

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

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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.

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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.

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 complications³. 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.

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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/AFBMT/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) × 10 ⁹ /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 × 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		Neutrophil engraftment days	≤14	56	55.4
	High	78	77.2			>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-occlusive disease (VOD)	Yes	6	5.9	
	Negative	96	95		No	95	94.1	
Pretransplant TB status	Positive	5	5	CMV reactivation	≤2000 copies (IU/ml)	5	4.9	
	Negative	96	95		>2000	32	31.7	
Conditioning regimen used	MAC	90	89.1	Acute GVHD incidence and severity	None	64	63.4	
	RIC	11	10.9		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: Cyclosporin; 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 ⁶ /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)
Haemorrhagic cystitis	None	63(70)	1(9.1)
	Yes	13(14.4)	3(27.3)
Veno-occlusive disease	No	77(85.6)	8(72.7)
	Yes	6(6.7)	0
Gut toxicity incidence and severity	No	84(93.3)	11(100)
	Mild	15(16.7)	1(9.1)
	Moderate	7(7.8)	2(18.2)
	Severe	14(15.6)	2(18.2)
Landmark achieved	None	54(60)	6(54.5)
	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) $>0.5 \times 10^9/l$ 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 $>101^\circ F$, or a temperature of $>100.4^\circ F$ sustained over 1 hour, with an absolute neutrophil count (ANC) of $< 0.5 \times 10^9/l$ or an ANC that is expected to decrease to $<0.5 \times 10^9$ 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 \pm 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 $4.25 \times 10^8/l$ (IQR $2.0 \times 10^8/l$ - $13.79 \times 10^8/l$) and a CD34 dose of $3.5 \times 10^6/l$ (IQR $1.15 \times 10^6/l$ - $8.70 \times 10^6/l$). 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		
Gender mismatch	High (78)	71.8		0.61
	Yes (47)	70.2	77.31-93.87	
Blood group mismatch	No (54)	74.1	81.84-95.60	0.12
	Major (10)	90.0	90.56-102.83	
Type of Allo-HSCT	Minor (11)	90.9	99.21-100.23	0.47
	None (80)	67.5	77.83-90.92	
Conditioning regimen	MSD (90)	71.1	80.60-92.37	0.47
	Haplo (11)	81.8	85.56-101.71	
Neutrophil engraftment day	MAC (90)	71.1	80.60-92.37	0.47
	RIC (11)	81.8	85.56-101.71	
Febrile neutropenia	≤ 14 (56)	96.4	98.59-100.26	<0.01
	>14 (35)	54.3	84.00-94.79	
Mucositis incidence and severity	Not achieved (10)	0	8.52-14.87	0.77
	Yes (77)	71.4	81.48-93.35	
Gut toxicity incidence and severity	No (24)	75.0	74.88-98.69	<0.01
	Grade I (20)	100		
	Grade II (30)	100		
	Grade III (20)	60		
Veno-occlusive disease	Grade IV (21)	4.8		0.90
	No Mucositis (10)	100		
	Mild (16)	75.0	83.01-102.48	
	Moderate (9)	77.8	65.0-104.10	
Haemorrhagic cystitis	Severe (16)	75.0	90.74-100.25	0.24
	No (60)	70.0	76.18-91.48	
Pre-transplant serum ferritin (mg/dl)	Yes (6)	50	77.05-99.27	0.39
	No (95)	73.7	81.58-92.84	
Total nucleated cells dose (x $10^8/l$)	Yes (16)	81.3	86.43-100.19	<0.01
	No (85)	70.6	79.95-92.30	
	≤ 1000 (7)	100		
	1001-2000 (35)	94.3		
CD34 Cells dose (x $10^6/l$)	2001-2500 (12)	83.3		0.17
	>2500 (47)	48.9		
	≤ 5.0 (75)	74.7		
GVHD prophylaxis	5.1-10.0 (22)	59.1		0.75
	>10.0 (4)	100		
CMV copies (IU/ml)	≤ 3.5 (54)	74.1	78.30-93.62	0.98
	>3.5 (47)	70.0	81.44-96.09	
	CSA (13)	69.2	88.39-100.98	
	CSA + MTX (82)	73.2	79.82-92.51	
Acute GVHD incidence and severity	CSA + MMF (3)	66.7	54.06-110.60	0.71
	CSA+MTX+MMF (3)	66.7	73.99-106.00	
None (64)	≤ 2000 (5)	4.9		0.07
	>2000 (32)	31.7		
	Grade I (12)	11.9		
	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 ≤ 1000 mg/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).

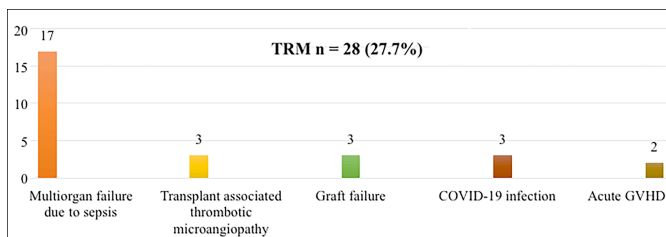


Figure 1: Treatment-related mortality (TRM) in the first 100 days of Allo-HSCT.

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/AFBMT/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.

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