Validation of Different Prognostic Scoring Systems to Assess the Mortality Risk in Children Received Allogeneic Hematopoietic Stem Cell Transplantation in Egypt, a Retrospective Study

Sayed HA[1], Shibl A[1], Zakaria M[1], Elhaddad A[2]

[1] Pediatric Oncology Department, South Egypt Cancer Institute, Assiut University, Assiut, Egypt
[2] Pediatric Oncology Department, National Cancer Institute, Cairo University, Cairo, Egypt

Abstract:

Background: Despite major advances in the field of hematopoietic stem cell transplantation (HSCT), life-threatening complications still occur. Quantifying the risk of toxicity for individual patients is challenging, but essential for accurate pre-HSCT counseling.

Aim: Validate 6 prognostic scoring systems for prediction of mortality risk in pediatrics post allogeneic HSCT [Hematopoietic cell transplantation comorbidity index (HCT-CI), Augmented HCT-CI, European Society for Blood and Marrow Transplantation score (EBMT), Pre-transplantation assessment of mortality score (PAM), disease risk index (DRI) and Endothelial Activation and Stress index (EASIx)].

Methods: We retrospectively analyzed 401 pediatric patients who underwent their first allogeneic HSCT in the period between January 2015 to December 2019. Patients are stratified into different risk groups according to these prognostic indices. We assessed the validation of different risk groups of these systems in predicting OS of the patients. Many patients, transplant-related risk factors and different scoring systems were studied to detect predictors of OS.

Results: 3-years Overall survival of benign group was 77%, where in malignant group was 73.2%. HCT-CI (AUC 53% & 61.8% in benign & malignant group respectively) and Augmented HCT-CI (AUC 52.3% in benign and 61.7% in malignant patients) were found to have most sensitive scores to predict 3-year OS in both disease groups. With comparing risk categories of each scoring system, we found that Augmented HCT-CI (P=0.039 & 0.03) in benign & malignant patients respectively) and EASIx (P=0.02 & 0.045 in benign and malignant groups respectively) had a significant power for prediction of 3-year OS in both disease groups where, PAM score (P=0.04) showed significance in benign group and DRI (P=0.023) in malignant group. After adjusting many patients and transplant related factors, Augmented HCT-CI showed the most significant score to predict the mortality risk in pediatrics (P=0.042).

Conclusion: Augmented HCT-CI was found to have a strong power to predict mortality risk in pediatric patients post allo-HSCT. Female gender, older age and high ferritin level pre-transplant were associated with increased mortality risk in pediatrics post allo-HSCT.

Keywords: Allogeneic hematopoietic stem cell transplantation; Prognostic scoring systems; Mortality risk.

Received: 7 March 2024
Accepted: 7 April 2024

Authors Information:

Heba Abdel-Razik Sayed
Pediatric Oncology Department, South Egypt Cancer Institute, Assiut University, Assiut, Egypt
email: Hebadina2007@aun.edu.eg

Azza Shibl
Pediatric Oncology Department, South Egypt Cancer Institute, Assiut University, Assiut, Egypt
email: azzashibl@aun.edu.eg

Mohamed Zakaria Ahmed
Pediatric Oncology Department, South Egypt Cancer Institute, Assiut University, Assiut, Egypt
email: Mohammed.zakarya.3140@gmail.com

Alaa Elhaddad
Pediatric Oncology Department, National Cancer Institute, Cairo University, Cairo, Egypt
email: alaaelhaddad@hotmail.com

Corresponding Author:
Mohamed Zakaria Ahmed
Pediatric Oncology Department, South Egypt Cancer Institute, Assiut University, Assiut, Egypt
email: Mohammed.zakarya.3140@gmail.com

Background:

Allogeneic hematopoietic stem cell transplantation (HSCT) is the treatment of choice for many pediatric diseases, from several life-threatening malignancies to non-malignant disorders such as autoimmune diseases, primary immune deficiencies, and innate metabolism errors [1]. Given the potential benefits and perils associated with allogeneic HSCT, informed risk

estimation is an integral part of candidate evaluation. The last 20 years have seen the proliferation of risk indices for the prediction of HSCT outcomes in adults. These models can be useful for patient counseling, treatment strategy optimization, and statistical analysis across cohorts [2].

Some of these models use variables of patients' health status, for example, the hematopoietic cell transplantation-comorbidity index (HCT-CI) [3] and Augmented HCT-CI [4]. Other scores focus on cancer-related variables, for example, the disease-risk index (DRI), whereas others incorporate a number of patient- and disease-specific risk variables into combined models, as the European Society for Blood and Marrow Transplantation (EBMT) and pre-transplantation assessment of mortality (PAM) risk scores [5]. Table (1).

Also, the Endothelial Activation and Stress Index (EASIx) [6], a laboratory biomarker-based formula including serum creatinine, lactate dehydrogenase, and platelet count, was developed for the prediction of survival in patients developing acute graft-versus-host disease; this score has been extended into the general prediction of mortality when measured pre-transplantation [7].

However, it has been confirmed the usefulness of these scores to predict outcomes in adults but has not been validated widely in children yet. The aim of this analysis was to determine the prognostic factors affecting OS and which of these prognostic scores accurately predict mortality risk in pediatric patients undergoing allo-HSCT. We externally validate and compare the performance of those 6 scoring systems in a contemporary cohort of transplantation patients across overall survival.

Methods:

Study design

We designed a retrospective study of 401 pediatric patients (age ≤ 18 years) underwent their first allo-HSCT at bone marrow transplantation unit of Nasser Institute Hospital for research and treatment, Cairo, Egypt, during the period between January 2015 and December 2019. The study was approved from ethical committee of South Egypt Cancer Institute, Asyut, Egypt, and the internal review board of Nasser Institute Hospital for research and treatment, Cairo, Egypt. Almost all patients received their grafts from matched related donors (MRD) and patients analyzed in two disease groups: benign and malignant.

Data collection and outcome measures

The following data were obtained by extensive review of the patients' medical records: demographic data; including patient age and sex, donor sex, disease-related data; including disease diagnosis, date of diagnosis, and transplantation-related data; including time interval from diagnosis to time of transplant, HLA (human leucocytic antigen) matching, conditioning regimen intensity, cytomegalovirus (CMV) serostatus recipient/donor, pre-transplant laboratory data as; serum albumin, ALT, creatinine, ferritin, LDH level and platelet count. Comorbidities were measured by a transplant physician using definitions provided by the HCT-CI [3].

Prognostic scores were calculated for each patient using the definitions provided in the publications of these prognostic indices: the HCT-CI [3], the Augmented HCT-CI [4], the EASIx [6], the PAM score [8], DRI [9] and the EBMT score [10]. Pulmonary function test (FEV1 and Corrected DLco values) was excluded from calculation of HCT-CI, Augmented HCT-CI and PAM score as it couldn't be performed in most of pediatric patients. So, PAM score was modified by exclusion FEV1 and DLco values points (10 points) from each category. Also, patients transplanted for benign conditions were excluded from the assessment of the DRI and EBMT scoring systems as they applicable only in malignant diseases.

The primary endpoint for this analysis was probability of overall survival (which was defined as death from any cause or lost follow up) post HCT. We analyzed the distribution of included patients (as 2 groups benign and malignant) among different risk groups of the studied scoring systems, then we assessed the validation of different risk groups of these systems in predicting OS of the patients. Many patients, transplant-related risk factors and different scoring systems were studied to detect predictors of OS.

Statistical analysis

Mean and standard deviation (Mean, SD) used to describe continuous variables. Chi-square test and fisher exact test used to compare between categorical variables where compare between continuous variables by independent t-testing. The scores were grouped into 3 to 5 levels each for estimating overall survival (OS) incidence using the Kaplan Meier and compared using the log-rank. Score discrimination was measured using the area under the receiver operating characteristic curve (AUC). Discrimination reflects the ability of a prediction model to differentiate between those who do and do not experience the studied outcome. An AUC equals 1 means a perfect discrimination (the predicted risk for individuals who developed the outcome is higher than individuals who did not experience the outcome). While, AUC of 0.5 is indicative of a random predictor, that is, a coin toss [11]. AUCs were calculated across the entire cohort for the prediction of OS incidence at 3-year time points in each of the scores independently. Univariate and Multivariable Proportionate Cox Hazard regression analysis was calculated to investigate the significant factors influencing OS (Hazard Ratio, 95% confidence interval). All analyses were performed with the IBM SPSS 26.0 software.

Table 1. Components of different HSCT scoring systems.

Score	Component	
HCT-CI	Arrhythmia	
	Cardiac (coronary artery disease, congestive heart failure, LVEF ≤50%)	
	Inflammatory bowel disease	
	Diabetes mellitus requiring treatment	
	Cerebrovascular disease	
	Hepatic (mild or moderate/severe†)	
	Obesity	
	Infection (requiring antimicrobial treatment after date of transplantation)	
	Rheumatologic disease	
	Peptic ulcer disease	
	Renal disease (serum creatinine >2 mg/dL, on dialysis or prior renal transplantation)	
	Pulmonary disease (moderate or severe‡)	
	Heart wall disease, excluding mitral prolapse	
Augmented HCT-CI	All of the above plus:	
	High ferritin level ≥ 2500 ng/dl	
	Serum albumin level < 3 mg/dl & 3-3.5 mg/dl	
	Thrombocytopenia < 100.000 x 10^3 µL	
PAM score	Age (<50, 50-60, >60 years)	
	Donor type (HLA-identical related, HLA-identical unrelated, mismatched)	
	Disease risk (low, intermediate, high)	
	Conditioning regimen	
	Renal disease (serum creatinine ≤1.2 mg/dL, >1.2 mg/dL)	
	Hepatic disease (serum ALT ≤49 U/L, >49 U/L)	
	Pulmonary disease (FEV1 >80, 70-80, <70; DLCO >80, 70-80, <70)	
	CMV serostatus between recipient and donor	
DRI	**Disease**	**Stage**
	Myeloproliferative neoplasm	Any
	Hodgkin lymphoma	CR, PR, advanced
	Indolent NHL	CR, PR, advanced
	Aggressive NHL	CR, PR, advanced
	T cell NHL	CR, PR, advanced
	Chronic lymphocytic leukemia	CR, PR, advanced
	Mantle cell lymphoma	CR, PR, advanced
	Chronic myelogenous leukemia	CP, AP, blast crisis
	Acute myelogenous leukemia	CR, advanced
	Burkitt lymphoma	CR, advanced
	Acute lymphoblastic leukemia	CR 1, CR 2, CR 3, advanced
	Myelodysplastic syndrome	Early, advanced
	Multiple myeloma	CR, VGPR/PR, advanced
EBMT score	Donor (HLA-identical sibling or matched unrelated)	
	Stage (early, intermediate, late*)	
	Age (<20, 20-40, >40 years)	
	Sex match, donor/recipient (female donor/male recipient, all others)	
	Time from diagnosis to HSCT (<12 months, >12 months)	

HSCT, hematopoietic stem cell transplantation; EBMT, European Group for Blood and Marrow Transplantation; ALT, alanine aminotransferase; AST, aspartate aminotransferase; LVEF, left ventricular ejection fraction; FEV1, forced expiratory volume in 1 second; DLCO, diffusing capacity of the lung for carbon monoxide; NHL, non-Hodgkin lymphoma; CR, complete response; PR, partial response; CP, chronic phase; AP, advanced phase; VGPR, very good partial response.

* Early disease stage includes acute leukemia in CR1; myelodysplastic syndrome (MDS), multiple myeloma (MM), NHL either untreated or in CR1; and chronic myelogenous leukemia (CML) in first chronic phase. Intermediate disease stage includes acute leukemia in CR2, CML in all other stages than chronic phase or blast crisis, MDS, MM, NHL in CR2 or PR, or stable disease. Late disease stage includes acute leukemia in all other disease stages, CML in blast crisis, and MDS, MM, and NHL in all other disease stages.

† Mild hepatic disease includes chronic hepatitis, bilirubin exceeding the upper limit of normal (>ULN) to 1.5× the ULN, and ALT/AST >ULN to 2.5× ULN. Moderate/ severe hepatic disease includes cirrhosis, bilirubin >1.5× ULN, and ALT/AST >2.5× ULN.

‡ Moderate pulmonary disease includes DLCC and/or FEV1 66% to 80% or dyspnea on slight activity. Severe pulmonary disease includes DLCO and/or FEV1 ≤66%, dyspnea at rest, and oxygen requirement.

Results:

Patients' characteristics, transplant related data and outcome

We studied 401 pediatric patients who underwent their first allo-HSCT. Most of them (75.4%) were transplanted for benign diseases (mainly hemolytic anemias, 41.1%) and the remaining (24.6%) had malignant disease (mainly AML, 29.9%). Median age of the patients at the time of transplant was 12 years for malignant group and 7 years for benign group. All patients received their grafts from MRD, except 6 only (received grafts from related donors with one locus mismatch 7/8). Myeloablative conditioning (MAC) regimen was the most commonly used regimen in both disease groups, TBI used only in 15 patients with malignant diseases. Table (2)

Regarding patients' outcome, mortality at the end of study was reported in 70 (23%) of benign and 26 (26.8%) of malignant patients. There was insignificant difference in 3-year OS between two disease categories (p=0.456) i.e., benign group 3-year OS was 77% (95% CI, 70%-84%) while malignant group 3-year OS was 73.2% (95% CI, 61%-82%). Malignant cases had shorter median survival time 37.5 ± 2.7 months than benign cases 45.4 ± 1.5 months. Figure (1)

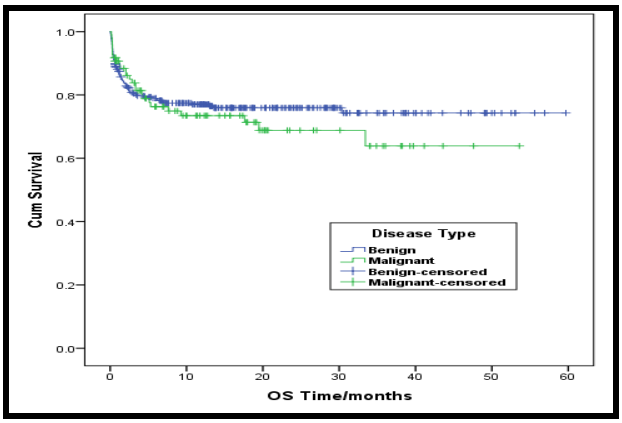

Figure 1. Effect of Disease Type on the 3-year overall survival among the studied patients.

Distribution of the studied patients among different risk groups of scoring systems:

According to HCT-CI scoring system of the patients it showed no significant difference; as most of studied patients had intermediate risk score in both benign and malignant groups (49% & 54.6% respectively), followed by low risk found in 37.5% in benign and 36.1% in malignant groups (P=0.462). While in Augmented HCT-CI; a significant difference (P=0.001) was reported among distribution of patients in both disease groups, as 56.9% & 45.4% reported to have intermediate risk, while 32.9% & 28.9% had high risk and 10.2% & 25.8% had low risk in benign and malignant group respectively.

Also, the distribution of benign and malignant patients among different risk groups of PAM & EASIx scoring systems showed significant difference (P < 0.001). While EBMT and DRI scoring systems were assessed for the malignant disease group only. Scores 1 and 3 of EBMT score were the commonest scores (represents 19.6% for each group). Intermediate DRI risk score was the commonest score (35.1%), followed by the low-risk group (20.6%) then high-risk group (17.5%). Table (3)

Assessment of validity of different scoring systems in predicting the risk of mortality in both disease groups

Benign group

Regarding the Augmented HCT-CI, we found that patients with high risk (≥ 3 score) had double risk for mortality compared to those with low-risk group (P=0.039). For PAM score, it was found that patients with intermediate risk (10-15) had 56% reduction in mortality risk compared with low-risk group (6-9) (P=0.029), where patients with high risk (16-20) had 43% less mortality risk (P=0.045). Very high-risk group (21-40) had 2.6 times increase the mortality risk (P=0.040). Although these finding was statistically significant, but clinically unreliable (except finding with very high-risk group). Also, the very high-risk group of ESIAx (> 3.76 score) found to have double risk of mortality when compared with those of low-risk group (< 0.89 score) (P=0.020). HCT-CI was invalid in predicting mortality risk in benign group based on different risk groups.

Malignant group

According to Augmented HCT-CI; it was found that patients with intermediate risk (1-2 scores) had double the mortality risk compared with low-risk group (0 score) (P=0.044), where those with high-risk group (≥ 3 score) had 3.5 times mortality risk (P=0.031). Where in using DRI to predict mortality risk; we found that patients with intermediate risk had 2.4 times mortality risk when compared with low-risk group (P=0.045). Also, patients in very high-risk group showed 3.7 times risk of mortality (P=0.023). Regarding EASIx; in comparison to low-risk group (< 0.89 score), patients with very high-risk group (≥ 3.76 score) had 2.4 times for mortality risk (P=0.045). HCT-CI, EBMT score and PAM score were invalid in predicting mortality risk in malignant group based on different risk groups. Table (4)

According to area under the receiver operating characteristic curve; HCT-CI had the highest predictability of 3-year OS, represented by the highest area under the curve in both benign (AUC=53%) and malignant (AUC=61.8%) groups. While Augmented HCT-CI was the second scoring system in predicting 3-year OS in both disease groups (AUC=52.3% in benign and AUC=61.7% in malignant groups). PAM score showed AUC=51.6% in benign group, where EASIx showed AUC= 59.8% in malignant group. Figures (2&3).

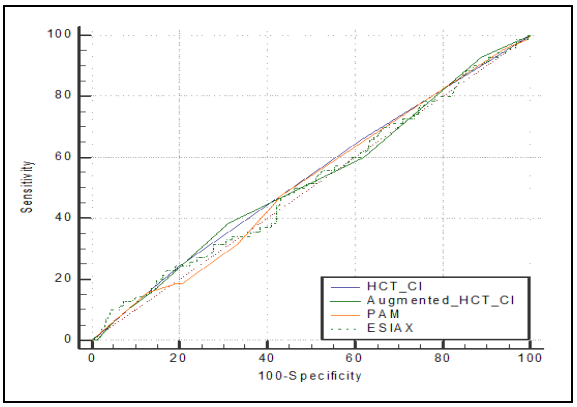

Figure 2. Sensitivity of different prognostic scoring systems on predicting 3-year overall survival of benign patients.

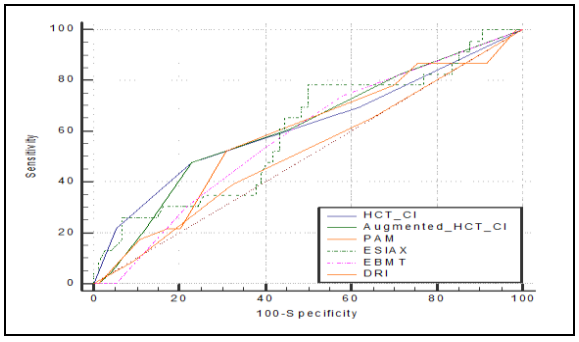

Figure 3. Sensitivity of different prognostic scoring systems on predicting 3-year overall survival of malignant patients.

Assessment of possible prognostic factors affecting OS

After studying factors affecting OS including different scoring systems, we found 4 predictors were identified (recipient sex, ferritin category, augmented HCT-CI and ESIAX Score) to affect 3-year OS in univariate analysis. It was found that male patients had 50% (p=0.017) less liability for death compared with females. Patients with higher ferritin category had 37% (p=0.010) more risk for mortality. Also, with a one-point increase in the augmented HCT-CT, there was 28% increase in risk of mortality (p=0.002). As regards EASIX score, with a one-point increase in the score, there was 22% rise in mortality risk (P=0.035). Other scores (HCT-CI, PAM, EBMT, and DRI) didn't show significant association on 3-year OS.

While with multivariate analysis, Augmented HCT-CT still had the power to predict mortality risk as one-point increase in the score was associated with 30% increase (p=0.042) in the mortality risk, while EASIx lost its significant. Also, the two other factors (sex of the patient and ferritin category) had significant effect on mortality risk. Also, the age of patients was found to affect OS, where with a one–year increase in the patient's age there was a 5% (p=0.034) increase in the chance of mortality. Table (5)

Discussion:

Use of HSCT has been expanded in last years. Increasing complexity of the procedure coupled with the effects of immunosuppression regimens required for management of complications can lead to death [12]. As a result, decision-making about referral to allogeneic HCT is a challenging task, both for physicians and patients. Therefore, there is a great need for robust tools for help physicians to identify which patients should be treated with MAC regimens, and who are best suited for RIC regimens, and patients should not be offered allogeneic HCT [5].

In this retrospective study, we tried to compare six prognostic models which used worldwide in adult age group. Score prediction performance, in terms of risk stratification and discrimination, varied considerably, both across outcome and subgroups. Most models successfully grouped patients into lower- and higher-risk strata, supporting their use for risk classification. Augmented HCT-CI, PAM score and EASIx had a significant difference in risk stratification between 2 disease groups.

Although, pre-transplant comorbidities were more common on malignant group, but we found increased incidence of thrombocytopenia (<100.000) in benign group which led to higher percent of patients categorized in low-risk group in malignant set of patients; where the platelet count is one of 3 parameters added to HCT-CI in augmented model. Also, this significant difference of platelet counts between 2 disease groups led to significant difference in higher risk groups of EASIx (where platelet count is the dominator in the equation). Higher disease risk of malignant group included in PAM score, led to increase percent of malignant patients in the very high-risk group (score 21-40) of the score. Also, the lower disease risk of benign group made a significant difference in the low-risk group (score 6-9) of the PAM score. Three-year overall survival in our study was higher in benign than malignant patients but not statistically significant, this result agreed with the Korean study, where 5-year OS was 64.1% for malignant and 73.9% for non-malignant cases [13].

The best score performance needed to approach an AUC of 0.70 on a scale of 0.50 to 1.00, which necessities caution when making individual clinical decisions based on these tools. Although, all scores didn't show significant prediction in AUC (all < 0.70) in our study, HCT-CI and Augmented HCT-CI showed the best sensitive indexes of 3-year OS in both disease groups.

Few studies reported the predictability of HCT-CI in pediatrics; Smith et al, 2011 and Turienzo et al, 2016 in their studies found that HCT-CI is a useful tool to predict survival and assess the mortality risk among children and adolescents who received allo-HCT [14&15]. However, a new Broglie et al, 2021 study showed that HCT-CI did not affect OS in children after adjusting for performance status, age, disease, donor, conditioning intensity, GVHD prophylaxis, and graft source [16]. In our study, HCT-CI didn't show significant prediction of OS after adjusting other factors, however Augmented HCT-CI kept the significance among other factors.

Table 2. Patients' characteristics, pre-transplant assessment and transplant related data.

Characteristic	Benign group 304 (75.4%)	Malignant group 97 (24.6%)
Disease Diagnosis	Anemias= 125 (41.1%) BMF= 123 (40.5%) Immune dis.= 29 (9.5%) Osteopetrosis= 15 (4.9%) IMD= 12 (3.9%)	AML= 29 (29.9%) ALL= 22 (22.7%) HLH= 19 (19.6%) CML= 10 (10.3%) Lymphoma= 6 (6.2%) MPAL= 6 (6.2%) MDS= 5 (5.2%)
Age of recipient:		
Median (range) years	7 (0.11-18)	12 (0.11-18)
Recipient gender:		
Male	186 (61.2%)	65 (67%)
Time interval from diagnosis to date of transplant:		
≤12 months	92 (30.3%)	45 (46.4%)
>12 months	212 (69.7%)	52 (53.6%)
Donor/Recipient gender:		
Female to male	101 (33.3%)	32 (33%)
HLA matching:		
Fully matched related donor	300 (98.7%)	95 (97.9%)
One locus mismatch (7/8)	4 (1.3%)	2 (2.1%)
Regimen intensity:		
MAC	176 (57.9%)	63 (65%)
RIC	124 (40.8%)	19 (19.5%)
TBI containing	0	15 (15.5%)
Dumping	4 (1.3%)	0
ALT:		
≤ 49 U/L	248 (81.6%)	73 (75.3%)
> 49 U/L	56 (18.4%)	24 (24.7%)
Creatinine:		
≤ 1.2 mg/dl	303 (99.7%)	96 (99%)
> 1.2 mg/dl	1 (0.3%)	1 (1%)
LDH elevation*:		
Normal	159 (52.3%)	60 (61.9%)
Grade 1	145 (47.7%)	37 (38.1%)
Platelets level:		
< 100.000 x 10^3 / µL	119 (39.1%)	6 (6.2%)
> 100.000 x 10^3 / µL	185 (60.9%)	91 (93.8%)
Ferritin level:		
< 2500 ng/ml	214 (70.4%)	68 (70.1%)
≥ 2500 ng/ml	90 (29.6%)	29 (29.9%)
Hypoalbuminemia:		
< 3 mg/dl	30 (9.9%)	10 (10.3%)
3-3.5 mg/dl	93 (30.7%)	26 (26.8%)
> 3.5 mg/dl	181 (59.4%)	61 (62.9%)
CMV IgG recipient/donor:		
-/-	9 (3%)	2 (2.1%)
-/+	24 (7.9%)	4 (4.1%)
+/-	20 (6.6%)	8 (8.2%)
+/+	251 (82.6%)	83 (85.6%)
Comorbidities:**		
Cardiac:		
Arrhythmia	0	1 (1%)
Cardiac dysfunction	2 (0.7%)	9 (9.3%)
Heart valvular disease	2 (0.7%)	0
Cerebrovascular disease:	1 (0.3%)	3 (3.1%)
Hepatic impairment:		
Mild	103 (33.9%)	38 (39.2%)
Moderate-severe	39 (12.8%)	5 (5.2%)
Obesity:	31 (10.2%)	9 (9.3%)
Infection:	38 (12.5%)	21 (21.6%)
Rheumatologic disease:	1 (0.3%)	1 (1%)

AML: acute myeloid leukemia, ALL: acute lymphoblastic leukemia, HLH: hemophagocytic lympho-histiocytosis, CML: chronic myeloid leukemia, MPAL: mixed phenotypic acute leukemia, MDS: myelodysplastic syndrome, BMF: bone marrow failure syndromes, IMD: inherited metabolic disorders, TBI: total body irradiation, MAC: myeloablative conditioning, RIC: reduced intensity conditioning, HLA: human leukocytic antigen, CMV: cytomegalovirus, ALT: alanine transferase, LDH: lactate dehydrogenase.
*LDH evaluated with CTCEA, version 5. ** According to HCT-CI.

Table 3. Distribution of the studied patients among different scoring systems.

	Benign (n=304)	**Malignant(n=97)**	**P. Value**
	No. %	**No. %**	
HCT_CI risk group			
0	114 (37.5%)	35 (36.1%)	0.462
1-2	149 (49.0%)	53 (54.6%)	
>=3	41 (13.5%)	9 (9.3%)	
Augmented HCT_CI risk group			
0	31 (10.2%)	25 (25.8%)	**0.001****
1-2	173 (56.9%)	44 (45.4%)	
>=3	100 (32.9%)	28 (28.9%)	
PAM score risk group			
6-9	58 (19.1%)	9 (9.3%)	**< 0.001****
10-15	76 (25%)	18 (18.6%)	
16-20	167 (54.9%)	58 (59.8%)	
21-40	3 (1%)	12 (12.4%)	
EASIX risk group			
<0.89	106 (34.9%)	41 (42.3%)	**< 0.001****
0.90-1.40	38 (12.5%)	24 (24.7%)	
1.41-3.76	58 (19.1%)	29 (29.9%)	
>3.76	102 (33.6%)	3 (3.1%)	
DRI score risk group			
low	-	20 (20.6%)	
Intermediate	-	34 (35.1%)	-
high	-	17 (17.5%)	
very high	-	6 (6.2%)	
EBMT score risk group			
0	-	17 (17.5%)	
1	-	19 (19.6%)	
2	-	18 (18.6%)	-
3	-	19 (19.6%)	
4	-	4 (4.1%)	

* Statistically significant difference ($p<0.05$)**, **** highly statistically significant difference ($p<0.01$).

HCT-CI: hematopoietic cell transplantation comorbidity index, EBMT: European Society for Blood and Marrow Transplantation, PAM: pre-transplantation assessment of mortality, DRI: disease risk index, EASIx: Endothelial Activation and Stress Index.

Table 4. Validity of different scoring systems in predicting risk of mortality based on different risk groups in each scoring system.

Variable	Benign		Malignant	
	HR (95% CI)	**P-value**	**HR (95% CI)**	**P-value**
HCT-CI Risk Category				
• **0**	Ref		Ref	
• **1-2**	1.196 (0.705 – 2.031)	= 0.507	1.888 (0.748 – 4.763)	= 0.178
• **>=3**	1.618 (0.819 – 3.193)	= 0.166	1.547 (0.312 – 7.676)	= 0.596
Augmented HCT-CI Risk Category				
• **0**	Ref		Ref	
• **1-2**	1.179 (0.460 – 3.009)	= 0.735	2.019 (1.001 – 6.090)	**= 0.044**
• **>=3**	2.039 (1.002 – 5.244)	**= 0.039**	3.467 (1.012 – 5.030)	**= 0.031**
EBMT-score Risk group				
• **0**	------	------	Ref	
• **1**	------	------	invalid	= 0.941
• **2**	------	------	invalid	= 0.941
• **3**	------	------	invalid	= 0.940
• **4**	------	------	invalid	= 0.933
PAM-score Risk group				
• **6-9**	Ref		Ref	
• **10-15**	0.460 (0.229 – 0.925)	**= 0.029**	1.047 (0.192 – 5.171)	= 0.958
• **16-20**	0.569 (0.329 – 0.986)	**= 0.045**	1.516 (0.351 – 6.567)	= 0.578
• **21-40**	2.640 (1.006 – 9.319)	**= 0.040**	1.817 (0.114 – 5.769)	= 0.823
DRI-score risk group				
• **Low**	------	------	Ref	
• **Intermediate**	------	------	2.422 (1.068 – 8.613)	**= 0.045**
• **High**	------	------	1.488 (0.333 – 6.655)	= 0.603
• **Very High**	------	------	3.676 (1.045 – 6.082)	**= 0.023**
EASIx Risk group				
• **< 0.89**	Ref		Ref	
• **0.90-1.40**	1.576 (0.659 – 3.568)	= 0.275	1.047 (0.412 – 2.660)	= 0.923
• **1.41-3.76**	1.738 (0.859 – 3.515)	= 0.124	0.735 (0.275 – 1.960)	= 0.578
• **> 3.76**	2.058 (1.112 – 3.773)	**= 0.020**	2.433 (1.008 – 7.970)	**= 0.045**

HR, Hazard Ratio; CI, Confidence Interval

Univariate and Multivariable Proportionate Cox Hazard regression analysis.

HCT-CI: hematopoietic cell transplantation comorbidity index, EBMT: European Society for Blood and Marrow Transplantation, PAM: pre-transplantation assessment of mortality, DRI: disease risk index, EASIx: Endothelial Activation and Stress Index.

Table 5. Prognostic factors affecting 3-year OS of the studied patients.

Variable	Univariate		Multivariable	
	HR (95% CI)	**P-value**	**HR (95% CI)**	**P-value**
Age/years	1.036 (0.968 – 1.109)	= 0.304	1.052 (1.004 – 1.102)	**= 0.034**
Recipient Sex (Male)	0.497 (0.280 – 0.883)	**= 0.017**	0.544 (0.339 – 0.874)	**= 0.012**
Disease Type (Malignant)	1.114 (0.446 – 2.786)	= 0.817		
Diagnosis-Transplant (> 12 m)	1.218 (0.841 – 4.227)	= 0.254		
Ferritin Category	1.373 (1.079 – 1.748)	**= 0.010**	1.483 (1.202 – 1.831)	**< 0.001**
Conditioning Regimen (MAC)	1.004 (0.819 – 1.222)	= 0.991		
HCT-CI	1.214 (0.988–1.491)	= 0.065		
Augmented HCT-CI	1.280 (1.098–1.492)	**= 0.002**	1.298 (1.110–1.628)	**= 0.042**
EBMT Score	0.882 (0.553–1.406)	= 0.598		
PAM Score	0.963 (0.912–1.016)	= 0.168		
DRI Score	1.199 (0.631–2.276)	= 0.580		
EASIx Score	1.223 (1.014–1.473)	**= 0.035**		

HR, Hazard Ratio; CI, Confidence Interval

Univariate and Multivariable Proportionate Cox Hazard regression analysis.

MAC: myeloablative conditioning, HCTI-CI: hematopoietic cell transplantation comorbidity index, EBMT: European Society for Blood and Marrow Transplantation, PAM: pre-transplantation assessment of mortality, DRI: disease risk index, EASIx: Endothelial Activation and Stress Index.

Elsawy et al found that higher augmented comorbidity/age index (where age < 40 years scored 0 and age > 40 years scored 1) scores were statistically significantly associated with lower OS, although this study was carried on recipients received alternative donors [17]. Also, Vaughn et al found with adjusted multivariate models in their study, that the augmented HCT-CI was highly significant to predict OS in their patients [4]. These studies were in scope with our results, where we found Augmented HCT-CI had a significant prediction power of OS in pediatrics.

EASIx was established by Luft and his colleagues as a predictor of individual risk of mortality after allo-HSCT, independently from clinical criteria, based on a standard laboratory biomarker panel (this study contained a pediatric cohort) [18]. Also, a study carried out by Shouval et al concluded that EASIX had comparable performance for mortality risk but no predictive value for relapse [19]. Here, we found that EASIx had a good prediction of mortality risk and prognostic for OS in univariate analysis only, especially with the highest risk group.

Although, Shouval et al found that PAM score had the greatest predictive capacity across all outcomes, it had a predictive power only with benign group in our study (in the very high-risk group only) [19]. Also, the former study agreed with our results, where DRI had a significant prediction of mortality risk in malignant patients. Although Grathwohl et al found that, EBMT score had a reasonable risk estimate of mortality [20]; we found that this score had no significance in evaluating mortality risk in malignant group of this pediatric cohort.

Older age, female gender and higher ferritin level were significant risk factors for higher mortality in our study. Also, with adjustment of many patients and transplant related data, Augmented HCT-CI was found to predict OS of both patients' groups strongly. In Chee et al study, they also found that, pre-transplant high ferritin level (>1000) was independent risk factor for higher mortality post-transplant [21]. Where in the Brazilian study, in contrast to our and the former studies they found that increasing age in years was associated with lower mortality [22].

Conclusion:

However, many adult studies found the different scoring systems had a good prediction power of mortality risk, still these scores hadn't studied hugely in pediatric age group and many scores didn't meet the risk criteria in pediatric patients. Also, due to inability to perform some investigations in pediatrics, application of many scores meet obstacles in pediatrics. Augmented HCT-CI was found to have a good predictive power of mortality risk, as many laboratory parameters incorporated in its' detection which easily performed in pediatrics. EASIx had a reasonable predictive power to assess the risk of mortality in pediatric age group. Female gender, older age and high ferritin level pre-transplant were associated with increased mortality risk in pediatrics post allo-HSCT.

List of abbreviations:

Allo-HSCT: allogeneic hematopoietic stem cell transplantation.
AUC: area under the curve.
Augmented HCT-CI: augmented hematopoietic cell transplantation comorbidity index.
CMV: cytomegalovirus.
DRI: disease risk index.
EASIx: Endothelial Activation and Stress Index.
EBMT: European Society for Blood and Marrow Transplantation score.
GVHD: graft versus host disease.
HCT-CI: hematopoietic cell transplantation comorbidity index.
MAC: myeloablative conditioning regimen.
MRD: matched related donor.
OS: overall survival.
PAM score: Pre-transplantation assessment of mortality score.

Conflict of Interest: The authors declare that they have no conflict of interest.

Authors' Contributions: All authors made substantial contributions to the conception and design of the work, acquisition, analysis, and interpretation of data.

References:

1- Kanate AS, Majhail NS, Savani BN, et al. Indications for hematopoietic cell transplantation and immune effector cell therapy: guidelines from the American Society for Transplantation and Cellular Therapy. Biol Blood Marrow Transplant. 2020 Jul;26(7):1247-1256.
2- Carreras E, Dufour C, Mohty M, et al. (eds.). The EBMT handbook: hematopoietic stem cell transplantation and cellular therapies. 7th edition. Cham (CH): Springer; 2019.
3- Sorror ML, Maris MB, Storb R, et al. Hematopoietic cell transplantation (HCT)-specific comorbidity index: a new tool for risk assessment before allogeneic HCT. Blood. 2005 Oct 15;106(8):2912-9.
4- Vaughn JE, Storer BE, Armand P, et al. Design and validation of an augmented hematopoietic cell transplantation-comorbidity index comprising pretransplant ferritin, albumin, and platelet count for prediction of outcomes after allogeneic transplantation. Biol Blood Marrow Transplant. 2015 Aug;21(8):1418-24.
5- Elsawy M, Sorror ML. Up-to-date tools for risk assessment before allogeneic hematopoietic cell transplantation. Bone Marrow Transplant. 2016 Oct;51(10):1283-1300.
6- Luft T, Benner A, Jodele S, et al. EASIX in patients with acute graft-versus-host disease: a retrospective cohort analysis. Lancet Haematol. 2017 Sep;4(9):e414-e423.
7- Luft T, Benner A, Jodele S, et al. It is Easix to predict non-relapse mortality (NRM) of allogeneic stem cell transplantation (alloSCT). Blood 2016;

128(22), 519.

8- Parimon T, Au DH, Martin PJ, et al. A risk score for mortality after allogeneic hematopoietic cell transplantation. Ann Intern Med. 2006 Mar 21;144(6):407-14.

9- Armand P, Gibson CJ, Cutler C, et al. A disease risk index for patients undergoing allogeneic stem cell transplantation. Blood. 2012 Jul 26;120(4):905-13.

10- Gratwohl A. The EBMT risk score. Bone Marrow Transplant. 2012 Jun;47(6):749-56.

11- Estey E, Gale RP. How good are we at predicting the fate of someone with acute myeloid leukaemia? Leukemia. 2017 Jun;31(6):1255-1258.

12- Thomas ED. Transplante de medula óssea: uma revisão histórica. Medicina (Ribeirão Preto) 2000; 33(3), 209-218.

13- Lee KM, Ahn WK, Han JW, et al. Acute Complications of Pediatric Allogeneic Hematopoietic Stem Cell Transplantation and Their Effects on Survival: A Single-Center Experience in Korea. Clin Pediatr Hematol Oncol 2023;30(1):11-20.

14- Smith AR, Majhail NS, MacMillan ML, et al. Hematopoietic cell transplantation comorbidity index predicts transplantation outcomes in pediatric patients. Blood. 2011 Mar 3;117(9):2728-34.

15- Figueroa Turienzo CM, Cernadas C, Roizen M, et al. Validation of the hematopoietic cell transplantation-specific comorbidity index in a retrospective cohort of children and adolescents who received an allogeneic transplantation in Argentina. Arch Argent Pediatr. 2016 Aug 1;114(4):337-42.

16- Broglie L, Ruiz J, Jin Z, et al. Limitations of applying the hematopoietic cell transplantation comorbidity index in pediatric patients receiving allogeneic hematopoietic cell transplantation. Transplant Cell Ther. 2021 Jan;27(1):74.e1-74.e9.

17- Elsawy M, Storer BE, Milano F, et al. Prognostic performance of the augmented hematopoietic cell transplantation-specific comorbidity/age index in recipients of allogeneic hematopoietic stem cell transplantation from alternative graft sources. Biol Blood Marrow Transplant. 2019 May;25(5):1045-1052.

18- Luft T, Benner A, Terzer T, et al. EASIX and mortality after allogeneic stem cell transplantation. Bone Marrow Transplant. 2020 Mar;55(3):553-561.

19- Shouval R, Fein JA, Shouval A, et al. External validation and comparison of multiple prognostic scores in allogeneic hematopoietic stem cell transplantation. Blood Adv. 2019 Jun 25;3(12):1881-1890.

20- Gratwohl A, Stern M, Brand R, et al. Risk score for outcome after allogeneic hematopoietic stem cell transplantation: a retrospective analysis. Cancer. 2009 Oct 15;115(20):4715-26.

21- Chee L, Tacey M, Lim B, et al. Pre-transplant ferritin, albumin and haemoglobin are predictive of survival outcome independent of disease risk index following allogeneic stem cell transplantation. Bone Marrow Transplant. 2017 Jun;52(6):870-877.

22- Tavares RCB, Bonfim CS, Seber A, et al. Hematopoietic cell transplantation in pediatric patients with acute leukemias or myelodysplastic syndrome using unrelated adult or umbilical cord blood donors in Brazil. Pediatr Transplant. 2020 Nov;24(7):e13789.