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Transplant Outcome of Patients with Hematological Malignancies Using Bone Marrow Graft

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Abstract

Objective: This analysis aimed to evaluate the outcome of bone marrow (BM) in terms of survival rates, GVHD relapse-free survival (GRFS), and disease-free survival (DFS) in patients who underwent Allo-HSCT for a diverse group of hematological malignancies by comparing various parameters.

Methodology: This cross-sectional study analyzed 118 patients who underwent Allo-HSCT from July 2022 to June 2023 at the Armed Forces Bone Marrow Transplant Centre, Rawalpindi, Pakistan. Patients received peripheral blood stem cells (PBSC) or with incomplete data were excluded.

Results: The mean age of the study was 25.5 years, with predominant males (71.2%). Acute lymphoblastic leukemia (ALL) was the most prevalent (34%), followed by acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS), each accounting for 29%. In 90.7% of cases, fully matched transplants were performed, and myeloablative conditioning (MAC) was employed in 92.4% of cases. The median engraftment time for neutrophils and platelets was 13 and 22.9 days, respectively. Post-transplant complications included febrile neutropenia (90.7%), mucositis (69.5%), and cytomegalovirus (CMV) reactivation (53.4%). Out of 118 cohorts, 26.3% developed acute GVHD (Grade II-IV), and 34.7% had chronic GVHD (cGVHD) with mild severity in the majority of cases. The overall survival (OS) rate was 54.2%, with a median survival of 2,370 days. Disease-free survival (DFS) and GVHD relapse-free survival (GRFS) were 33% and 41.5%, respectively.

Conclusion: This study indicated that BM as a stem cell source has lower GVHD rates and improved OS compared to PBSC; however, relapse and post-transplant complications remain significant challenges, particularly in high-risk patients. The results highlight the efficacy of BM in reducing GVHD and improving survival in a developing country setting, emphasizing the need for individualized treatment approaches and enhanced post-transplant care.

Keywords: Allogeneic hematopoietic stem cell transplant (Allo-HSCT) bone marrow (BM), malignancies, disease-free survival (DFS)

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Introduction

Hematopoietic stem cell transplantation (HSCT) represents an effective therapeutic modality for various benign and malignant disorders. However, the success of HSCT is limited by several factors, including treatment-related mortality, disease relapse, and graft-versus-host disease(GVHD).[1, 2] The choice of graft source is a critical determinant of transplant outcomes, as it directly impacts engraftment, GVHD incidence, and relapse rates.[3,4] Peripheral blood stem cell (PBSC) has become the preferred choice of graft source for malignant diseases due to its ease of collection, donor safety, and comparable clinical outcomes; however, bone marrow (BM) serves as a potential graft source due to its association with delayed hematological recovery, which may allow for higher immune reconstitution, lowering the severity of post-transplant complications, particularly in cases where GVHD-related morbidity must be effectively managed.[4] Numerous observational studies have explored the effectiveness of BM as graft sources in HSCT, each offering unique insights and guidelines.

The US Blood and Marrow Transplantation Clinical Trial Network (BMT CTN) conducted a randomized trial that demonstrated that PBSC was associated with a lower risk of engraftment failure, whereas BM was associated with reduced incidence of chronic GVHD (cGVHD), and no significant differences were observed in the health-related quality of life of donors, except for physical discomfort following bone marrow harvest (BMH).[5] BM results in slower engraftment, higher relapse rates, and reduced acute GVHD (aGVHD) which is linked to improved OS.[6] However, for high-risk patients, relapse rates were comparable with no substantial differences were observed between the two graft source.[6] In developing nations, improving OS remains a significant

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challenge, not only due to the underlying disease but also because of complications associated with HSCT. [7]

The main objective of this study is to assess the outcomes of Allo-HSCT with BM as graft source in a low-income nation such as Pakistan, where improving OS remains a substantial challenge due to limited resources, increased treatment-related complications, and disease burden. This study attempts to evaluate whether BM, with its associated decreased GVHD rates, gives superior survival outcomes, GVHD relapse-free survival (GRFS), and disease-free survival (DFS) in the context of resource-constrained healthcare settings by analyzing various pre- and post-HSCT parameters.

Methodology

A cross-sectional observational study was conducted at the Armed Forces Bone Marrow Transplant Centre (AFMBTC) in Rawalpindi, Pakistan. The study was approved by the institutional review board (IRB-028/AFBMTC/Approval/2022), and informed consent was obtained from all participants. Using a non-probability convenience sampling technique, clinical records of 118 patients who underwent Allo-HSCT between Jan 2013 and June 2023 were reviewed and followed till 31st December 2023. The study included all patients who received Allo-HSCT using BM as graft source, regardless of age, gender, type of malignancy, or conditioning regimen. Patients who received PBSC or had incomplete or missing data were excluded.

The collected data included patient demographics, diagnosis, and disease risk stratification. Risk stratification for acute leukemias was based on ELN & NCCN guidelines respectively [8, 9, 10]; for chronic myeloid leukemia (CML) on EUTOS scoring([1], and for myelodysplastic syndrome (MDS) on R-IPSS.[12,13] Additional factors were pre-transplant remission status, and pre-transplant analysis according to the guidelines of European Society for Blood and Marrow Transplantation (EBMT).[14]

Conditioning intensity was categorized based on Consensus Center for International Blood and Marrow Transplant Research (CIBMTR) criteria. MAC was defined as a dose of busulfan (Bu) > 6.4 mg/kg intravenously, while reduced-intensity conditioning (RIC) was defined as a dose of 6.4 mg/kg or less of Bu and Melphalan (Mel) 140 mg/m² intravenously. GVHD prophylaxis for matched related donor transplants comprised of combination of cyclosporine (CSA) and tacrolimus, anti-thymocyte globulin (ATG) and methotrexate (MTX), while for Haplo-BMT CSA or tacrolimus, post-transplant cyclophosphamide (PTCy) at 50 mg/kg on days 3 and 4 post-BMT, and mycophenolate mofetil (MMF). All patients were given antimicrobial prophylaxis as per hospital policy, including antifungal agents (based on fungal risk), acyclovir, and co-trimoxazole.

Engraftment was defined as achieving an absolute neutrophil count (ANC) > 500/µL for 3 consecutive days and platelet counts > 20,000/µL for 7 days without transfusion.[15] After discharge, patients were monitored regularly with disease assessment on days 30, 60, 90, 180, and 365 post-HSCT, or as clinically indicated (16). Post-transplant complications were assessed using standardized criteria: oral mucositis was graded per WHO guidelines[17], and febrile neutropenia (FN) was defined as a temperature >101°F or >100.4°F sustained for over an hour with an ANC <0.5 × 10^9/L or expected to drop below this threshold within 48 hours.[18] Gut toxicity and hemorrhagic cystitis were graded using CTCAE guidelines.[19], while veno-occlusive disorder (VOD) was diagnosed on EBMT criteria(20).Acute and cGVHD were diagnosed and graded according to Glucksberg and NIH criteria[21] and treated with corticosteroids as first-line therapy.

Key survival metrics were defined as follows:

- OS: From the time of HSCT to death from any cause.
- DFS: The period from HSCT to the first occurrence of any disease-related event.
- GRFS: The presence of grade III-IV acute GVHD, extensive cGVHD, relapse, or death within one year post-transplant.[22]
- Relapse: Malignancy recurrence confirmed on imaging, bone marrow examination, immunophenotyping, and/or disease-specific molecular markers.

SPSS version 25.0 was used for data analysis. For categorical variables, frequencies and percentages were calculated, while to demonstrate the normality of distribution of continuous variables, a Shapiro-wilk test was performed, and mean ± standard deviation (range)

or median (IQR) was calculated. Kaplan-Meier method was used for survival analysis, and survival differences were compared using the log-rank test. Statistical significance was determined with a p-value < 0.05.

Results

The study comprised 118 patients, having a mean age of 25.5 ± 11.32 years (4–53). Out of the total population, 84 (71.2%) were male, and 34 (28.8%) were female. Acute lymphoblastic leukemia (ALL) was the most prevalent indication for HSCT, accounting for 34% of the cohort, followed by acute myeloid leukemia (AML) and MDS, each contributing 24.5%, while 17% of the cohort was CML. Cytogenetic data were available for 115 patients, of whom 87 (74%) had normal cytogenetics, while 28 (24%) exhibited cytogenetic abnormalities. Among those with abnormalities, 6 patients (5%) had a complex karyotype. Patients were further stratified into high, intermediate, and standard risk categories, which are summarized in Table I.

Table I: Risk stratification of different Malignancies.

		Risk Stratification						
		Standard Risk		High Risk		Intermediate risk		
		n	%	N	%	N	%	p-value
Malignancies	ALL	6	35.3	34	58.6	0	0.0	0.001
	CML	2	11.8	9	15.5	9	20.9	
	AML	3	17.6	5	8.6	21	48.8	
	MDS	6	35.3	10	17.2	13	30.2	

Note: Chi- square was applied

Fully matched-HSCT was done in 107(90.7%) patient and 11 patients (9.3%) underwent haplo-HSCT. Out of 118 patients 79(66.9%) had no ABO mismatch, 11(9.3%) had major, 18(15.3%) had minor while bidirectional ABO mismatch was in 10(8.5%) patients which is summarized in Table II.

The mean age of donors was 25.0 ± 12.23 (3.5-60) years, while gender mismatch was present in 46.6%. The median CD34 dose received was 3.67 x 10^6 (IQR: 2.52-5.47), while the median TNC/MNC dose was 4.30 x 10^6 (IQR: 3.64-5.30). The median duration for neutrophil and platelet engraftment was 13 (IQR: 12-15) days and 22.9±6.72 (0-42), respectively. Post-transplant complications observed are summarized in Table 2. Post-HSCT 41 (34.7%) patients relapsed, in which 23 (19.5%) had morphological relapse, 8 (6.8%) molecular, 7 (5.9%) extra medullary and 3 (2.5%) CNS relapse.

Table II: Transplant characteristics and its outcome.

		n	%
Molecular remission before HSCT	CR1	65	55.1
	CR2	20	16.9
	CR3	2	1.7
	Unknown	31	26.3
Conditioning	MAC	109	92.4
	RIC	9	7.6
Source of stem cells	BMH	97	82.2
	BMH+PBSC	21	17.8
GVHD Prophylaxis	MTX+CSA	97	82.2
	CSA+PTCy	9	7.6
	CSA	7	5.9
	CSA+MTX+MMF	4	3.4
	CSA+MMF+Tacrolimus	1	0.8
	ATG	78	66.1
Mucositis	Yes	96	81.4
	No	22	18.6
Grades of mucositis	Grade II	38	32.2
	Grade III	36	30.5
	Grade IV	8	6.8
Hepatotoxicity	Yes	41	34.7
	No	77	65.3
FN	Yes	107	90.7
	No	11	9.3
Gut toxicity	Yes	54	45.8
	No	64	54.2
Azotemia	Yes	21	17.8
	No	97	82.2
Transplant associated thrombotic microangiopathy (TA-TMA)	Yes	7	5.9
	No	111	94.1
Engraftment Syndrome	Yes	5	4.2
	No	113	95.8
Other complications(EBV & HBV reactivation, RHS, PVT, CRS, bell's palsy and foot drop)*	Yes	34	28.8
	No	84	71.2
aGVHD	Yes	47	39.8
	No	71	60.2
Grade of aGVHD	Grade II	12	10.2
	Grade III	12	10.2
	Grade IV	7	5.9
VOD	Yes	6	5.1
	No	112	94.9
CMV reactivation	Yes	63	53.4
	No	55	46.6

Hemorrhagic cystitis	Yes	24	20.3
	No	94	79.6
PRCA**	Yes	3	2.5
	No	115	97.4
cGVHD	Yes	41	34.7
	No	77	64.5
Severity of cGVHD	Limited	22	18.6
	Extensive	19	16.1
Main cause of death	Relapse	16	13.6
	HSCT related	16	13.6
	Other Complications***	10	8.5
	Unknown	12	10.2

**EBV (Ebstein bar virus), HBV (Hepatitis B virus), RHS(Ramsay Hunt syndrome), PVT (Postal vein thrombosis), CRS (Cytokine release syndrome)*
***PRCA (Pure red cell aplasia)*
****Invasive aspergillosis, TRALI (Transfusion related acute lung injury), TACO (Transfusion associated circulatory overload), Pulmonary embolism, COVID pneumonia, acute pancreatitis, neutropenic sepsis*

Out of total, the OS was 54.2% with median survival days were 2370 (IQR: 371.6-4368.3) (Figure 1). The graft vs relapse free survival (GRFS) was 41.5% (Figure 3) with median GRFS days of 268 (IQR: 142.8-393.1). The diseases free survival (DFS) rate was 33% (Figure 2) while median DFS days were 684 (IQR: 507.4-860.5). The significant association of our cohort's variables with OS, DFS and GRFS is summarized in Table III.

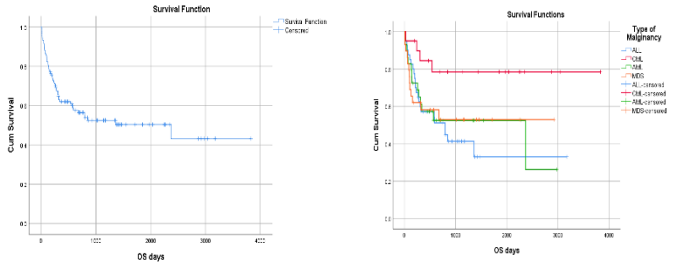

Figure 1. The Overall survival (OS) and OS in Different Hematological Malignancies.

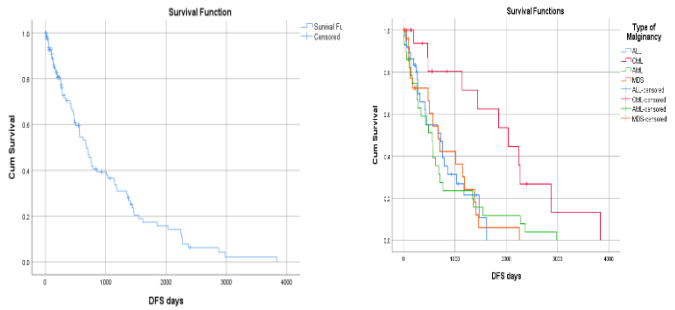

Figure 2. The Disease-free survival (DFS) and DFS in Different Hematological Malignancies.

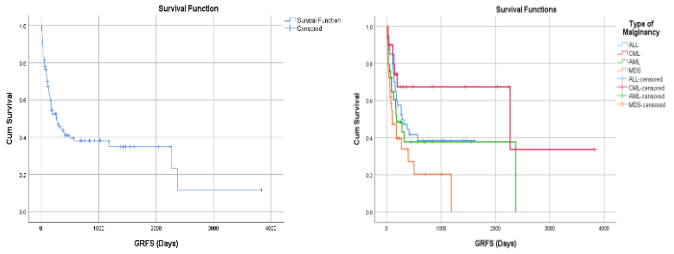

Figure 3. The GVHD-relapse free survival (GRFS) and GRFS in Different Hematological Malignancies

Discussion

To the best of our knowledge, this is the first formal report on HSCT outcomes for hematological malignancies in a low-income country, Pakistan, focusing on BM as a graft source. The study highlights better OS and a lower incidence of cGVHD with BM grafts. BM and PBSC grafts differ significantly, with PBSCs containing higher T-cell levels that enhance immune recovery but increase the risk of GVHD.[23, 24, 25] These findings align with previous studies, such as the randomized trial by BMT CTN, which demonstrated a lower incidence of cGVHD with BM compared to PBSC transplantation (PBSCT).[5] Similarly, the CIBMTR reported that BM grafts reduced non-relapse mortality and improved OS in full matched transplants with MAC. These results emphasize the advantages of BM in minimizing GVHD-related complications and improving long-term survival.[26]

The cohort had an OS rate of 54.2%, with CML showing the highest survival rate compared to MDS and AML, aligning with previously reported outcomes for BMT in similar cases. A median survival time of more than 6 years highlights the long-term benefits of BMT, particularly for patients with favorable risk profiles. Key factors influencing survival included cytogenetics and donor compatibility; patients with normal cytogenetics had a slightly better OS, which is consistent with prior research identifying cytogenetics as a critical prognostic factor in hematological malignancies.[27] Additionally, fully matched transplants demonstrated superior OS, DFS compared to Haplo-BMT, emphasizing the significance of donor compatibility in achieving optimal outcomes.

Most of the patients in cohort received MAC, which was associated with increased engraftment rate, OS, and GRFS. RIC was used especially in MDS, with co morbidities, or advanced age, and has been proven to have a higher DFS than MAC.[28] Similarly median CD34+

Table III: The significant association of various parameter with OS , DFS and GRFS,

		OS			DFS			GRFS		
		Alive	Dead	p - value	Yes	No	p - value	Yes	No	p -value
		n (%)	n		n (%)	N		n (%)	n	
Cytogenetics	Abnormal	19(67.90)	9	0.15	10(35.7)	18	0.001	15(53.6)	13	0.09
	Normal	44(50.60)	43		29(33.3)	58		33(37.9)	54	
	Not available	1(33.30)	2		0(0.0)	3		1(33.3)	2	
Transplant	Full matched	60(56.10)	47	0.09	35(32.7)	72	0.03	45(42.1)	62	0.3
	Haplo matched	4(36.40)	7		4(36.4)	7		4(36.4)	7	
Source of stem cell	BMH	56(57.7)	41	0.1	33(34.0)	64	0.05	46(47.4)	51	0.02
	BMH+PBSC	8(38.1)	13		6(28.6)	15		3(14.3)	18	
Conditioning	MAC	63(57.8)	46	0.001	34(31.2)	75	0.01	48(44)	61	0.001
	RIC	1(11.1)	8		5(55.6)	4		1(11.1)	8	
GVHD Prophylaxis	MTX+CSA	56(57.7)	41	0.002	30(30.9)	67	0.001	43(44.3)	54	0.2
	CSA+PTCy	3(33.3)	6		3(33.3)	6		3(33.3)	6	
	CSA	2(28.6)	5		4(57.1)	3		2(28.6)	5	
	CSA+MTX+MMF	3(75)	1		2(50)	2		1(25)	3	
	CSA+MMF+Tacrolimus	0(0.00)	1		0(0.0)	1		0(0.0)	1	
	ATG	38(48.7)	40		46(58.9)	32		60(76.9)	18	
Engraftment syndrome	Yes	2(40)	3	0.3	0(0.0)	5	0.5	2(40)	3	0.3
	No	62(54.9)	51		39(34.5)	74		47(41.6)	66	
TA-TMA	Yes	1(14.30)	6	0.03	3(42.9)	4	0.04	1(14.3)	6	0.08
	No	63(56.80)	48		36(32.4)	75		48(43.2)	63	
aGVHD	Yes	23(48.90)	24	0.46	12(25.5)	35	0.1	14(29.8)	33	0.04
	No	41(57.70)	30		27(38)	44		35(49.3)	36	
Grades of aGVHD	Grade I	12(75.0)	4	0.01	3(20)	12	0.005	6(40)	9	0.001
	Grade II	6(50.0)	6		2(16.7)	10		5(41.7)	7	
	Grade III	4(33.3)	8		4(33.3)	8		2(16.7)	10	
	Grade IV	1(14.30)	6		2(28.6)	5		1(14.3)	6	
	NA	41(57.70)	30		28(38.9)	44		35(48.6)	37	
aGVHD outcome	CR	21(67.7)	10	0.001	8(25.8)	23	0.001	13(41.9)	18	0.001
	PR	1(33.30)	2		0(0.0)	3		1(33.3)	2	
	Refractory	0(0.0)	9		3(33.3)	6		0(0.0)	9	
	NA	39(56.5)	30		25(36.2)	44		32(46.4)	37	
	Progressed to cGVHD	3(50.0)	3		3(50)	3		3(50)	3	
CMV reactivation	Yes	30(47.60)	33	0.001	21(33.3)	42	0.001	19(30.2)	44	0.001
	No	34(63.0)	20		17(32.1)	36		30(56.6)	23	
	NA	0(0.0))	1		1(50)	1		0(0.0)	2	
cGVHD	Yes	26(63.40)	15	0.001	11(26.8)	30	0.3	20(48.8)	21	0.04
	No	38(51.40)	36		26(35.1)	48		29(39.2)	45	
	NA	0(0.0)	3		2(66.7)	1		0(0.0)	3	
Severity of cGVHD	Limited	17(77.3)	5	0.03	5(23.8)	16	0.07	14(66.7)	7	0.1
	Extensive	9(47.40)	10		6(31.6)	13		6(31.6)	13	
	NA	38(49.40)	39		28(35.9)	50		29(37.2)	49	
cGVHD outcome	CR	17(68.0)	8	0.02	6(24)	19	0.1	11(44)	14	0.3
	PR	8(80.0)	2		3(30)	7		8(80)	2	
	Refractory	1(16.70)	5		2(33.3)	4		1(16.7)	5	
	NA	38(49.40)	39		28(36.4)	49		29(37.7)	48	
Post-HSCT maintenance	No	11(44.0)	14	0.01	9(36)	16	0.04	10(40)	15	0.001
	Yes	20(80.0)	5		10(40)	15		18(72)	7	
	NA	33(48.5)	35		20(29.4)	48		21(30.9)	47	

Note: Log rank test was performed, a p-value <0.05 was considered statistically significant.

cell dosage of 3.67 × 10^6/kg was within the recommended range for effective engraftment.[26] Gender mismatch has been associated with a higher risk of GVHD, in accordance with previous studies [29]; however, the impact on survival outcomes remains debatable.[4]

The median engraftment time for neutrophils and platelets of the cohort was 13 and 23 days, which correlates with international standards for HSCT.[30] Post-transplant complications, including FN and mucositis, were observed in majority of patients, respectively, albeit these were not statistically significant. More than half of the cohort had CMV reactivation, which is consistent with a Pakistani study[31], and had a significant impact on survival, relapse, and GRFS. The rates of TA-TMA and VOD were relatively low, most likely due to meticulous patient monitoring and supportive care.

aGVHD (grade II-IV) in the cohort was associated with a reduced OS, DFS, and GRFS, whereas cGVHD had a positive impact on survival. These rates are comparable with previous international studies ([5]). cGVHD, a frequent complication of allo-HSCT, has a negative effect on quality of life and long-term survival ,with a lower incidence in BMT compared to PBSCT.[32] Relapse occurred in one-fourth of patients, mostly as morphological relapse, followed by molecular and extra medullary relapses which highlights the need for improved post-transplant maintenance strategies as it has significant impact on survival and GRFS particularly in high-risk patients.[33]

While PB is the preferred graft source in many centers due to faster engraftment, but BM has distinct advantages, particularly in reducing cGVHD however, the choice of graft source often depends on institutional protocols, donor availability, and patient-specific factors.[32]

Limitations: This single centre study's generalizability is limited by its inclusion of diverse hematological malignancies with different prognoses and outcomes, potential selection bias, and retrospective data collection method. Prospective studies with large sample sizes and follow up times in the future would be necessary to define different methods of prevention of relapse and survival benefits.

Conclusion

This study indicated that BM is a preferable stem cell source for patients at higher risk of GVHD, especially in resource-constrained settings where managing GVHD-related consequences might be challenging. However, significant relapse rates, particularly among high-risk patients, highlight the importance of careful patient selection and the development of relapse prevention strategies, such as post-transplant maintenance therapy. This study also underlined the importance of tailoring graft source selection based on individual patient profiles, including disease risk, donor availability, and the capacity to manage post-transplant complications like infections and GVHD. Hence, in developing countries, where supportive care resources are limited, BM serves as a viable option to reduce GVHD-related morbidity and improve quality of life, provided adequate infection control and post-transplant monitoring. These findings can guide transplant decisions to optimize outcomes in diverse clinical and resource-constrained settings.

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