Prognostic Factors Affecting Day+100 Survival in Patients Undergoing Allogeneic Haematopoietic Stem Cell Transplantation for Acute Leukaemia - A Single Centre Experience

Awais Siddiq, Mehreen Ali Khan, Jehanzeb Ur Rehman, Yasir Abbas, Hashim Khan and Uzma Rahim

Department of Clinical Haematology, Armed Forces Bone Marrow Transplant Centre, CMH Medical Complex, Rawalpindi, Pakistan

ABSTRACT

Objective: To determine the factors affecting the first 100 days of survival in acute leukaemia patients undergoing allogeneic haematopoietic stem cell transplantation (Allo-HSCT).

Study Design: Descriptive study.

Place and Duration of the Study: Bone Marrow Transplant Centre, Rawalpindi, Pakistan, from March 2016 to February 2022.

Methodology: Patients with acute myeloid leukaemia (AML) or acute lymphoblastic leukaemia (ALL) in complete remission (CR) undergoing Allo-HSCT were included. Data were collected on patient demographics, diagnosis, remission status, pre-transplant analysis, donor compatibility, conditioning regimen, GVHD prophylaxis, engraftment times, post-transplant complications, mortality causes, and overall survival (OS) at 100 days.

Results: Among 101 transplant recipients (mean age of 24 ± 11.05 years; n = 76 males, n = 25 females), 41 had AML and 60 had ALL. Ninety patients underwent matched sibling donor (MSD)-HSCT, while 11 had haplo-identical sibling-HSCT. Patients ≤13 years had higher survival rates than older patients (94.4% *vs*. 67.5%, p = 0.03). High pre-transplant serum ferritin levels (>2500 mg/dl) predicted lower OS (48.9% *vs*. 100% in ferritin <1000 mg/dl, p <0.01). AML patients had a survival advantage over ALL patients (82.9% *vs*. 65%, p = 0.05). Early neutrophil engraftment within 14 days correlated with better survival (96.4% *vs.* 54.3%, p <0.01). Lastly, severe mucositis also adversely affected survival (60% in Grade III *vs*. 9.5% in Grade IV, p <0.01).

Conclusion: Identifying modifiable factors can improve long-term support and follow-up, enhancing the patient outcomes in underdeveloped nations.

Key Words: *Haematopoietic stem cell transplant, Day + 100 survival, Acute leukaemia, Pakistan.*

How to cite this article: Siddiq A, Khan MA, Rehman JU, Abbas Y, Khan H, Rahim U. Prognostic Factors Affecting Day+100 Survival in Patients Undergoing Allogeneic Haematopoietic Stem Cell Transplantation for Acute Leukaemia - A Single Centre Experience. *J Coll Physicians Surg Pak* 2024; **34(11)**:1287-1293.

INTRODUCTION

Acute leukaemia incidence has risen considerably during the past few years. International Agency for Research on Cancer (IARC) statistical data showed that there were 474,519 new cases globally in the year 2020 only.[1] However, the true incidence may not be derived from this subject due to the lack of statistical data and uniform healthcare services in low- middle-income countries (LMIC).[2] Allogeneic haematopoietic stem cell transplantation (Allo-HSCT) is a potentially curative treatment.

Correspondence to: Dr. Awais Siddiq, Department of Clinical Haematology, Armed Forces Bone Marrow Transplant Centre, CMH Medical Complex, Rawalpindi, Pakistan
E-mail: awaissiddiq@live.com

Received: April 22, 2024; Revised: July 20, 2024;
Accepted: October 04, 2024
DOI: https://doi.org/10.29271/jcpsp.2024.11.1287

Survival outcomes depend on several variables, i.e., disease risk category, donor compatibility, type of conditioning regimen, graft source, stem cell dose, and post-HSCT complications[3]. In developed countries, HSCT outcomes in terms of overall survival (OS) have improved over time to 86% in the first 100 days.[4]

However, developing countries still struggle with the improvements in terms of OS being challenged by the complications of not only diseases but also the complications associated with HSCT.[5] This analysis can inform evidence-based adjustments in clinical protocols, refine patient selection criteria, and optimise management strategies. Ultimately, these improvements could lead to enhanced survival rates and clinical outcomes for transplant patients in LMICs. The aim of this study was to analyse various identifiable pre- and post-transplant factors for their statistical significance on the 100-day survival outcome to identify critical predictors of transplant success.

METHODOLOGY

This descriptive study was executed at the Bone Marrow Transplant centre, in Rawalpindi, Pakistan, from March 2016 to February 2023.

Patients of acute myeloid leukaemia (AML) or acute lymphoblastic leukaemia (ALL), who were in complete remission (CR) and opted for HSCT, were included. Patients not in remission or who did not opt for HSCT after achieving CR were excluded from the study.

The Hospital's Ethical Committee and Review Board approved this study (Ref: IRB-018/AFBMTC/Approval/2022), and informed consent was acquired from all the participants, consistent with the Declaration of Helsinki. The data were obtained from hospital records online and from patients' files. Study data included patients' age, gender, diagnosis, disease risk stratification at diagnosis as per National Comprehensive Cancer Network (NCCN) criteria,[6,7] pretransplant remission status, transplant indication, donor compatibility, pre-transplant analysis as per European Society for Blood and Marrow Transplantation (EBMT) guidelines,[8] types of conditioning regimen, stem cells source and dose, type of graft *vs*. host disease (GVHD) prophylaxis, neutrophil engraftment time, post-transplant complications, treatment-related mortality (TRM), and OS at 100 days.

Table I: Demographic data of acute leukaemia cases (n = 101).

Variables		Number	Percentage (%)			Number	Percentage (%)
	Total number	101	100				
Age groups	≤13 years	18	17.8	Total nucleated cells (TNC) x 10^8/l	≤5.0	75	74.3
	>13 years	83	82.2		5.1-10.0	22	21.8
					>10.0	4	4
Patient gender	Male	76	75.2	CD34 Cells x 10^6/l	≤3.5	54	53.5
	Female	25	24.8		>3.5	47	46.5
Disease category	AML	41	40.6	GVHD prophylaxis	CSA	13	12.9
	ALL	60	59.4		CSA + MTX	82	81.2
					CSA + MMF	3	3
Risk stratification	Standard	2	1.9		CSA + MTX + MMF	3	3
	Intermediate	21	20.7				
	High	78	77.2	Neutrophil engraftment days	≤14	56	55.4
					>14	35	34.6
CR status	CR1	69	68.3		Not achieved	10	9.9
	CR2	32	31.7				
HSCT indication	Intermediate risk disease	21	20.8	Landmark achieved	Yes	73	72.3
	High risk disease	35	34.6		No	28	27.7
	Primary refractory disease	14	13.9	Febrile neutropenia	Yes	77	76.2
	Relapsed disease	31	30.7		No	24	23.8
Type of HSCT	MSD	90	89.1	Mucositis incidence	Yes	91	90
	Haplo	11	10.9		No	10	10
Gender mismatch	Yes	47	46.5	Mucositis grade	Grade I	20	19.8
	No	54	53.5		Grade II	30	29.7
Blood group mismatch	Major	10	9.9		Grade III	20	19.8
	Minor	11	10.9		Grade IV	21	20.7
	None	80	79.2	Gut toxicity	Mild	16	15.8
Pre-transplant disease status	MRD negative remission	3	3		Moderate	9	8.9
	MRD positive remission	3	3		Severe	16	15.8
	Morphological remission with an unknown MRD	95	94.1		None	60	59.4
Pre-transplant serum ferritin (ng/ml)	≤1000	7	6.9	Transaminitis	Yes	35	34.7
	Between 1001-2000	35	34.6		No	66	65.3
	Between 2001-2500	12	11.8	Haemorrhagic cystitis	Yes	16	15.8
	>2500	47	46.5		No	85	84.1
Pre-transplant HBV/HCV status	Positive	5	5	Veno-oclusive disease (VOD)	Yes	6	5.9
	Negative	96	95		No	95	94.1
Pretransplant TB status	Positive	5	5	CMV reactivation copies (IU/ml)	≤2000	5	4.9
	Negative	96	95		>2000	32	31.7
Conditioning regimen used	MAC	90	89.1		None	64	63.4
	RIC	11	10.9	Acute GVHD incidence and severity	Grade I	12	11.9
Stem cell source	Bone marrow (BM)	58	57.4		Grade II	6	5.9
	Peripheral blood (PB)	31	30.7		Grade III	8	7.9
	BM+PB	12	11.9		Grade IV	7	6.9
					None	68	68.4

**AML: Acute myeloid leukaemia; ALL: Acute lymphoblastic leukaemia; CR: Complete remission; HSCT: Haematopoietic stem cells transplant; MSD: Matched sibling donor; Haplo: Haploidentical sibling donor; MRD: Minimal residual disease; HBV: Hepatitis B virus; HCV: Hepatitis C virus; TB: Tuberculosis; MAC: Myeloablative conditioning; RIC: Reduced-intensity regimen; CSA: Ciclosporin; MTX: Methotrexate; MMF: Mycophenolate mofetil; CMV: Cytomegalovirus; GVHD: Graft vs. host disease.*

Table II: Transplant details as per type of Allo-HSCT (MSD *vs.* Haplo) (n = 101).

Variable		Matched sibling donor (MSD) n = 90 (%)	Haplo-identical sibling (Haplo) n = 11 (%)
Age groups (years)	≤13	16(17.8)	2(18.2)
	>13	74(82.2)	9(81.8)
Disease category	ALL	56(62.2)	4(36.4)
	AML	34(37.8)	7(63.6)
Disease risk stratification	Standard	2(2.2)	0
	Intermediate	18(20)	3(27.3)
	High	70(77.8)	8(72.7)
Gender mismatch	Yes	42(46.7)	5(45.5)
	No	48(53.3)	6(54.5)
Blood group mismatch	Major	9(10)	1(9.1)
	Minor	10(11.1)	1(9.1)
	None	71(78.9)	9(81.8)
Total nucleated cells (TNC) dose (x 10^8/l)	≤5.0	71(78.9)	4(36.4)
	5.1-10.0	18(20)	4(36.4)
	>10	1 (1)	3(27.3)
CD34 dose (x 10^6/l)	≤3.5	44(48.9)	10(90.9)
	>3.5	46(51.1)	1(9.1)
GVHD prophylaxis	CSA	12(13.3)	1(9.1)
	CSA + MTX	75(83.3)	7(63.6)
	CSA + MMF	1(1.1)	2(18.2)
	CSA + MTX + MMF	2(2.2)	1(9.1)
Neutrophil engraftment days	≤14	53(58.9)	3(27.3)
	>14	27(30)	8(72.7)
Febrile neutropenia	Yes	67(74.4)	10(90.9)
	No	23(25.6)	1(9.1)
Mucositis incidence and severity	No Mucositis	9(10)	1(9.1)
	Grade I	17(18.9)	3(27.3)
	Grade II	28(31.1)	2(18.2)
	Grade III	17(18.9)	3(27.3)
	Grade IV	19(21.1)	2(18.2)
Acute GVHD incidence and severity	No GVHD	61(67.8)	7(63.6)
	Grade I	11(12.2)	1(9.1)
	Grade II	5(5.6)	1(9.1)
	Grade III	6(6.7)	2(18.2)
	Grade IV	7(7.8)	0
CMV reactivation and copies (/ml)	≤2000	27(26.7)	1(9.1)
	>2000	23(25.6)	9(81.8)
	None	63(70)	1(9.1)
Haemorrhagic cystitis	Yes	13(14.4)	3(27.3)
	No	77(85.6)	8(72.7)
Veno-oclusive disease	Yes	6(6.7)	0
	No	84(93.3)	11(100)
Gut toxicity incidence and severity	Mild	15(16.7)	1(9.1)
	Moderate	7(7.8)	2(18.2)
	Severe	14(15.6)	2(18.2)
	None	54(60)	6(54.5)
Landmark achieved	Yes	64(71.1)	9(81.8)
	No	26(28.9)	2(18.2)

***AML: Acute myeloid leukaemia; ALL: Acute lymphoblastic leukaemia; CR: Complete remission; CSA: Ciclosporin; MTX: Methotrexate; MMF: Mycophenolate mofetil; CMV Cytomegalovirus; GVHD: Graft vs. host disease.*

Neutrophil engraftment was defined as achieving absolute neutrophil count (ANC) >0.5 x 10^9/l for three consecutive days.[9] Among post-transplant complications, oral mucositis was graded as per the World Health Organization (WHO) criteria,[10] and acute GVHD was diagnosed and graded according to EBMT criteria.[11] Febrile neutropenia was defined as a single oral temperature of >101°F, or a temperature of >100.4°F sustained over 1 hour, with an absolute neutrophil count (ANC) of < 0.5 x 10^9/l or an ANC that is expected to decrease to <0.5 x 10^9 over the next 48 hours.[12] Gut toxicity, haemorrhagic cystitis, and transaminitis was defined and graded as per the Common Terminology Criteria for Adverse Events (CTCAE).[13] Veno-occlusive disease (VOD) was diagnosed following the revised EBMT criteria.[14] The landmark achieved was defined as survival beyond 100 days following the initiation of the allogeneic graft infusion (DAY 0), and TRM was defined as death from any cause not attributable to disease relapse.

SPSS 25.0 was used for data analysis. Frequencies and percentages were calculated for categorical variables, whereas mean ± standard deviation was calculated for continuous variables. Survival analysis was performed using the Kaplan-Meier test, survival differences were compared with the Log-rank test, and a p-value <0.05 was considered statistically significant.

RESULTS

A total of 101 patients underwent HSCT for acute leukaemia, including 41 (40.6%) AML and 60, (59.4%), ALL cases. The mean age of patients was 24 ± 11.05 years. Ninety (89.1%) had a matched sibling donor-HSCT, whereas 11(10.8%) had

a haplo-identical sibling-HSCT. Bone marrow harvest (BMH) was the preferred choice for stem cell source for 58 (57.4%) patients, whereas 31(30.7%) patients received stem cells from peripheral blood, and 12(11.9%) received both BMH and peripheral blood stem cells (PBSC). Recipients were given a median total nucleated cell count (TNC) dose of 4.25 x 10^8/l (IQR 2.0 x 10^8/l - 13.79 x 10^8/l) and a CD34 dose of 3.5 x 10^6/l (IQR 1.15x 10^6/l - 8.70 x 10^6/l). The most common post-transplant complications were mucositis (n = 91, 90%) and febrile neutropenia (n = 77, 76.2%) (Table I and II).

Using the Kaplan-Meier test, the 100-day survival was n = 73 (72.3%), and the mean survival days were 88.2 ± 2.68 days (CI 95%: 83.01-93.53). Patients ≤13 years of age had an OS of 94.4% (17/18 patients), and OS was 67.5% (56/83 patients) in the age group >13 years (p = 0.03).

Table III: Results of statistical tests of association between day + 100 survival and study variables in acute leukaemia (n = 101).

Day + 100 Survival	Variable (n)	Survival percentage (%)	95% CI	p-value
Age categories	≤13 years (18)	94.4	86.28-104.27	**0.03**
	>13 years (83)	67.5	80.79-92.84	
Patient gender	Male (76)	73.7	83.24-94.77	0.51
	Female (25)	68.0	69.63-94.28	
Disease category	ALL (60)	65.0	76.60-91.52	**0.05**
	AML (41)	82.9	84.87-99.03	
Risk stratification	Standard (2)	100		0.71
	Intermediate (21)	71.4		
	High (78)	71.8		
Gender mismatch	Yes (47)	70.2	77.31-93.87	0.61
	No (54)	74.1	81.84-95.60	
Blood group mismatch	Major (10)	90.0	90.56-102.83	0.12
	Minor (11)	90.9	99.21-100.23	
	None (80)	67.5	77.83-90.92	
Type of Allo-HSCT	MSD (90)	71.1	80.60-92.37	0.47
	Haplo (11)	81.8	85.56-101.71	
Conditioning regimen	MAC (90)	71.1	80.60-92.37	0.47
	RIC (11)	81.8	85.56-101.71	
Neutrophil engraftment day	≤14 (56)	96.4	98.59-100.26	**<0.01**
	>14 (35)	54.3	84.00-94.79	
	Not achieved (10)	0	8.52-14.87	
Febrile neutropenia	Yes (77)	71.4	81.48-93.35	0.77
	No (24)	75.0	74.88-98.69	
Mucositis incidence and severity	Grade I (20)	100		**<0.01**
	Grade II (30)	100		
	Grade III (20)	60		
	Grade IV (21)	4.8		
	No Mucositis (10)	100		
Gut toxicity incidence and severity	Mild (16)	75.0	83.01-102.48	0.90
	Moderate (9)	77.8	65.0-104.10	
	Severe (16)	75.0	90.74-100.25	
	No (60)	70.0	76.18-91.48	
Veno-oclusive disease	Yes (6)	50	77.05-99.27	0.24
	No (95)	73.7	81.58-92.84	
Haemorrhagic cystitis	Yes (16)	81.3	86.43-100.19	0.39
	No (85)	70.6	79.95-92.30	
Pre-transplant serum ferritin (mg/dl)	≤1000 (7)	100		**<0.01**
	1001-2000 (35)	94.3		
	2001-2500 (12)	83.3		
	>2500 (47)	48.9		
Total nucleated cells dose (x 10^8/l)	≤5.0 (75)	74.7		0.17
	5.1-10.0 (22)	59.1		
	>10.0 (4)	100		
CD34 Cells dose (x 10^6/l)	≤3.5 (54)	74.1	78.30-93.62	0.75
	>3.5 (47)	70.0	81.44-96.09	
GVHD prophylaxis	CSA (13)	69.2	88.39-100.98	0.98
	CSA + MTX (82)	73.2	79.82-92.51	
	CSA + MMF (3)	66.7	54.06-110.60	
	CSA+MTX+MMF (3)	66.7	73.99-106.00	
CMV copies (IU/ml)	≤2000 (5)	4.9		0.71
	>2000 (32)	31.7		
	None (64)	63.4		
Acute GVHD incidence and severity	Grade I (12)	11.9		0.07
	Grade II (6)	5.9		
	Grade III (8)	7.9		
	Grade IV (7)	6.9		
	None (68)	68.4		

**AML: Acute myeloid leukaemia; ALL: Acute lymphoblastic leukaemia; HSCT: Haematopoietic stem cells transplant; MSD: Matched sibling donor; Haplo: Haploidentical sibling donor; MAC: Myeloablative conditioning; RIC: Reduced-intensity regimen; CSA: Ciclosporin; MTX: Methotrexate; MMF: Mycophenolate mofetil; CMV: Cytomegalovirus; GVHD: Graft vs. host disease.*

Subgroup survival analysis on disease categories showed that AML patients had an OS of 82.9% (34/41 patients) *vs*. 65% (39/60 patients) in ALL (p = 0.05). Data analysis for serum ferritin showed that pre-transplant serum ferritin levels >1000 mg/dl had adverse OS as compared to the patients with serum ferritin values ≤1000mg/dl (0/7) had 100% survival *vs*. 48.9% in patients having > 2500 mg/dl (24/47) (p <0.001). Early neutrophil engraftment ≤14 days had a better survival outcome of 96.4% (54/56) in comparison to 54.3% (19/35) in patients where neutrophil engraftment was achieved >14 days (p <0.001). The incidence and severity of mucositis also influenced survival outcomes, with 100% (10/10) survival in those with no mucositis, to 60% (12/20) in those patients with Grade III mucositis and plummeting to 9.5% (2/21) in patients having Grade IV mucositis (p <0.001 Table III).

Treatment-related mortality (TRM) was n = 28 (27.7%). Multiorgan failure secondary to septicaemia was the most frequent cause of death, i.e., n = 17 (60.7%, Figure 1).

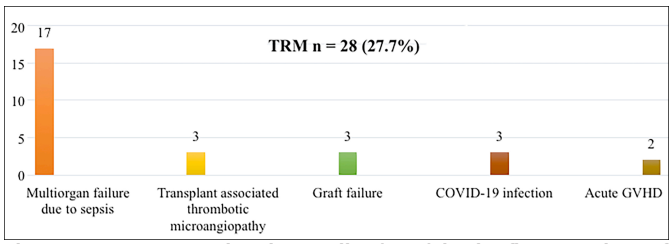

Figure 1: Treatment-related mortality (TRM) in the first 100 days of Allo-HSCT.

DISCUSSION

The first 100 days post-HSCTs are critical due to patients' vulnerability to early adverse effects stemming from both compromised immune status and conditioning-related toxicities. This analysis sought to identify individuals who reached this crucial milestone and those at heightened risk of adverse outcomes to improve resource allocation in LMIC.

This study found that age significantly impacted OS. Patients ≤13 years had a better survival rate of 94.4% than patients >13 years (p = 0.03). This aspect has been well-established in a previous study by Wood *et al*.[15]

Patients proceeding to transplants generally remain transfusion-dependent for prolonged periods, leading to iron overload. A meta-analysis done by Yan *et al.* showed that higher serum ferritin levels (cut-off level >1000 mg/dl) severely affected OS and NRM in post-transplant patients.[16] The current analysis showed that patients having serum ferritin of <1000 mg/dl had 100% survival compared to patients having serum ferritin levels higher than 2500 mg/dl i.e. 48.9% (p <0.001). The rationale behind this lies in the detrimental effects of elevated serum iron, including impaired immune function and direct organ toxicity.[17]

Disease biology was found to impact survival as those patients with AML outperformed patients with ALL in terms of OS in the first 100 days. i.e., (82.9% (34/41) *vs*. 65% (39/60) (p = 0.05). Study by Natarj *et al*. from India, showed a 100-day survival for AML to be 71.3%.[18] Although a formal 100-day analysis for ALL has yet to be conducted. Ahmed *et al.* demonstrated a 3-year OS of merely 25% in high-risk cases.[19] How disease biology contributes to these outcomes was beyond the scope of this study.

Post-transplant variables were also analysed, and achievement of neutrophil engraftment in 14 days or less was found to have a statistically significant survival outcome (96.4% *vs*. 54.3%) (p <0.001). Tecchio *et al*. have previously reported that neutrophils are among the initial cells that regenerate, making them the sole cells of the immune system during the early weeks following HSCT.[20]

Additionally, mucositis was found to be statistically significant in frequency and severity. A 100 % survival was observed in patients with mild mucositis (Grade I and II) *vs.* 60% with grade III and 9.5% with Grade IV mucositis (p <0.001). This inferior outcome can be explained by an increased susceptibility to infections (direct invasive infections) supplemented by poor nutritional health in patients.[21,22]

The frequency of acute GVHD was 33 (32.6%) and while survival analysis showed inferior outcomes for patients with Grade III and IV GVHD (7.9% and 6.9%, respectively), it was not statistically significant. Similarly, CMV reactivation occurred in 37 (36.6%) of the cohort, but its effect on survival was not statistically significant. A previous study in Pakistan by Iftikhar *et al*. in 2023, showed pretransplant CMV seropositivity in 99% of recipients and donors, while the incidence of CMV reactivation was 66.1%.[23]

The limitations of this study include its retrospective design, which may introduce selection and recall biases. Additionally, the single-centred nature of the study limits the generalisability of the findings to other settings or populations. Finally, the relatively small sample size may reduce the power to detect significant associations for some variables.

CONCLUSION

This research emphasises crucial elements that occur during the initial 100 days after HSCT, offering insights that could aid in anticipating outcomes over an extended period. While it remains challenging to pinpoint factors that can be modified to reduce hospitalisations and enhance overall survival, the study contributes additional evidence to identify patients at risk. This identification could lead to better long-term support and more vigilant follow-up for those in need.

ETHICAL APPROVAL:

Ethical approval was obtained from the Institutional Review Board of the Armed Forces Bone Marrow Transplant Centre. (REF: IRB-018/AFBMTC/Approval/2022).

PATIENTS' CONSENT:
Informed consent was obtained from the patients' parents.

COMPETING INTEREST:
The authors declared no conflict of interest.

AUTHORS' CONTRIBUTION:
AS: Data analysis, drafting of the work, and critical revision.
JR, MAK: Critical revision of the manuscript for important intellectual content.
YA, UR, HK: Data collection and analysis.
All authors approved the final version of the manuscript to be published.

REFERENCES

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, *et al*. Global Cancer Statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2021; **71(3)**: 209-49. doi: 10.3322/caac.21660.
2. Tebbi CK. Etiology of acute leukemia: A review. *Cancers* 2021; **13(9)**:2256. doi: 10.3390/cancers13092256.
3. Solh MM, Bashey A, Solomon SR, Morris LE, Zhang X, Brown S, *et al*. Long term survival among patients who are disease free at 1-year post allogeneic hematopoietic cell transplantation: A single center analysis of 389 consecutive patients. *Bone Marrow Transplant* 2018; **53(5)**:576-83. doi: 10.1038/s41409-017-0076-2.
4. Patel SS, Rybicki LA, Corrigan D, Bolwell B, Dean R, Liu H, *et al*. Prognostic factors for mortality among day +100 survivors after allogeneic hematopoietic cell transplantation. *Biol Blood Marrow Transplant* 2018; **24(5)**:1029-34. doi: 10.1016/j.bbmt.2018.01.016.
5. Faizan Zahid M, Ali N, Shaikh MU, Adil SN. Outcome of allogeneic hematopoietic stem cell transplantation in patients with hematological malignancies. *Int Hematol Oncol Stem Cell Res* 2014; **8(4)**:30-8.
6. Pollyea DA, Altman JK, Assi R, Bixby D, Fathi AT, Foran JM, *et al*. Acute myeloid leukemia, version 3.2023, NCCN clinical practice guidelines in oncology. *J Natl Compr Cancer Netw* 2023; **21(5)**:503-13. doi: 10.6004/jnccn.2023.0025.
7. Brown PA, Shah B, Advani A, Aoun P, Boyer MW, Burke PW, *et al*. Acute lymphoblastic leukemia, version 2.2021, NCCN clinical practice guidelines in oncology. *J Natl Compr Cancer Netw* 2021; **19(9**):1079-109. doi: 10.6004/jnccn.2021.0042.
8. Carreras E, Rambaldi A. Evaluation and counseling of candidates. In: Carreras E, Dufour C, Mohty M, Kroger N, Eds. The EBMT. Springer, Cham, International Publishing; 2019: p. 77-86. doi: 10.1007/978-3-030-022 78-5_11.
9. Hutt D. Engraftment, graft failure, and rejection. In: Kenyon M, Babic A, Eds. The European blood and marrow transplantation textbook for nurses. Springer International Publishing; 2018: p. 259-70. doi: 10.1007/978-3-319-500 26-3_13.
10. Chaudhry HM, Bruce AJ, Wolf RC, Litzow MR, Hogan WJ, Patnaik MS, *et al*. The incidence and severity of oral mucositis among allogeneic hematopoietic stem cell transplantation patients: A systematic review. *Biol Blood Marrow Transplant* 2016; **22(4)**:605-16. doi: 10.1016/j.bbmt.2015.09.014.
11. Holler E, Greinix H, Zeiser R. Acute graft-*versus*-host disease. In: Carreras E, Du four C, Mohty M, Kroger N, Eds. The EBMT Handbook: Hematopoietic stem cell transplantation and cellular therapies. Ed. 7th, Springer International Publishing; 2018: p. 323-30. doi: 10.1007/978-3-030-022 78-5_43.
12. Agrawal AK, Feusner J. Supportive care of patients with cancer. In: Lanzkowsky P, Lipton JM, Fish JD, Eds. Lanzkowsky's Manual of Pediatric Hematology and Oncology. Ed. 6th, Cambridge, Massachusetts; Elsevier; 2016: p.620-55. doi: 10.1016/B978-0-12-801368-7.000 33-80.
13. Common terminology criteria for adverse events (CTCAE). 2017; Available from: http://ctep.cancer.gov/protocol development/electronic_applications/docs/ctcae_v5_quick_reference_5x7.pdf.
14. Mohty M, Malard F, Alaskar AS, Aljurf M, Arat M, Bader P, *et al*. Diagnosis and severity criteria for sinusoidal obstruction syndrome/veno-occlusive disease in adult patients: A refined classification from the European society for blood and marrow transplantation (EBMT). *Bone Marrow Transplant* 2023; **58(7)**:749-54. doi: 10.1038/s41409-023-01992-8.
15. Wood WA, Lee SJ, Brazauskas R, Wang Z, Aljurf MD, Ballen KK, *et al*. Survival improvements in adolescents and young adults after myeloablative allogeneic transplantation for acute lymphoblastic Leukemia. *Biol Blood Marrow Transplant* 2014; **20(6)**:829-36. doi: 10.1016/j.bbmt.2014.02.021.
16. Yan Z, Chen X, Wang H, Chen Y, Chen L, Wu P, *et al*. Effect of pre-transplantation serum ferritin on outcomes in patients undergoing allogeneic hematopoietic stem cell transplantation: A meta-analysis. *Medicine* 2018; **97(27)**: e10310. doi: 10.1097/MD.0000000000010310.
17. Sivgin S, Baldane S, Deniz K, Zararsiz G, Kaynar L, Cetin M, *et al*. Increased hepatic iron content predicts poor survival in patients with iron overload who underwent allogeneic hematopoietic stem cell transplantation. *Clin Lymphoma Myeloma Leuk* 2016; **16**:S10-8. doi: 10.1016/j.clml.2016.02.005.
18. Nataraj KS, Prabhu S, Bhat S, Badiger S, Vasundhara PK, Annapandian VM, *et al*. Hematopoietic stem cell transplant outcomes in Patients with acute myeloid leukemia from a tertiary care center in South India. *Biol Blood Marrow Transplant* 2020; **26(3)**:S123-4. doi: 10.1016/j.bbmt.2019.12.638.
19. Ahmed U, Ahmed D, Awan MN, Ahmad U, Ahsan B, Iftikhar R, *et al*. Outcomes of Philadelphia positive acute lymphoblastic leukemia in adolescent and young adults. *Cureus* 2022; **14(12)**:e32467. doi: 10.7759/cureus.32467
20. Tecchio C, Cassatella MA. Uncovering the multifaceted roles played by neutrophils in allogeneic hematopoietic stem cell transplantation. *Cell Mol Immunol* 2021; **18(4)**:905-18. doi: 10.1038/s41423-020-00581-9.
21. Facchini L, Martino R, Ferrari A, Pinana JL, Valcarcel D, Barba P, *et al*. Degree of mucositis and duration of neutropenia are the major risk factors for early post-transplant febrile neutropenia and severe bacterial infections

after reduced-intensity conditioning. *Eur J Haematol* 2012; **88(1)**:46-51. doi: 10.1111/j.1600-0609.2011.01724.x.

22. Shetty SS, Maruthi M, Dhara V, de Arruda JAA, Abreu LG, Mesquita RA, *et al*. Oral mucositis: Current knowledge and future directions. *Dis Mon* 2022; **68(5)**:101300. doi: 10.1016/j.disamonth.2021.101300.

23. Iftikhar R, Farhan M, Khan M, Chaudhry QUN, Ghafoor T, Shahbaz N, *et al*. Cytomegalovirus infection post-allogeneic stem cell Transplantation: Experience from a country with high Seropositivity. *Transplant Cell Ther* 2023; **29(8)**: 521.e1-7. doi: 10.1016/j.jtct.2023.04.023.