The Evaluation of Inflammatory Biomarkers in Predicting the Severity and Outcome of Cytokine-Release Syndrome after Haplo-identical Transplant

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Original Article

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ABSTRACT

Background: Haploidentical bone marrow transplantation is a life-saving procedure for patients with hematologic malignancies and other blood disorders. We aimed to assess the role of the Endothelial Activation and Stress Index (EASIX) formula, C-reactive protein (CRP), IL-6, and Ferritin in patients with cytokine release syndrome (CRS) in Haploidentical Transplants.

Methods: This cohort study was performed on 49 patients aged from 10 to 60 years old, both sexes, who underwent Haplo Transplant. All patients were subjected to receiving T-cell replete haploidentical stem cell transplant utilizing post-transplant cyclophosphamide platform as graft versus host disease and graft failure prophylaxis. The conditioning regimen is reduced intensity conditioning.

Results: At a cut-off point of 4.15, the specificity and sensitivity of the EASIX score in predicting the death of haploidentical bone marrow transplant (BMT) patients with CRS is 76.9 % and 60%respectively. The EASIX score, and the studied biomarkers increased significantly from baseline to day 7 of BMT ($P < 0.05$). A significant relationship between Chimerism 60 results and the patients' diagnosis was observed ($P = 0.026$). There was significant difference within CRS group between EASIX score at baseline and EASIX score at CRS onset ($P= 0.0003$), and between serial EASIX score measurements among CRS patients ($P < 0.001$).

Conclusions: EASIX score was a poor predictor of response to CRS severity and mortality in BMT patients. Also, inflammatory markers (IL-6, CRP and Ferritin) were not reliable to predict the response to CRS and mortality in BMT patients. EASIX score, IL-6, CRP and Ferritin have no association with outcome or CRS severity.

Key Words: Cytokine-release syndrome; haplo-identical transplant , inflammatory biomarkers..

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INTRODUCTION

Allogeneic Hematopoietic Stem Cell Transplantation (HSCT) is a potentially well-established treatment for many Non-Malignant and Malignant Disorders[1]. HSCT is associated with several life-threatening complications. Specifically, the Cytokine Release Syndrome (CRS) development could lead to significant morbidity and mortality[2]. Haplo-allo-HSCT is an Allo-HSCT form in which the donor only shares one Human Leukocyte Antigen (HLA) Haplotype with the recipient and is mismatched for a variable HLA genes number. Without significant measures, this significant HLA mismatch leads to early and excessive alloreactive T cells activation which results in fatal and severe GVHD[3].

CRS refers to the Immunological Phenomenon triggered by Immunotherapy for example Haploidentical Allogeneic HSCT (Haplo-allo-HSCT), Chimeric Antigen Receptor-T Cells or Bi-specific T cell Engagers[3]. After therapy, the onset and climax of CRS typically occur within the first week. These symptoms can range from moderate, flu-

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like symptoms to severe, life-threatening multiorgan failure that is the result of uncontrolled CRS. Response to Inflammation [4]. Cytokine-induced cardiac dysfunction is characterized by a swiftly progressing cardiomyopathy that exhibits clinical characteristics of stress cardiomyopathy[5]. In fulminant CRS, it is possible to observe DIC, renal failure, hepatic failure, neurologic toxicity, and cardiac dysfunction. Additionally, CRS has been documented in patients who are receiving ATG Infusion, a polyclonal antibody preparation that is derived from either horse or rabbit immunized with human thymocytes or the human Jurkat T cell leukemia cell line. CRS is a common occurrence, as are mild and severe infusion-related reactions[6]. Haploidentical transplantation employing T cell-repleted peripheral blood stem cell grafts mobilized by Granulocyte Colony-stimulating factor carries a significant risk of CRS. CRS typically manifests during the initial post-transplant days prior to the administration of Cyclophosphamide[7].

Formula for calculating the Endothelial Activation and Stress Index (EASIX) score: A marker of endothelial injury and a predictor of survival in patients with CRS following allogeneic hematopoietic cell transplant (Allo-HCT) has been identified as lactic dehydrogenase [LDH; U/L] * creatinine [mg/dL]/platelets [PLTs; 10^9 cells/L]. EASIX-assessed pre-HCT has also been demonstrated to predict substantial fluid overload after transplant and an increased risk of acute Graft-versus-host disease. Additionally, it is associated with non-relapse mortality and overall survival after allo-HCT[8].

The aim of this work was to estimate the level of EASIX formula, IL-6, Ferritin and C- reactive protein (CRP) in Patient with CRS in Haplo-identical Transplant, and to assess the discriminant power of the EASIX formula, IL-6, CRP and Ferritin in detecting the CRS and its severity in Haploidentical Transplants.

PATIENTS AND METHODS

This cohort study was conducted on 49 patients aged from 10 to 60 years old, both sexes, with clinical criteria haematological Diseases indicated for Allogeneic Peripheral Blood Stem Cell Transplantation, malignant haematological disorders should be in complete remission before proceeding to Stem Cell Transplantation, available Haploidentical Stem Cell donors with 3/6 matching in the HLA-B, HLA-C, HLA-A, HLA-DR, receiving reduced intensity conditioning (RIC), including ATG, and who underwent Haplo Transplant.

The patient or their relatives provided written consent that was informed. The study was conducted with the Ethical Committee's approval Haematology and Bone marrow Transplant Department, Armed Forces College of Medicine Ethical Review Committee from the period between January 2020 to March 2023 in accordance with Helsinki Declaration of biomedical ethics.

Exclusion criteria were patients with a contraindication to Stem Cell transplantation like End-organ Dysfunction or Disseminated cancers, with the Refractory Malignant Hematologic Disorder, with active or chronic infections, and with altered kidney functions.

All patients were subjected to Clinical and Laboratory data of the enrolled subjects who underwent Haplo HSCT, laboratory [LDH, ferritin, IL-6 and CRP level as well as PLT count at different time points early after and before infusion in recipients Haplo-HSCT) day 0, day +7 and day of CRS onset)], dates of admission, discharge, stem cell infusion and onset of CRS, full medical history and clinical examination, receiving T-cell replete haploidentical stem cell transplant using post-transplant cyclophosphamide (PTCy) platform as graft versus host disease (GVHD) and graft failure prophylaxis. The conditioning regimen is RIC.

Diagnostic Intervention:

At day 0 / day +7 of Stem Cell infusion date and the onset of CRS: Calculation of EASIX score, assay of CRP, Ferritin, IL6 & LDH, cases were followed up for the occurrence of CRS. Timing and Severity will be recorded using American Society for Transplantation and Cellular Therapy (ASTCT) grading score, and assess the Complete Response (CR) and Overall Response Rate (ORR) rates of the studied group during the period of the study

Transplant procedure:

All patients will receive RIC regimen, and GVHD prophylaxis will be composed of cyclophosphamide 50 mg/kg /day on days +3 and +4, mycophenolate mofetil (MMF) 15 mg/kg/day capped at 3 gm per day divided in three doses starting on day +5 and cyclosporine 3-5 mg/kg/day aiming at a trough serum level between 200-400 ng/mL. Both MMF and cyclosporine will be given 24 hours after the last cyclophosphamide dose.

Sample Size Calculation:

Using a two-sided z-test at a significance level of 0.050, a convenient sample of 15 from the positive group and 24 from the negative group achieves 82% power to detect a difference of 0.26 between the area under the ROC Curve (AUC) and the null hypothesis of 0.5. The data are responses that are continuous. The AUC is calculated for false positive rates ranging from 0.0 to 1.0. The ratio of the standard deviation of the responses in the negative group to the standard deviation of the responses in the positive group is 1. After adding 20% for dropout rates. the minimum required sample size will be 49 patients with 19 CRS patients.

Statistical analysis

SPSS v28 (IBM Inc., Armonk, NY, USA) was employed to conduct the statistical analysis. The mean and standard deviation (SD) of quantitative variables were presented

and contrasted between the two groups utilizing an unpaired Student's t-test. The Chi-square test or Fisher's exact test was employed to analyse qualitative variables, which were presented as frequency and percentage (%) when appropriate. The overall diagnostic performance of each test was evaluated utilizing Receiver Operating Characteristic curve (ROC) analysis. A curve that extends from the lower left corner to the upper left corner and then to the upper right corner is regarded as a faultless test. The overall test performance is assessed by the area under the curve (AUC), with an area under the curve greater than 50% indicating acceptable performance and an area at or near 100% indicating the greatest performance for the test. Statistical significance was defined as a two-tailed *P value* that was < 0.05.

RESULTS

Table 1 shows the mean age of the studied group was 35 ± 11.2. They included 36 males (73.5%), and 13 females (26.5%). Acute myelogenous leukemia (AML) was the most common diagnosis 24 (49%), AML/ALL/MDS-High risk was the most common bone marrow transplant (BMT) indication 30 (61.2%), ABO matched, and minor mismatch was in 17 (34.7%) patients, major mismatch was in 15 (30.6%), cell depletion 34 cell dose was with 4.2 ± 1.4, day of engraftment was with 23.0 ± 5.2 days, and 25 (51%) patients were alive. Regarding causes of death, acute GVHD was in 5 (21.7 %) patients, chronic GVHD was in 1 (4.3 %) patient, CRS was in 2 (8.7 %) patients, sepsis was in 8 (34.8 %) patients, pneumonia was in 3 (13 %) patients, and relapse was in 4 (17.4 %) patients.

Table (1): Baseline and clinical characteristics of the studied group (n = 49)

		Patients (n = 49)
Age (years)		35.0 ± 11.2
Sex	Male	36 (73.5%)
	Female	13 (26.5%)
Diagnosis	AML	24 (49 %)
	ALL	19 (38.8 %)
	CML	3 (6.1 %)
	MDS	2 (4.1 %)
	HL	1 (2 %)
BMT indication	AML/ALL/MDS-High risk	30 (61.2 %)
	AML/ALLCR2	15 (30.6 %)
	CML-BP	3 (6.1 %)
	HL-Early relapse post autograft	1 (2 %)
ABO status	ABO matched.	17 (34.7 %)
	Major mismatch	15 (30.6 %)
	Minor mismatch	17 (34.7 %)
CD 34 cell dose		4.2 ± 1.4
Day of engraftment (n=47)		23.0 ± 5.2
Overall survival	Alive	25 (51 %)
	Dead	23 (46.9 %)
	Lost follow up	1 (2.1 %)
Cause of death (n=23)	Acute GVHD	5 (21.7 %)
	Chronic GVHD	1 (4.3 %)
	CRS	2 (8.7 %)
	Sepsis	8 (34.8 %)
	Pneumonia	3 (13 %)
	Relapse	4 (17.4 %)

Data are presented as mean ± SD or frequency (%). AML: Acute Myeloid leukemia, ALL: acute lymphoblastic leukemia, MDS: myelodysplastic syndrome, CML: Chronic Myeloid Leukemia. HL: Hodgkin Lymphoma. CML-BP : Chronic Myeloid Leukemia-Blastic Phase. BMT: bone marrow transplant, GVHD: Graft versus host disease CRS: cytokine release syndrome, CD: cell depletion.

The EASIX score, and the studied biomarkers increased significantly from baseline to day 7 of BMT ($P < 0.05$), but there was insignificant difference between AML & ALL regarding Score and outcome of the studied group, and between CRS group and no CRS group regarding demographic and baseline clinical characteristics. the rate of good responsiveness among those treated with steroids was 10 (45.5%), and with tocilizumab in 10 (83.3%) patients. Table 2

Table (2) : Score, biomarkers, Difference between AML & ALL regarding Score and outcome of the studied group, demographic, clinical, and treatment characteristics of the CRS group and no CRS group

		On day 0	On day +7	*P value*
EASIX score		2.0 ± 0.9	3.6 ± 1.8	<0.001 *
Ferritin		477.6 ± 413.8	816.4 ± 814.3	<0.001 *
CRP (mg/dL)		26.8 ± 29.8	77.1 ± 68.5	<0.001 *
IL-6		31.8 ± 63.0	99.3 ± 161.5	0.005 *
		AML (n=24)	ALL (n=19)	
EASIX score		2.1 ± 0.8	2.0 ± 1.1	0.732
Day-100 survival	Alive	10 (41.7%)	13 (68.4 %)	0.080
	Dead	14 (58.3 %)	6 (31.6 %)	
Cause of death	Acute GVHD	4 (28.6 %)	1 (14.3 %)	0.474
	Chronic GVHD	0	1 (14.3 %)	
	CRS	1 (7.1 %)	1 (14.3 %)	
	Sepsis	6 (42.9 %)	1 (14.3 %)	
	Pneumonia	1 (7.1 %)	1 (14.3 %)	
	Relapse	2 (14.3 %)	2 (28.6 %)	
		CRS (N=22)	No CRS (N=27)	
Age (Years)		37.5 ± 12.7	32.6 ± 7	0.106
Sex	Male	18 (81.82%)	18 (66.7%)	0.3328
	Female	4 (18.18%)	9 (33.3%)	
Diagnosis	AML	10 (45.5 %)	14 (51.9%)	0.4659
	ALL	9 (40.9 %)	10 (37%)	
	CML	1 (4.5 %)	2 (7.4%)	
	MDS	2 (9 %)	-	
	HL	-	1 (3.7%)	
BMT indication	AML/ALL/MDS-High risk	15 (68.2 %)	15 (55.6%)	0.6966
	AML/ALLCR2	6 (27.3 %)	9 (33.3%)	
	CML-BP	1 (4.5 %)	2 (7.4%)	
	HL-Early relapse post autograft	-	1 (3.7%)	
ABO status	ABO matched	7 (30.4 %)	10 (37%)	0.0904
	Major mismatch	4 (21.7 %)	11 (40.7%)	
	Minor mismatch	11 (47.8 %)	6 (22.2%)	
CD 34 cell dose		4.1 ± 1.3	4.2 ± 1.4	0.423
		n=22	n=25	
Day of engraftment		23.1 ± 5.9	22.9 ± 4.7	0.44
		Good Responders	Poor Responders	
Steroids (N=22)		10 (45.5 %)	12 (54.6 %)	-
Tocilizumab 8mg/kg (N=12)		10 (83.3%)	2 (16.7 %)	-

Data are presented as mean ± SD or frequency (%). EASIX: Endothelial Activation and Stress Index, CRP: C-reactive protein, AML: Acute myelogenous leukemia, ALL: acute lymphoblastic leukemia, MDS: myelodysplastic syndrome BMT: bone marrow transplant, GVHD: Graft versus host disease CRS: cytokine release syndrome, CD: cell depletion. *: significant as P value < 0.05.

The rate of full donor Chimerism was 79.6% at Chimerism Day+30, then 71.4% at Chimerism Day+ 60, and 55.1% at Chimerism Day+ 90.

A significant relationship was indicated between Chimerism Day +60 results and the patients' diagnosis (P = 0.026), while no significant relationship was detected regarding Chimerism Day+ 30 and Day+ 90. Table 3

Table (3): Relationship between diagnosis and Chimerism Day 30 characteristics of the studied group (N=49).

Full donor Chimerism (n=39) Graft rejection (n=1)		Chimerism Day+ 30			P value
		Died (n=9)			
Diagnosis	AML	17 (43.6 %)	0	6 (66.7 %)	0.403
	ALL	17 (43.6 %)	0	2 (22.2 %)	
	CML	3 (7.7 %)	1 (100 %)	0	
	MDS	2 (5.1 %)	0	0	
	HL	0	0	1 (11.1 %)	
Chimerism Day+60					
		Full donor Chimerism (n=35)		Died (n=14)	
Diagnosis	AML	13 (37.1 %)		11 (78.6 %)	0.026*
ALL		17 (48.6 %)	2 (14.3 %)		
CML		3 (8.6 %)	0		
MDS		2 (5.7 %)	0		
HL		0	1 (7.1 %)		
Chimerism Day+90					
		Full donor Chimerism (n=27)		Died (n=22)	
Diagnosis	AML	9 (33.3 %)		15 (68.2 %)	0.070
ALL		14 (51.9 %)	5 (22.7 %)		
CML		2 (7.4 %)	1 (4.5 %)		
MDS		2 (7.4 %)	0		
HL		0	1 (4.5 %)		

Data are presented as mean ± SD or frequency (%). AML: Acute myelogenous leukemia, ALL: acute lymphoblastic leukemia, MDS: myelodysplastic syndrome. *: significant as *P value* < 0.05.

Table 4 shows a significant difference within CRS group between EASIX score at Day zero and EASIX score at CRS onset (P= 0.0003), and between serial EASIX score measurements among CRS patients (P < 0.001), the mean ferritin, CRP levels at CRS onset, and IL-6 were significantly different from their correspondent measures at Day zero, but insignificant difference between those with and without CRS regarding initial EASIX score measurements. No significant relationship was detected between 100-day survival rate and either EASIX score or other biomarkers among the CRS patients.

Table (4): Relationship between initial biomarkers and the biomarkers at occurrence of CRS (N=49), between initial EASIX score and the occurrence of CRS (N=22), and biomarkers of CRS group

		CRS (N=22)	No CRS (N=27)	P Value
EASIX score Day 0		2.1 ± 1.0	1.9 ± 0.9	0.557
EASIX score on day 7 from BMT		3.7 ± 1.8	3.5 ± 1.8	0.625
Ferritin Day 0		422.8 ± 329.6	488.05 ± 433.1	0.182
Ferritin Day 7		638.5 ± 305.1	526.8 ± 465.2	0.078
CRP Day 0 (mg/dL)		19.5 ± 14.36	33.45 ± 38.8	0.058
CRP Day 7 (mg/dL)		69.7 ± 56.4	82.3 ± 75	0.254
Il-6 Day 0		29.1 ± 40.3	32.3 ± 72.4	0.42
IL-6 Day 7		131.9 ± 193.1	80.6 ± 152.5	0.142
Serial measurements	EASIX score at Day zero	2.1 ± 1.0	-	<0.001*
	EASIX score at onset of CRS	3.6 ± 1.9	-	
	EASIX score on day 7 from BMT	3.7 ± 1.8	-	
		EASIX score at Day zero	EASIX score at CRS onset	
CRS (N=22)		2.05 ± 1.0	3.4 ± 1.9	0.0003*
		Day zero	At onset	
Ferritin		422.8 ± 239.6	852.5 ± 549.0	0.0017*
CRP (mg/dL)		19.5 ± 14.4	69.3 ± 62.5	0.0005*
IL-6		29.1 ± 40.3	181.5 ± 222.6	0.0015*
		Alive (n=11)	Dead (n=11)	
EASIX score at onset		3.5 ± 2.0	3.8 ± 1.8	0.701
Ferritin at onset		733.2 ± 381.2	952.3 ± 715.4	0.354
CRP at onset (mg/dL)		49.9 ± 34.9	92.3 ± 80.2	0.101
IL-6 at onset		239.4 ± 262.8	113.4 ± 111.3	0.172
EASIX score at day zero		2.1 ± 1.1	2.0 ± 0.99	0.45
Ferritin score at day zero		375.5±242.7	470.1 ± 405.41	0.25
CRP score at day zero (mg/dL)		19.9 ± 14.36	19.18 ± 15.07	0.46
IL-6 score at day zero		20.6 ±19.3	37.73 ± 53.6	0.19

Data are presented as mean ± SD. EASIX: Endothelial Activation and Stress Index, BMT: bone marrow transplant, CRS: cytokine release syndrome, CRP: C- reactive protein. *: significant as P value < 0.05

Insignificant relationship was observed between the CRS severity and EASIX score or other biomarkers. Table 5

Table (5): Relationship between CRS severity and score and biomarkers of the CRS group (n=22)

	1 (n=٢)	2 (n=1٢)	3 (n=٧)	4 (n=1)	P value
EASIX Day 0	2.26 ± 0.75	2.26 ± 1.11	1.55 ± 1.03	1.98 ± 0.0	0.5690
EASIX score at onset	3.9 ± 2.8	3.6 ± 1.8	3.3 ± 2.0	6.0 ±0.0	0.630
Ferritin Day 0	426 ± 282.89	448.91 ± 37.92	361.16 ± 319.12	470 ± 0.0	0.959
Ferritin at onset	825.3 ± 585.2	718.9 ± 376.7	972.2 ± 851.6	1400 ± 0.0	0.599
CRP Day 0 (mg/dL)	24 ± 13.89	15.25 ± 13.94	27.5 ± 14.52	10 ± 0.0	0.251
CRP at onset (mg/dL)	48.3 ± 37.3	61.2 ± 58.2	73.6 ± 66.9	190 ± 0.0	0.218
IL-6 Day 0	23 ± 23.89	31.583 ± 52.02	32.33 ± 20.39	0.0 ± 0.0	0.7779
IL-6 at onset	121.3 ± 124.5	201.1 ± 255.4	205.3 ± 187.8	36 ± 0.0	0.855

Data are presented as mean ± SD. EASIX: Endothelial Activation and Stress Index, CRP: C-reactive protein

At a cut-off point of 4.15, the specificity and sensitivity of the EASIX score in predicting the death of haploidentical BMT patients with CRS is 76.9 % and 60%respectively. Figure 1

Q2

with and without CRS regarding initial EASIX score measurements. No significant relationship was detected between 100-day survival rate and either EASIX score or other biomarkers among the CRS patients.

DISCUSSION

The number of people who may get life-saving blood or marrow transplantation (BMT) from related Haploidentical donors has increased. Before advances in GVHD prevention, such as high-dose Post transplantation Cyclophosphamide PTCy, Haplo-identical Bone marrow transplant was not possible due to high graft rejection and GVHD rates. Quiescent T cells, and notably memory T cells, are somewhat resistant to PTCy due to their production of aldehyde dehydrogenase early after BMT, but proliferating alloreactive T cells are particularly vulnerable to PTCy at this time. Results from Haplo-BMT with PTCy are becoming closer to those with matched donors, and there may be less GVHD than with standard GVHD prevention techniques, according to several major registry studies[9].

In our study, we found that CRS was common among 44.9% of patients subjected to bone marrow transplantation. Among them, the prevalence of severe CRS (grade 3 – 4) was 14.28% of included patients (7 patients). This was consistent with what was reported by Imus et al.,[12] who retrospectively studied the medical records of 146 patients subjected to Haplo peripheral blood transplantation. They reported that CRS had occurred among most included patients but was of mild degree with a prevalence of 89% of included patients. On the other hand, severe form of CRS (CRS grade 3 – 4) was reported among 17% of included patients.

Our results were also consistent with what was indicated by Abid et al. who retrospectively studied the incidence of fever represented as CRS syndrome following Haploidentical cell transplantation among 78 patients in the duration between 2012 and 2018. They reported that CRS was common among patients following the procedure. However, it was a mild form among 71% of included patients. While it was severe among 9 included patients with a cumulative prevalence of 90% of included patients[13].

On the other hand, our results were slightly higher than what was reported by Otoukesh et al.[14] reported that severe CRS was prevalent among 5% of included patients; grade 3 occurred among 3% of included patients., while grade 4 occurred among 2% of included patients. They also reported that a mild form of CRS occurred among 89% of included patients with grade 1 being prevalent among 49% of included patients and grade 2 being prevalent among 39% of included patients. This difference may be related to the difference in sociodemographic characteristics of included patients in both studies.

In our study, we found that the mean EASIX score was higher among patients who suffered from post-transplantation CRS compared to the control group (2.1 ± 1.0 vs 1.9 ± 0.9). in addition, in following up on EASIX scores among patients who developed CRS, we found there was a significant increase in mean EASIX scores from Day zero to the onset of CRS 2.1 ± 1.0 to 3.6 ± 1.9.

In addition, we used the EASIX for trying to predict the mortality among patients who developed CRS post bone marrow transplantation and found that with a cutoff point of 4.15, EASIX showed a sensitivity of 60% and specificity of 67.9% in early prediction of mortality among those patients.

Similarly, Kulkarni et al.[15] studied the predictive role of EASIX scores for determining the success rates of peripheral blood stem cell transplantation among cases suffering from thalassemia major in order not to experience GVHD. They recruited 281 patients with thalassemia major who underwent HSCT between January 2012 and December 2019. They measured the mean EASIX scores before starting the procedure. They reported higher mean EASIX scores among patients with high 100-day postoperative mortality rates when compared to others (1.09 versus.75; P =.008). In addition, they mentioned that a cutoff point of 4.85 achieved a specificity of 62% and a sensitivity of 70.4% in the early prediction of 100–a 100-day mortality rate.

In addition, we studied the role of other laboratory markers; Ferritin, CRP, and Interleukin 6 in the development of CRS among patients subjected to bone marrow transplantation and found that there was an increase in the mean levels of the three markers after the development of CRS (p0.0017, *P*: 0.005, *P*: 0.015) respectively.

Regarding ferritin, it is known that Iron overload negatively affects HSCT results in thalassemia cases. However, it is less clear what effect iron overload plays in the context of Haploidentical Bone marrow transplant for patients without thalassemia[16].

In our study, we found that the mean ferritin serum levels on Day zero were 422.8 ± 239.6 mg/dl. There has been a significant increase in its mean serum levels to reach 852.5 ± 549.0 on development of CRS. This was statistically significant (p = 0.0017). In addition, we assessed the association between serum ferritin levels and mortality among cases subjected to bone marrow transplant and found that ferritin serum levels were higher among patients who died compared to the survivals (470.1 ± 405.41 vs

375.5 ± 242.7) respectively. However, this difference was no significant (p = 0.250).

Our results match what was reported by Teachey et al,[17] who studied the predictive value of inflammatory markers on CRS among those treated with Antigen receptor T cells for acute lymphoblastic leukemia. They reported a significant increase in the median serum levels of ferritin among those with severe CRS when compared to others (130,000 (11,200 – 299,000) vs 8,290 (280 – 411,936) ng/dl respectively.

In our study, we found that there has been a significant elevation in the mean serum levels of CRP among patients after the onset of CRS when compared to Day zero (69.3 ± 62.5 vs 19.5 ± 14.4) respectively. This was statistically significant (p:0.0005). In addition, we assessed the relationship between CRP serum levels and mortality among patients and found that CRP serum levels were elevated among those who died.

Our results were consistent with what was indicated by Li et al. who studied the relation between the inflammatory markers and CRS among children diagnosed with refractory acute B lymphocytic leukemia. They reported mean CRP levels to be high among patients with severe CRS degrees (grade 3 – 5) when compared to those with milder forms (Li & Li, 2021).

In our study, we found a significant increase in IL-6 serum levels from 31.8 ± 63.0 mg/dl to 99.3 ± 161.5 mg/dl 7 days after they were diagnosed with CRS after bone marrow transplantation. This was consistent with what was detected by Abboud et al.,[18] who studied impact of IL-6 in diagnosis and prognosis of patients with severe CRS following T-cell replete peripheral blood Haploidentical Bone marrow transplant. They reported an increase in mean levels of serum IL-6 among those who developed severe CRS. In addition, they reported a critical reduction in the morbidity and mortality of patients who developed severe CRS post-bone marrow transplant.

Our results were also higher than what was reported by Abid et al.,[19] who reported the mortality rate to be high among patients with high CRS. They reported the mortality rate to be 5% among patients with grade 1, 11% among cases with grade 2, and 30% among cases with grade 3 to 5 after 21 days postoperative.

We recommend that additional comparative studies with a larger sample size and a longer follow-up period are necessary to verify our findings and identify risk factors for adverse events. These studies should include a representative sample of patients with similar age, gender, and disease severity, and will collect data using standardized tools and protocols at regular intervals. In order to accurately evaluate long-term outcomes, future studies should have a longer follow-up period, and the sample size should be sufficient to provide meaningful conclusions and control for confounding factors postoperatively. Additionally, future research should include multicenter studies to validate our findings.

Limitations: Small sample size, being a single center study, the lack for similar studies for comparison and relatively short follow up period. Also, the current study is limited by the lack of comparisons with the patients not experiencing the studied complications at the time of onset of each so, predictability of those parameters was deficiently assessed.

CONCLUSIONS

Our study showed a significance difference regarding serial EASIX score and the studied biomarkers between the cases CRS. Our study was not able to confirm prognostic accuracy of EASIX score in predicting the mortality of BMT patients with CRS

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All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by [Abdelrahman Ahmed Habashy], [Mohamed Hamed Khalaf], [Sara Elsayed Abdelghany] and [Mervat Mohammed Mattar], [George Bahig Soryal], [Mohamed Tarek Mansour]. The first draft of the manuscript was written by [Mahmoud Salah Abdelsalam] and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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