aimed to identify clinically relevant thresholds for both scoring systems to facilitate early prediction of endothelial injury in routine practice.

## 2 Materials and methods

### 2.1 Study population

This single-center, prospective, observational cohort study was conducted from 11/28/2022 to 1/18/2024. Eligibility criteria included patients aged 22 years or younger who weighed at least 10 kg. Individuals were excluded if they exceeded the age or weight limits or if consent was not provided. Study follow-up extended through Day 100 post-HCT for endpoint ascertainment. There were 28 allogeneic and three autologous transplants. The study protocol was approved by the Institutional Review Board at St. Jude Children's Research Hospital, and written informed consent was obtained from all participants or their guardians, as appropriate.

### 2.2 Data collection

Comprehensive data were collected for each participant, including demographic variables (i.e., age, sex, race, and ethnicity) and details about their underlying malignancy, HCT type, donor characteristics, conditioning regimen, and survival outcomes. Clinical information on ICU admission, the use of invasive mechanical ventilation, the administration of vasopressors or inotropic agents (e.g., norepinephrine, epinephrine, dobutamine, phenylephrine, vasopressin, dopamine, and milrinone), and renal replacement therapy was also documented. Blood samples were taken at baseline (day of HCT, Day 0) and on Days 7, 14, 21, 28, and 100 after the transplantation. At each time point, laboratory parameters, including serum creatinine, LDH, platelet count, and CRP were measured and recorded.

### 2.3 Definitions

Endothelial complications were defined by the occurrence of TMA and/or SOS. The earliest date of diagnosis was used as the index date for analysis. A diagnosis of TMA was made based on a documented clinical evaluation and management by the treating physician, histologic confirmation, or fulfillment of the Modified Jodele Criteria (13). These criteria include laboratory and clinical markers, such as elevated LDH, proteinuria, and refractory cytopenias. Similarly, SOS was diagnosed according to the pediatric criteria determined by the European Society for Blood and Marrow Transplantation (5) or based on a clinical diagnosis documented in the medical records and managed accordingly. The EASIX score was calculated using the following formula: serum LDH level (U/L)  $\times$  creatinine level (mg/dL)/platelet count ( $10^9/L$ ) (14). The m-EASIX score was calculated based on the following formula: serum LDH level (U/L)  $\times$  CRP (mg/dL)/platelet count ( $10^9/L$ ) (15). The values from both scores were normalized using  $\log_2$  transformation to reduce skewness, as reported in the literature.

### 2.4 Statistical analysis

Descriptive statistics were used to summarize patient characteristics. Continuous variables were reported as medians with interquartile ranges (IQR) and were compared using the Wilcoxon signed-rank test. Categorical variables were compared using the Chi-square test or Fisher's exact test if fewer than five observations were included.

The EASIX and m-EASIX scores were  $\log_2$ -transformed and analyzed at Days 0, 7, 14, 21, 28, and 100. These predefined time points were selected to capture peri-transplant endothelial dynamics and potential predictive windows for post-HCT complications. Due to the limited number of individual events, we used a composite endpoint of SOS/TMA to increase statistical power. Separate analyses for each complication were not feasible, given the small sample size.

Univariate logistic regression was used to identify factors associated with SOS and/or TMA. A small number of events precluded reliable multivariable modeling, and larger studies are needed for adjusted analyses. Results were reported as odds ratios (OR) and 95% confidence intervals (CI). At landmark time points (Days 7, 14, and 21), predictive performance was evaluated using receiver operating characteristic (ROC) analysis, with areas under the curve (AUCs) and optimal cutoffs determined by the Youden index, closest-to-(0,1) method, and  $\geq 90\%$  sensitivity criterion (16). Dynamic changes ( $\Delta$ EASIX and  $\Delta$ m-EASIX) were defined as the difference between each post-HCT value and the corresponding baseline value, and their predictive utility was similarly evaluated using ROC analysis. All statistical tests were two-sided, with  $p < 0.05$  considered significant. Analyses were performed using SAS version 9.4.

## 3 Results

A total of 31 children participated in this prospective study. Within the first 100 days after HCT, six (19%) children experienced either TMA or SOS. The median age of the group was 11 years, and males comprised 58% of the cohort (Table 1). Patients with or without SOS and/or TMA had similar median ages (10 vs 12.5 years,  $p = 0.82$ ) and sex distributions (50% vs 60% male,  $p = 0.68$ ). Most patients received allogeneic HCT (90%), mainly with reduced-intensity conditioning (68%) and a mismatched related donor (MMRD) (64%). The main reason for HCT was malignant disease (77%), most often acute myeloblastic leukemia (AML).

The rate of use of reduced-intensity conditioning (RIC) regimens is 68% (21 of 31). The rate of use of Busulfan is 19% (6 of 31). The median day of diagnosis for SOS/TMA was Day 21 (Day 10–94). Four events occurred on or before Day 21, and two occurred after (Days 63 and 94). Of the four SOS cases, three were severe, and one was moderate.

Our institutional practice for a significant portion of allogeneic transplants, often driven by concerns about organ toxicity, prior receipt of intensive therapy, or the underlying diagnoses, is to use a

TABLE 1 Characteristics of the cohort.

Characteristic	All cohort (N = 31)	SOS/TMA (n = 6)	No SOS/TMA (n = 25)	P-value
Age (years)	11 (2–22)	10 (2–18)	12.5 (2–22)	0.82
Sex				0.67
<i>Female</i>	13 (41.94)	3 (50.00)	10 (40.00)	
<i>Male</i>	18 (58.06)	3 (50.00)	15 (60.00)	
Ethnicity				0.34
<i>Hispanic</i>	12 (38.71)	4 (66.67)	8 (32.00)	
<i>Non-Hispanic</i>	18 (58.06)	2 (33.33)	16 (64.00)	
<i>Unknown</i>	1 (3.23)	0 (0.00)	1 (4.00)	
Race (%)				0.64
<i>White</i>	19 (61.29)	3 (50.00)	16 (64.00)	
<i>Black</i>	5 (16.13)	1 (16.67)	4 (16.00)	
<i>Unknown</i>	4 (12.90)	2 (33.33)	2 (8.00)	
<i>American Indian/Alaskan Native</i>	1 (3.23)	0 (0.00)	1 (4.00)	
<i>Mixed</i>	1 (3.23)	0 (0.00)	1 (4.00)	
<i>Native Hawaiian/Other</i>	1 (3.23)	0 (0.00)	1 (4.00)	
Conditioning regimen				0.32
<i>Myeloablative</i>	9 (30.00)	3 (50.00)	6 (25.00)	
<i>Reduced intensity</i>	21 (68.00)	3 (50.00)	18 (75.00)	
Donor type				0.49
<i>Mismatched-related</i>	18 (64.29)	3 (50.00)	15 (68.18)	
<i>Matched sibling</i>	3 (10.71)	1 (16.67)	2 (9.09)	
<i>Matched-unrelated</i>	7 (25.00)	2 (33.33)	5 (22.73)	
Type of HCT				1
<i>Allogeneic</i>	28 (90.32)	6 (100.00)	22 (88.00)	
<i>Autologous</i>	3 (9.68)	0 (0.00)	3 (12.00)	
HCT indication				0.70
<i>ALL</i>	6 (19.35)	2 (33.33)	4 (16.00)	
<i>AML</i>	12 (38.71)	2 (33.33)	10 (40.00)	
<i>CML</i>	2 (6.45)	1 (16.67)	1 (4.00)	
<i>Nonmalignant hematologic disorder</i>	7 (22.58)	1 (16.67)	6 (24.00)	
<i>Lymphoma</i>	1 (3.23)	0 (0.00)	1 (4.00)	
<i>Solid tumor</i>	3 (9.68)	0 (0.00)	3 (12.00)	
ICU Admission				0.11
<i>No</i>	24 (77.42)	3 (50.00)	21 (84.00)	
<i>Yes</i>	7 (22.58)	3 (50.00)	4 (16.00)	

ALL, acute lymphoblastic leukemia; AML, acute myeloblastic leukemia; AUTO, autologous; CML, chronic myelogenous leukemia; HCT, hematopoietic cell transplantation; ICU, intensive care; SOS, sinusoidal obstruction syndrome; TMA, thrombotic microangiopathy.

RIC regimen. This represents a specific population. None received TBI.

Notably, seven (22%) patients underwent HCT for nonmalignant hematologic conditions. Seven (22%) patients needed ICU admission. Among the six patients who experienced SOS and/or TMA, two had isolated TMA, one had isolated SOS, and three had both conditions concurrently (SOS/TMA). All patients with SOS received defibrotide, and four of five patients with TMA received eculizumab. Of those who experienced SOS/TMA, two required invasive mechanical ventilation, two needed vasopressors, and two underwent renal replacement therapy. Three patients in the cohort died, with two deaths occurring more than 100 days after HCT.

### 3.1 EASIX and SOS and/or TMA

On the day of transplantation, EASIX scores did not differ significantly between children who later developed TMA and/or SOS and those who did not (Table 2). However, by Day 21 post-HCT, patients in whom SOS/TMA developed had significantly higher median EASIX scores (2.27, IQR -0.35-3.91) compared to those in whom these complications did not develop (-0.44, IQR -1.72-3.19;  $p = 0.01$ ) (Table 3). Furthermore, we observed higher median EASIX scores at Day 28 in children with SOS/TMA (1.55, IQR -0.70-4.61) than in those without (0.58, IQR -1.92-4.25;  $p=0.05$ ). Both groups showed an increase in EASIX scores by Day 7; however, EASIX scores continued to rise only in those in whom SOS/TMA developed, with scores peaking at Day 14 (Figure 1).

Across all time points, the mean EASIX scores were higher in the SOS/TMA group compared to controls, with statistically significant differences on Days 21 ( $p=0.01$ ) and 28 ( $p=0.05$ ).

### 3.2 Modified EASIX and SOS/TMA

At baseline, there was no difference in m-EASIX scores between children who experienced SOS/TMA and those who did not (Table 4), thus mirroring the findings for EASIX scores. However, children in whom SOS/TMA developed showed significantly higher m-EASIX scores on Days 14 and 21 post-HCT than those without the complications. On Day 14, the median m-EASIX score was 5.81 (IQR 3.52-9.63) in the SOS/TMA group versus 3.69 (IQR -0.56-6.17;  $p = 0.01$ ) in the non-SOS/TMA group. Similarly, on Day 21, the median score was 4.73 (IQR 2.39-7.54) compared to 1.31 (IQR -1.15-6.24;  $p < 0.0001$ ). All participants experienced a peak in their mean m-EASIX scores at Day 7 post-HCT, but scores remained consistently higher in the SOS/TMA group than in those without these complications (Figure 1).

### 3.3 Predictive performance of static EASIX and m-EASIX scores

To evaluate the predictive accuracy of EASIX and m-EASIX scores, we performed a landmark analysis. At each predetermined prediction time point (Days 7, 14, and 21), we assessed biomarker performance only in patients who remained free of events and at

TABLE 2 Association of the EASIX score with the development of SOS and/or TMA after pediatric HCT.

Day post-HCT	EASIX (log <sub>2</sub> )			m-EASIX (log <sub>2</sub> )		
	SOS/TMA <sup>1</sup>	No SOS/TMA <sup>1</sup>	P-value	SOS/TMA	No SOS/TMA	P-value
0	0.35 (-3.10-3.78)	-0.04 (-4.06-2.99)	0.68	3.23 (-1.08-5.03)	0.54 (-3.40-6.99)	0.36
7	1.98 (0.21-3.82)	1.27 (-1.32-2.81)	0.17	5.92 (4.49-8.85)	5.05 (0.50-7.40)	0.14
14	2.69 (-0.19-4.54)	0.94 (-1.94-4.08)	0.23	5.81 (3.52-9.63)	3.69 (-0.56-6.17)	0.01
21	2.27 (-0.35-3.91)	-0.44 (-1.72-3.19)	0.01	4.73 (2.39-7.54)	1.31 (-1.15-6.24)	<0.0001
28	1.55 (-0.70-4.61)	-0.58 (-1.92-4.25)	0.05	2.66 (-1.41-7.14)	0.55 (-1.57-5.29)	0.07
100	0.40 (-2.08-3.84)	-0.51 (-1.90-3.19)	0.45	-1.38 (-1.76-9.86)	-0.72 (-2.14-7.50)	1.00
Day post-HCT	EASIX (log <sub>2</sub> )			m-EASIX (log <sub>2</sub> )		
	SOS/TMA <sup>1</sup>	No SOS/TMA <sup>1</sup>	P-value	SOS/TMA	No SOS/TMA	P-value
0	1.27 (49.00-13.72)	0.97 (0.06-7.97)	0.68	10.56 (0.47-32.70)	1.45 (0.09-126.84)	0.36
7	4.32 (49.00-14.13)	2.41 (0.40-7.01)	0.17	65.06 (22.52-460.02)	33.07 (1.41-168.41)	0.14
14	10.94 (49.00-23.34)	1.92 (0.26-16.97)	0.23	58.60 (11.48-791.49)	12.90 (0.68-72.20)	0.01
21	5.10 (49.00-14.99)	0.74 (0.30-9.13)	0.01	26.57 (5.23-186.63)	2.49 (0.45-75.43)	0.00
28	2.93 (49.00-24.46)	0.67 (0.26-19.01)	0.05	6.30 (0.38-141.30)	1.49 (0.34-39.20)	0.07
100	1.32 (49.00-14.36)	0.70 (0.27-9.15)	0.45	0.38 (0.30-929.95)	0.61 (0.23-180.65)	1.00

<sup>1</sup>Values presented are the medians of log<sub>2</sub> EASIX scores, with the ranges in parentheses.

EASIX, Endothelial Activation and Stress Index; HCT, hematopoietic cell transplant; SOS, sinusoidal obstruction syndrome; TMA, thrombotic microangiopathy.

TABLE 3 Univariate analysis of log<sub>2</sub>-EASIX.

Univariate analysis of SOS/TMA			
Day 21	Parameter	Category	P-value
	EASIX		0.03
	Age at HCT		0.66
	Conditioning regimen (ref=MAC)	RIC	0.14
	Donor type (ref=MMRD)	MSD	0.54
		MUD	0.55

CI, confidence interval; HCT, hematopoietic cell transplantation; MAC, myeloablative conditioning; MMRD, mismatched-related donor; MSD, matched-sibling donor; MUD, matched-unrelated donor; OR odds risk; RIC, reduced-intensity conditioning; SOS, sinusoidal obstruction syndrome; TMA, thrombotic microangiopathy.

risk for future complications. Accordingly, the at-risk populations included 31 patients (6 future cases, 25 controls) at Day 7, 28 patients (3 future cases, 25 controls) at Day 14, and 27 patients (2 future cases, 25 controls) at Day 21.

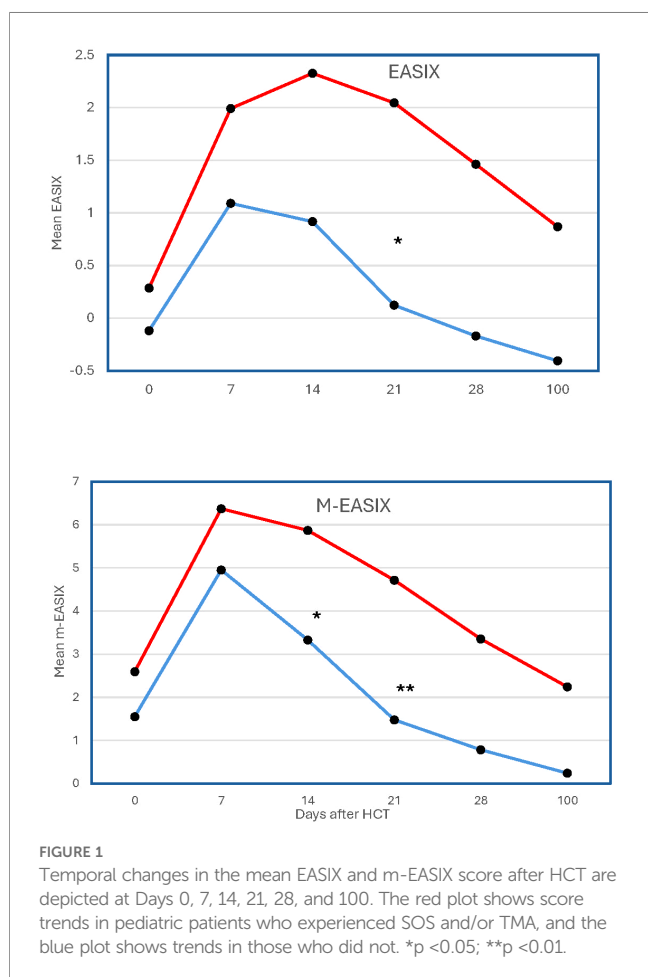
We performed ROC analysis to evaluate the discriminative ability of single-time-point (static) EASIX and m-EASIX scores to distinguish patients who subsequently experienced SOS and/or TMA from those who did not. The AUC values and their 95%

CI, which were calculated via bootstrap resampling to account for sample-size limitations, are presented in Table 5. Both scores demonstrated the strongest predictive ability at Day 21. The EASIX achieved its peak discrimination at this time point (AUC 0.807, 95% CI: 0.520-1.000), and the m-EASIX also performed well (AUC 0.865, 95% CI: 0.591-1.000). Predictive accuracy at earlier time points (Days 7 and 14) was moderate for both scores.

For clinical application, optimal cut-off points for EASIX and m-EASIX on Day 21 were identified using three methods: the Youden index, the point closest to (0,1) on the ROC curve, and a high-sensitivity ( $\geq 90\%$ ) criterion. Notably, all three methods identified the same threshold for each score, indicating robust cut-off points. For EASIX, the optimal threshold was 0.452 (sensitivity 1.00, specificity 0.67) (Figure 2A); for m-EASIX, the threshold was 2.197 (sensitivity 1.00, specificity 0.73) (Figure 2B).

### 3.4 Dynamic changes in EASIX and m-EASIX

We investigated whether the fold-change in biomarker levels ( $\Delta \log_2$ ) over time provided greater predictive accuracy than single-timepoint measurements. The AUC values for predicting future endothelial complications based on changes in EASIX and m-EASIX scores from baseline (Day 0) are summarized in Table 6. The fold-change from Day 0 to Day 21 ( $\Delta D21 - D0$ ) yielded the highest discrimination for both biomarkers. An increase in EASIX from baseline to Day 21 ( $\Delta EASIX D21 - D0$ ) was a strong predictor, with an AUC of 0.761; the corresponding rise in m-EASIX ( $\Delta m-EASIX D21 - D0$ ) was comparable (AUC 0.764). For the most predictive dynamic measure ( $\Delta D21 - D0$ ), the Youden index, the point closest to (0,1) on the ROC curve, and the high-sensitivity method identified the same optimal threshold for each composite score. For  $\Delta EASIX (D21 - D0)$ , the threshold was 0.170 (sensitivity 1.00, specificity 0.54) (Figure 2C); for  $\Delta m-EASIX (D21 - D0)$ , the threshold was -0.211 (sensitivity 1.00, specificity 0.50) (Figure 2D).



## 4 Discussion

This prospective study demonstrates that both EASIX and m-EASIX scores may serve as valuable indicators of endothelial stress and help identify patients at risk for sinusoidal obstruction syndrome (SOS) and transplant-associated thrombotic microangiopathy (TMA) after hematopoietic cell transplantation (HCT) in a single-center cohort. This work contributes to the expanding literature on endothelial biomarkers in pediatric HCT by prospectively evaluating these indices and introducing the modified EASIX (m-EASIX) score in this population. To date, this is the first study to examine m-EASIX's potential to predict SOS and TMA in children. Incorporating C-reactive protein (CRP) as a marker of inflammation, m-EASIX demonstrated encouraging discriminative performance (AUC 0.865 at Day 21) and slightly outperformed the classic EASIX score, possibly reflecting its ability to capture inflammatory endothelial stress. In addition to single-

TABLE 4 Univariate analysis of log<sub>2</sub> m-EASIX.

Univariate analysis of SOS/TMA			
Parameter	Category	OR (95% CI)	P-value
<b>Day 21</b>			
m-EASIX		1.84 (1.09-3.11)	0.02
Age at HCT		0.97 (0.83-1.13)	0.66
Conditioning regimen (ref=MAC)	RIC	0.24 (0.03-1.63)	0.14
Donor type (ref=MMRD)	MSD	2.33 (0.16-34.89)	0.54
	MUD	1.87 (0.24-14.65)	0.55
<b>Day 28</b>			
m-EASIX		1.63 (0.99-2.68)	0.05
Age at HCT		0.96 (0.82-1.11)	0.56
Conditioning regimen (ref=MAC)	RIC	0.33 (0.05-2.13)	0.25
Donor type (ref=MMRD)	MSD	1.63 (0.11-22.98)	0.72
	MUD	1.30 (0.18-9.47)	0.80

CI, confidence interval; HCT, hematopoietic cell transplant; MAC, myeloablative conditioning; MMRD, mismatched-related donor; MSD, matched-sibling donor; MUD, matched-unrelated donor; OR, odds risk; RIC, reduced-intensity conditioning; SOS, sinusoidal obstruction syndrome; TMA, thrombotic microangiopathy; MAC, myeloablative conditioning.

time-point measurements, dynamic changes in EASIX and m-EASIX relative to baseline also showed promising predictive value at Day 21. Notably, m-EASIX was elevated as early as Day 14, suggesting it may provide an earlier signal of endothelial injury than EASIX. These preliminary findings support further investigation into the utility of m-EASIX for risk stratification and monitoring in pediatric HCT. Given that SOS and TMA are biologically distinct entities, differences in biomarker kinetics are plausible. Low event rates necessitated the use of a composite endpoint, and larger studies are required to clarify whether these scores behave differently in SOS versus TMA.

These observations align with prior research. Muratore et al. reported that, in a cohort of 167 children after allogeneic HCT, the EASIX score at Day 7 was an independent predictor of SOS and nonrelapse mortality (17). In a multicenter study of 150 adults

undergoing allogeneic HCT with myeloablative conditioning, circulating endothelial cell counts greater than 17/ml were associated with increased SOS risk (18). Baseline EASIX scores did not differ between groups, but elevated scores at engraftment correlated with SOS development (odds ratio 1.06, 95% CI: 1.03–1.11,  $p = 0.001$ ). No relationship was observed between circulating endothelial cell levels and EASIX scores, suggesting that each has a marker for independent predictive value. Jiang et al. found that higher EASIX values on the day of transplant were associated with increased SOS/VOD incidence in both training and validation cohorts of adult patients, with odds ratios per log<sub>2</sub> increase of 1.31 (95% CI: 1.08–1.59,  $p = 0.0067$ ) and 1.57 (95% CI: 1.26–2.01,  $p = 0.0001$ ), respectively (19). Additionally, Luft et al. noted that higher pretransplant EASIX scores correlated with increased TMA incidence and worse outcomes in univariate analysis, though these

TABLE 5 Predictive performance of static EASIX and m-EASIX scores.

Predictor	Landmark timepoint (day)	At-risk set (cases/controls)	AUC	Bootstrap 95% CI
EASIX	7	6/25	0.682	0.381-0.954
	14	3/25	0.674	0.453-0.885
	21	2/25	0.807	0.520-1.000
m-EASIX	7	6/25	0.686	0.377-0.908
	14	3/25	0.684	0.427-0.933
	21	2/25	0.865	0.591-1.000
$\Delta$ EASIX	D21-D0	2/25	0.761	0.376-1.000
$\Delta$ m-EASIX	D21-D0	2/25	0.764	0.379-1.000

AUC, area under the curve; CI, confidence interval.

TABLE 6 Predictive performance of dynamic EASIX and m-EASIX changes from baseline.

Predictor	Interval	Prediction	Landmark AUC	Bootstrap 95% CI
$\Delta$ EASIX	D7–D0	D7	0.627	0.381–0.893
	D14–D0	D14	0.707	0.469–0.960
	D21–D0	D21	0.761	0.376–1.000
$\Delta$ m-EASIX	D7–D0	D7	0.578	0.422–0.759
	D14–D0	D14	0.748	0.385–1.000
	D21–D0	D21	0.764	0.379–1.000

AUC, area under the curve; CI, confidence interval; D, days after hematopoietic cell transplantation.

associations did not persist in multivariate models (20). Collectively, these studies and the present findings highlight the potential role of EASIX-based biomarkers in identifying patients at risk for serious endothelial complications following HCT. However, variability in timing and predictive strength across studies underscores the need for further research to define optimal assessment windows.

A notable observation was the lack of significant differences in EASIX and m-EASIX scores at baseline, suggesting similar initial endothelial stress across patients. Over time, however, persistent elevation of these scores distinguished those who developed complications, indicating that failure to resolve early endothelial

injury may be more predictive than the initial insult. The data also suggest that m-EASIX, which substitutes CRP for creatinine, may offer modestly improved accuracy at Day 21, likely due to its inclusion of an inflammatory marker. Both single-point and dynamic changes at Day 21 yielded thresholds with high sensitivity, which could help identify patients requiring closer monitoring or early intervention.

In clinical practice, incorporating EASIX and m-EASIX scores into routine post-HCT monitoring appears feasible and cost-effective, as these indices rely on standard laboratory tests. Scores exceeding established thresholds by Day 21 should prompt clinicians to consider proactive measures, such as optimizing fluid balance,

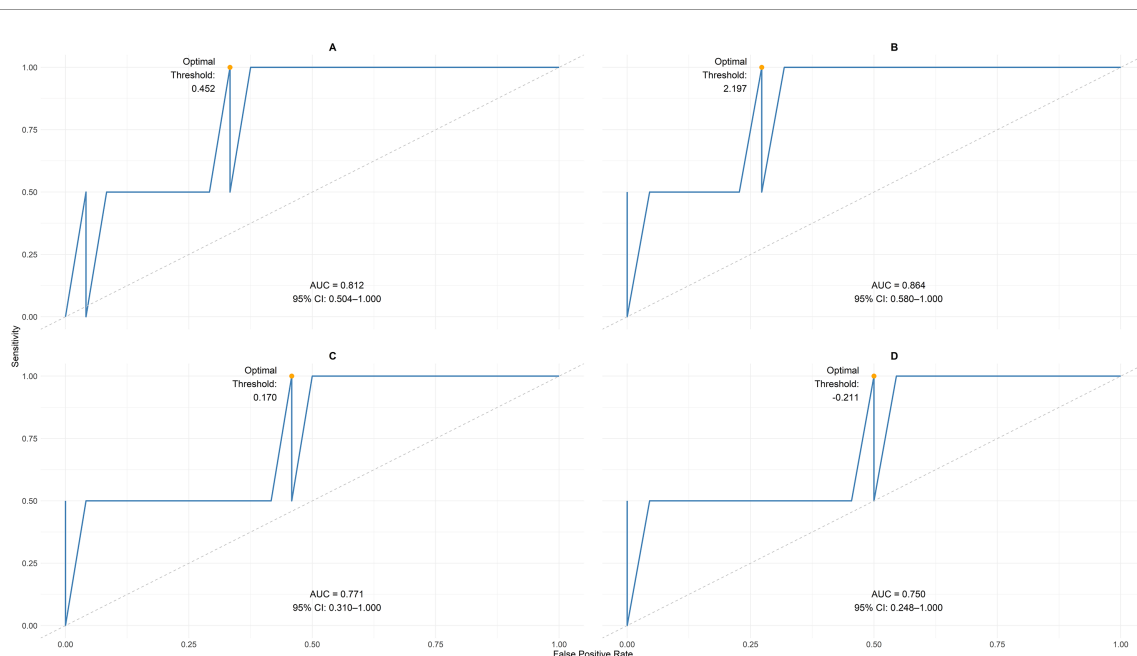


FIGURE 2

(A) The ROC curve derived from the statistic EASIX scores shows the predictive performance of the  $\log_2$ (EASIX) score on Day 21. The model achieved an AUC of 0.812 (95% CI: 0.504–1.000), indicating good discrimination. The optimal threshold (0.542) represents the best balance between sensitivity and specificity. (B) The ROC curve derived from the statistic modified-EASIX scores shows the predictive performance of the  $\log_2$ (m-EASIX) score on Day 21 post-HCT. The model achieved an AUC of 0.864 (95% CI, 0.580–1.00), indicating good discrimination. The optimal threshold (2.197) represents the best balance between sensitivity and specificity. (C) The ROC curve derived from dynamic EASIX scores shows the predictive performance of the  $\log_2$ (EASIX) score from baseline (Day 0) through Day 21 post-HCT. The model achieved an AUC of 0.771 (95% CI, 0.310–1.00), indicating good discrimination. The optimal threshold (0.170) represents the best balance between sensitivity and specificity. (D) The ROC curve derived from the dynamic m-EASIX scores shows the predictive performance of the  $\log_2$ (m-EASIX) score from baseline (Day 0) through day 21 post-HCT. The model achieved an AUC of 0.750 (95% CI, 0.248–1.00), indicating good discrimination. The optimal threshold (-0.211) represents the best balance between sensitivity and specificity.

adjusting immunosuppression, enhancing infection surveillance, or initiating targeted therapies, including defibrotide or complement inhibitors. These biomarkers may also serve as objective tools for risk stratification in clinical trials evaluating preventive or preemptive strategies. We acknowledge that the Day 21 landmark is most relevant for identifying patients at risk of later-onset or persistent endothelial injury, a clinically significant concern.

While this study provides novel insights, several limitations warrant caution. The small number of events and single-center design limit generalizability, and the proposed thresholds should be considered exploratory. The heterogeneous cohort, which included both malignant and non-malignant indications and varied conditioning regimens, may also influence applicability to other settings. However, our findings may be especially relevant in populations where RIC and alternative donors are commonly used. Future multicenter studies with larger, more uniform populations are needed to validate these findings and explore associations with other post-HCT complications, such as graft-versus-host disease.

## 5 Conclusion

In summary, EASIX and m-EASIX scores show promise as practical, dynamic biomarkers for early detection of endothelial stress in pediatric HCT recipients. Identification of a potential predictive window at Day 21 and establishment of preliminary thresholds may support a more personalized approach to post-transplant care. Early recognition and intervention could help reduce ICU admissions and improve outcomes, but further validation is essential before these strategies can be widely implemented.

## Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

## Ethics statement

The studies involving humans were approved by St. Jude Children's Research Hospital Internal Review Board. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation in this study was provided by the participants' legal guardians/next of kin.

## Author contributions

SG: Writing – review & editing, Validation, Investigation, Conceptualization, Supervision, Methodology, Formal analysis, Writing

– original draft. JM: Data curation, Conceptualization, Writing – review & editing. KU: Data curation, Conceptualization, Writing – review & editing. YA: Writing – review & editing. CH: Writing – review & editing. HP: Writing – review & editing. LE: Writing – original draft, Writing – review & editing.

## Funding

The author(s) declared that financial support was not received for this work and/or its publication.

## Acknowledgments

Angela McArthur, Scientific Editing Committee – St. Jude Children's Research Hospital.

## Conflict of interest

The author(s) declared that this work was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The authors LE, HP, JM declared that they were an editorial board member of *Frontiers*, at the time of submission. This had no impact on the peer review process and the final decision.

## Generative AI statement

The author(s) declare that Generative AI was used in the creation of this manuscript. An artificial intelligence (AI) tool was used to assist in language editing for some portions of the text. The authors reviewed, verified, and are fully responsible for all content. No AI tool was involved in data analysis, interpretation of results, content generation, or decision-making regarding the scientific conclusions.

Any alternative text (alt text) provided alongside figures in this article has been generated by *Frontiers* with the support of artificial intelligence and reasonable efforts have been made to ensure accuracy, including review by the authors wherever possible. If you identify any issues, please contact us.

## Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

## References

- Pagliuca S, Michonneau D, Sicre de Fontbrune F, Sutra Del Galy A, Xhaard A, Robin M, et al. Allogeneic reactivity-mediated endothelial cell complications after HSCT: a plea for consensual definitions. *Blood Adv.* (2019) 3:2424–35. doi: 10.1182/bloodadvances.2019000143
- Leimi L, Jahnukainen K, Olkinuora H, Meri S, Vetteranta K. Early vascular toxicity after pediatric allogeneic hematopoietic stem cell transplantation. *Bone Marrow Transpl.* (2022) 57:705–11. doi: 10.1038/s41409-022-01607-8
- Vythoulkas D, Tsigotis P, Griniezaki M, Konstantellos I, Lazana I. Endothelial dysfunction syndromes after allogeneic stem cell transplantation. *Cancers (Basel).* (2023) 15:680. doi: 10.3390/cancers15030680
- Schoettler ML, Lehmann L, Kao PC, Chen N, Jodele S, Chonat S, et al. Pediatric transplant-associated thrombotic microangiopathy health care utilization and implications of eculizumab therapy. *Blood Adv.* (2024) 8:1220–33. doi: 10.1182/bloodadvances.2023011078
- Corbacioglu S, Carreras E, Ansari M, Balduzzi A, Cesaro S, Dalle JH, 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. doi: 10.1038/bmt.2017.161
- Mohty M, Battista ML, Blaise D, Calore E, Cesaro S, Maximova N, et al. A multicentre, multinational, prospective, observational registry study of defibrotide in patients diagnosed with veno-occlusive disease/sinusoidal obstruction syndrome after haematopoietic cell transplantation: an EBMT study. *Bone Marrow Transpl.* (2021) 56:2454–63. doi: 10.1038/s41409-021-01265-2
- Higham CS, Collins G, Shimano KA, Melton A, Kharbanda S, Winestone LE, et al. Transplant-associated thrombotic microangiopathy in pediatric patients: pre-HSCT risk stratification and prophylaxis. *Blood Adv.* (2021) 5:2106–14. doi: 10.1182/bloodadvances.2020003988
- Kafa K, Hoell JI. Transplant-associated thrombotic microangiopathy in pediatrics: incidence, risk factors, therapeutic options, and outcome based on data from a single center. *Front Oncol.* (2024) 14:1399696. doi: 10.3389/fonc.2024.1399696
- Penack O, Luft T, Peczynski C, Benner A, Sica S, Arat M, et al. Endothelial Activation and Stress Index (EASIX) to predict mortality after allogeneic stem cell transplantation: a prospective study. *J Immunother Cancer.* (2024) 12:e007635. doi: 10.1136/jitc-2023-007635
- Elbahlwan L, Khiami M, Blackshear C, Ghafoor S, Schaller A, Johnson S, et al. Unraveling the Easix score: its association with vasopressor need in critically ill septic pediatric hematology-oncology patients. *J Clin Med.* (2025) 14:7105. doi: 10.3390/jcm14197105
- Yegin ZA, Savaş EM, Yıldız Ş, Kök M, Erdemir MB, Bostankolu Değirmenci B, et al. Preconditioning Modified-Easix as a predictor of prognosis in allogeneic hematopoietic stem cell transplant recipients. *Indian J Hematol Blood Transfus.* (2023) 39:586–97. doi: 10.1007/s12288-022-01623-0
- 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. doi: 10.1182/bloodadvances.2022007381
- Schoettler ML, Carreras E, Cho B, Dandoy CE, Ho VT, Jodele S, et al. Harmonizing definitions for diagnostic criteria and prognostic assessment of transplantation-associated thrombotic microangiopathy: a report on behalf of the European Society for Blood and Marrow Transplantation, American Society for Transplantation and Cellular Therapy, Asia-Pacific Blood and Marrow Transplantation Group, and Center for International Blood and Marrow Transplant Research. *Transplant Cell Ther.* (2023) 29:151–63. doi: 10.1016/j.jtct.2022.11.015
- 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–e23. doi: 10.1016/S2352-3026(17)30108-4
- Zińczuk A, Rorat M, Simon K, Jurek T. EASIX, Modified EASIX and Simplified EASIX as an early predictor for intensive care unit admission and mortality in severe COVID-19 patients. *J Pers Med.* (2022) 12:1022. doi: 10.3390/jpm12071022
- Nahm FS. Receiver operating characteristic curve: overview and practical use for clinicians. *Korean J Anesthesiol.* (2022) 75:25–36. doi: 10.4097/kja.21209
- Muratore E, Gambuti G, Leardini D, Baccelli F, Venturelli F, Larcinese L, et al. The EASIX score as a predictor of sinusoidal obstruction syndrome and nonrelapse mortality in paediatric patients receiving allogeneic haematopoietic stem cell transplantation. *Bone Marrow Transpl.* (2025) 60:346–52. doi: 10.1038/s41409-024-02489-8
- 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 allo-transplant recipients at high risk of hepatic veno-occlusive disease/sinusoidal obstruction syndrome. *Transplant Cell Ther.* (2024) 30:580. doi: 10.1016/j.jtct.2024.03.026
- 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. doi: 10.3324/haematol.2019.238790
- 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. doi: 10.1038/s41409-019-0703-1