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Original Article

Risk Factors and Outcomes of Graft Versus Host Disease in Acute Leukemia Patients Undergoing Hematopoietic Stem Cell Transplant

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ABSTRACT

Objective: To evaluate the risk factors and outcomes of Graft Versus Host Disease (GVHD) in Acute leukemia patients undergoing matched-related donor hematopoietic stem cell transplant.

Study Design: Retrospective observational study.

Place and Duration of Study: Armed Forces Bone Marrow Transplant Center, Rawalpindi Pakistan, from May 2006 to Aug 2022.

Methodology: This study enrolled a total of 101 patients diagnosed with Acute Myeloid Leukemia (AML) and Acute Lymphoblastic Leukemia (ALL) who underwent HSCT at the Armed Forces Bone Marrow Transplant Center (AFBMTC) between May 2006 and August 2022. Data variables included Patients demographic characteristics, disease and donor type, stem cells source and dose, post-transplant complications and survival status.

Results: The study included 76(75.2%) males and 25(24.7%) females, having a male-to-female ratio of 3:1. The mean age was 23.0±11.05 years. Total of 36 patients (35.1%) developed acute graft versus host disease (aGVHD) while Chronic GVHD (cGVHD) was identified in 23(22.8%) patients. Acute graft versus host disease had a statistically significant association with gender mismatch (*p*-value =0.01), mucositis (*p*-value =0.011), Cytomegalovirus reactivation (*p*-value =0.014) and higher total nucleated cell (*p*-value =0.018) while cGVHD had a statistically significant correlation with gender mismatch (*p*-value =0.021), CMV reactivation (<0.001) and higher Total nucleated cell (TNC) dose (5.7 x 108/kg *p*-value <0.001). The overall survival at median follow up of 09 months (OS) for ALL patients was 46.6% while it was 57.3% for AML patients. There was no statistically significant difference in OS for patients with or without GVHD (*p*=0.63).

Conclusion: Gender mismatch, CMV reactivation, mucositis and high stem cell dose are associated with increased risk of GVHD. Conditioning protocols should consider optimizing GVHD prophylaxis to reduce the incidence and severity of GVHD which is associated with significant morbidity and mortality in transplant recipients.

Keywords: Acute Myeloid Leukemia, Acute Lymphoblastic Leukemia, Graft Versus Host Disease.

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INTRODUCTION

Hematopoietic stem cell transplant (HSCT) is a potentially curative treatment option for patients with acute leukemia, providing a chance for long-term remission or even a cure.[1] However, the benefits come with significant risks, most notably graft versus host disease (GVHD), a complex immunological complication that can profoundly affect patient outcomes.[2] CIBMTR data suggests a mortality rate of 4% within 100 days in <18-year-old patients after a matched related donor transplant. For patients older than 18 years, 12% mortality is reported because of GVHD within and beyond 100 days post-MRD Transplant.[3] Identifying the risk factors associated with GVHD is crucial for risk assessment and guiding clinicians in designing appropriate preventive strategies. Commonly known risk factors include human leukocyte antigen (HLA) mismatch between donor and recipient, conditioning regimen intensity, patient age, donor source (related or unrelated), donor gender, source and dose of stem cells, GVHD prophylaxis and conditioning regimen.[4] Moreover, understanding the outcomes of GVHD is crucial for optimizing treatment strategies and improving patient care. GVHD can manifest in various forms, including acute graft versus host disease (aGVHD) and chronic graft versus host disease (cGVHD), each with its unique clinical features, treatment approaches, and impact on patient morbidity and mortality.[5] By analyzing the risk factors and outcomes of GVHD in acute leukemia patients at AFBMTC Rawalpindi, this article aims to provide valuable insights into the challenges faced by clinicians and patients in the

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context of HSCT. The findings may help in refining transplant protocols, developing novel interventions, and improving overall patient outcomes.

METHODOLOGY

This retrospective study enrolled a total of 101 patients diagnosed with acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML) who underwent hematopoietic stem cell transplantation at the Armed Forces Bone Marrow Transplant Center in Rawalpindi, Pakistan between May 2006 and August 2022. Sample size was calculated using WHO Sample Size Calculator, considering a prevalence of 0.5% for AML and ALL.[6]

Inclusion Criteria: Records of Patients of either gender of AML and ALL, who underwent HSCT at AFBMTC between May 2006 and August 2022 were included in the study.

Exclusion Criteria: Patients who experienced transplant related mortality (TRM), Primary Graft Failure (PGF) or did not achieve engraftment were excluded from the study, patients receiving a second HSCT and patients with incomplete medical records and insufficient follow up data were excluded from the study.

Informed consent was obtained from the parents or legal guardians of all participants, and the study protocol strictly adhered to ethical standards. The institutional review board formally approved the study, ensuring control and ethical conduct (IRB 04/HCT/23).

A data collection form was developed using standard classification and grading systems as employed by European Bone Marrow Transplant group and National Institute of Health. The data collection form was reviewed by panel of 3 transplant experts and approved after necessary corrections.

Data collection encompassed various factors, including the age and gender of the patients and donors, gender mismatch, the use and dosage of thymoglobulin (TG) in conditioning regimens, the source and dosage of infused stem cells, the incidence, stages, and grades of aGVHD, medications used for the prevention of aGVHD, the presence of mucositis, and CMV reactivation. Conditioning regimens employed in the study included myeloablative conditioning (MAC) and reduced intensity conditioning (RIC). Mucositis was diagnosed based on erythema, inflammation, or ulceration of the oral cavity, leading to oral pain and eating difficulties. The severity and grading of mucositis were assessed according to WHO criteria. Cytomegalovirus (CMV) reactivation was evaluated using CMV PCR on day 14 post bone marrow transplantation, with subsequent PCR testing conducted every 2 weeks. Recipients with a viral load of 2000 copies/ml or higher on PCR were classified as having CMV reactivation. Skin, gut, and liver GVHD were evaluated using the Glucksberg-Seattle criteria. Treatment of aGVHD was determined based on the stage and grade of aGVHD. Topical steroids were utilized for managing Grade I GVHD, while systemic therapy was employed for Grade II-IV aGVHD based on its severity.

In this study, the collected data was analyzed using IBM Statistical Package for Social Sciences (SPSS) version 26. Quantitative variables were assessed by Mean±SD and median with inter quartile range (IQR). Qualitative variables, including the recipient's and donor's gender, gender mismatch, underlying disease, type of transplant, source of graft, CMV infection, GVHD prophylaxis, and the incidence of aGVHD were analyzed to determine their frequency and percentages. The significance of various variables was calculated using the chi-square and independent-test, with p-value <0.05 considered as significant statistically. To determine Overall Survival (OS), Disease Free survival (DFS) and GVHD relapse free survival (GRFS), the Kaplan-Meier tests were applied.

RESULTS

The total number of patients included in this study was 101, with 76(75.2%) males and 25(24.7%) females and a male-to-female ratio 3:1. The mean age of patients was 23.0±11.05 years. The main source of graft was bone marrow harvest (BMH) in 57(56.4%) of cases, followed by peripheral blood stem cells (PBSC) in 31(30.7%), and a combination of BMH and PBSC in 12(11.94%). The median dose of TNC was 4.2 x 108/kg (IQR 11.79), and CD34 was 3.5x106/kg (IQR 7.55). The mean time for neutrophil recovery was 12.0±3.0 (days post-transplant, while platelet engraftment occurred at day 19.0±4.0 days. Patient and transplant characteristics are given under Table-I.

Out of 101 patients, 82(81.1%) experienced mucositis, with varying grades of severity. CMV reactivation was observed in a subset of patients, and 33(32.7%) of them received treatment with Valganciclovir. In study cohort, cumulative incidence of aGVHD was 35.1% (n=36) while incidence of Grade II-IV aGVHD was 20.8% (n=21), with a median onset

at 42 days. Among these cases, 27 patients (75%) were treated with steroids (both oral and intravenous), while 5 patients (13.8%) received additional therapy with mycophenolate mofetil (MMF) in conjunction with steroids as the first-line approach. One patient (2.75%) was managed with topical Tacrolimus, and 3 patients (8.45%) were not treated due to self-limiting Grade 1 aGVHD. Among those treated, 25 patients (69.4%) responded to the first-line therapy, with 18(72%) patients achieving a complete response and 7(28%) patients achieving a partial response. However, 9 patients (25%) showed no response to the initial treatment, and 2 patients (5.6%) developed progressive aGVHD. Amongst these cases, 7 patients with refractory or progressive aGVHD were treated with second-line therapy, with 4(57%) receiving MMF, 2(28%) receiving anti-thymocyte globulin (ATG) in combination with MMF, and 1(14%) patient receiving Ruxolitinib. Out of these, 3(42%) had a complete response, 1 patient (14%) had a partial response, and 2(28%) were non-responders. Amongst the non-responders, 1 patient was given mesenchymal cell therapy as a third-line treatment, leading to a complete response.

Table-I: Patients and Donor Demographic Features (n=101)

Variable(s)		n(%)
Recipient Gender	Male	76(75.2)
	Female	25(24.8)
Donor Gender	Female	38(37.6)
	Male	63(62.4)
Disease	Acute Myeloid Leukemia	41(40.6)
	BALL	39(38.6)
	BALL Phil + ve	6(5.9)
	TALL	15(14.9)
Types of Transplants	Haplo	11(10.9)
	MRD	90(89.1)
GVHD Prophylaxis	CSA	11(10.9)
	CSA+PTCy	8(7.9)
	CSA+MTX	76(75.1)
	CSA+MTX+MMF	3(3.0)
	CSA+PTCy+MMF	3(3.0)

BALL: B Cell Acute Lymphoblastic Leukemia, Phil: Philadelphia Chromosome, TALL: T Cell Acute Lymphoblastic Leukemia, HAPLO: Haplo Identical, MRD: Matched Related Donor, CSA: Cyclosporin, PTCy: Post Transplant Cyclophosphamide, MTX: Methotrexate, MMF: Mycophenolate Mofetil

Moreover, it was observed that patients receiving stem cells from female donor had higher incidence of aGVHD (*p*-value =0.01). Furthermore, aGVHD demonstrated statistically significant associations with the presence of mucositis (*p*-value =0.011) and CMV reactivation (*p*-value =0.014). The occurrence of aGVHD did not exhibit a statistically significant correlation with the total nucleated cell (TNC) or with the CD34 dose. Interestingly, aGVHD did not exhibit any statistically significant correlation with the underlying diagnosis, the risk stratification of the underlying diagnosis, cytogenetics, disease status at the time of transplant, the type of HSCT, the source of stem cells, type of GVHD Prophylaxis, or the use of ATG in the conditioning regimen. (Table-III).

Table-II: Association of aGVHD with Various Factors (n=101)

Variable(s)	aGVHD		
	Yes n(%)	No n(%)	*p*-value
Patient Gender			
Male	29(38.1%)	46(60.52%)	0.531
Female	7(28.0%)	18(72.0%)	
Donor Gender			
Male	14(22.5%)	48(77.4%)	0.001
Female	22(57.9%)	16(42.1%)	
Underlying Diagnosis			0.995
Type of Transplant			
Allo	32(35.9%)	57(64.1%)	0.940
Haplo	4(36.4%)	7(63.6%)	
GVHD Prophylaxis			
CSA	5(45.4%)	6(54.6%)	
CSA+PTCy	2(25.0%)	6(75.0%)	
CSA+MTX	26(34.7%)	49(65.3%)	0.96
CSA+MTX+MMF	1(33.3%)	2(66.7%)	
CSA+PTCy+MMF	2(66.7%)	1(33.3%)	
BMH Source			
BMH	16(28.0%)	41(71.0%)	0.289
BMH+PBSC	6(50.0%)	6(50.0%)	
PBSC	13(43.3%)	17(56.7%)	
Mucositis			
Yes	33(37.5%)	55(62.5%)	0.011
No	2(48.0%)	3(52.0%)	

HAPLO: Haplo Identical, MRD: Matched Related Donor, CSA: Cyclosporin, PTCy: Post Transplant Cyclophosphamide, MTX: Methotrexate, MMF: Mycophenolate Mofetil, BMH: Bone Marrow Harvest, PBSC: Peripheral Blood Stem Cells

Table-III: Comparison of GVHD with CD34, Total Nucleated Cells/Mono Nuclear Cells and Anti Thymocyte Globulin (n=101)

aGVHD			
Variable(s)	**Yes**	**No**	***p*-value**
CD34 (x106/Kg)	3.60 + 1.30	3.78 + 1.35	0.581
TNC/MNC (x108/kg)	5.20 + 2.70	4.60 + 1.70	0.162
ATG	8.94 + 3.04	8.83 + 2.91	0.896
cGVHD			
Variable(s)	**Yes**	**No**	***p*-value**
CD34 (x106/Kg)	3.49 + 1.26	3.79 + 1.36	0.349
TNC/MNC (x108/kg)	5.70 + 3.10	4.55 + 1.61	0.020
ATG	9.31 + 2.75	8.75 + 3.0	0.577

CD: Cluster of differentiation, TNC: Total nucleated cells, MNC: Mononuclear Cell, ATG: Anti Thymocyte Globulin

cGVHD was documented in twenty-three patients (22.8%). It was observed that female patients experienced more cGVHD, and this correlation was statistically significant in male patients who had a female donor (*p*-value =0.021). Furthermore, there was a significant relationship between cGVHD and CMV reactivation (*p*-value =0.000). Notably, the TNC dose also exhibited a statistically significant relationship with cGVHD (*p*-value =0.020).

In our study, there were 25 deaths, representing 51.4% of the participants. The overall survival at

median 09 months follow-up (OS) for ALL patients is 46.6%, and for AML patients, it was 57.3%. Survival analysis using Kaplan Meier test showed that 36 patients who developed aGVHD had an OS of 47.2% compared to OS of 50% in 64 patients who did not develop aGVHD, (log rank, Mantel Cox value = 0.9). In cGVHD arm, 23 patients developed cGVHD and had an OS of 52.2% compared with OS of 47.4% in 78 patients who did not develop cGVHD (log rank, Mantel Cox value =0.27).

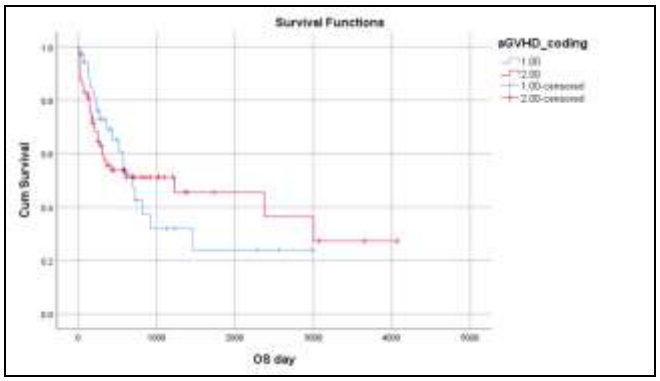

Figure-1a: OS at mean follow up of 9 months is better for patients without any evidence of aGVHD (50%, red line), as compared to patients with evidence of aGVHD (47.2%, blue line). However, this is not statistically significant (*p*=0.9)

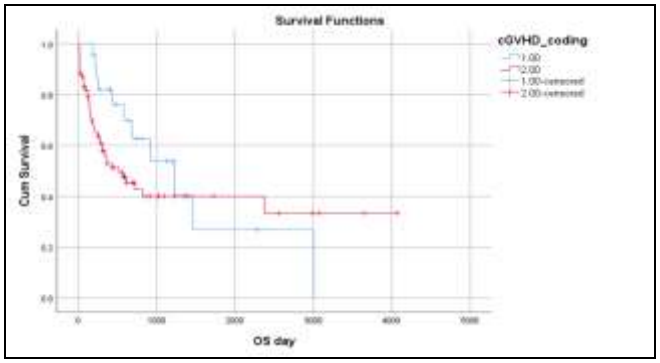

Figure-1b: OS for patients with cGVHD (52.2%, blue line) was found to be superior in comparison to patients without (47.4%, red line) cGVHD. However, this finding was not statistically significant (*p*=0.22)

DISCUSSION

The findings of this study shed light on the complex landscape of hematopoietic stem cell transplantation (HSCT) in acute leukemia patients, particularly in relation to graft-versus-host disease (GVHD), treatment outcomes, and their associated risk factors. We identified significant correlations between GVHD incidence and factors such as gender, early-onset mucositis, and CMV reactivation. Moreover, there's a notable association between higher TNC doses and increased GVHD occurrence. Despite traditional beliefs in the protective role of GVHD against relapse (GVL effect), our study did not find a positive correlation between the incidence of GVHD and improved OS.

GVHD is one of the most significant and dreaded complications of HSCT, affecting the post-transplant quality of life and survival.[7] It is also pertinent to mention that there is a scarcity of regional studies regarding various risk factors of GVHD in acute leukemia patients. Our study is one of its kind and it highlights several key findings regarding GVHD and treatment outcomes.

Over the past three decades, several studies have attempted to determine the factors enhancing the risk of GVHD in post-transplant patients.[8,9] Due to a diversity in transplant practices, disease status at transplant and variance in GVHD prophylaxis, there is a considerable difference in established risk factors for GVHD across the available studies. Our study is an effort to delineate the identified risk factors of GVHD, to facilitate future regional studies and collaboration for improving HSCT patients in resource-limited settings. In most of the studies, the median age of transplant in AML is more than 50 years, compared to a relatively younger age group in our study.[10] This disparity highlights the better standard of care and disease control achieved in patients being treated in resource-rich settings. However, there is no statistically significant relation between the incidence of GVHD and the median age at transplant in our study. A majority of our patients underwent MRD Transplant, while 10.9% patients received a haplo HSCT, in-keeping with the data published by Yu Akahoshi *et al*.[11] Their study also showed a higher incidence of aGVHD of (45%) occurring at median days of 30 as compared to an incidence of (35.1%) in our study, with an average onset occurring at 42.1 days post HSCT. Notably, a higher percentage of patients in current study (88.8% compared to 75% published by Yu Akaoshi *et al*.,) required treatment for aGVHD. We were able to demonstrate that female gender as a donor (female-to-male) had a higher incidence of aGVHD, (*p*-value =0.01), in keeping with the findings of Azari *et al*.[12] Nonetheless, there are several notable studies which did not establish gender mismatch (female donor, male recipient) as a significant risk factor for GVHD.[13,14] Interestingly in our study, we were able to draw a positive relation between CSA exposure and statistically significant

incidence of aGVHD. This finding needs further evaluation by considering CSA trough levels during the post-transplant course to remove the bias of low CSA levels as a plausible explanation.[15] Our study also demonstrated that patients who developed mucositis early in the post-transplant period had a higher incidence of GVHD. One possible explanation for this finding could be the increased risk of GVHD after tissue injury because of pre-transplant conditioning.[16] Thus, it is proposed that mucositis can be used as an indicator for increased risk for GVHD, after validating this finding on a larger cohort with more diverse disease patterns. Our study also showed a significant relationship between CMV Reactivation and GVHD. This can be attributed to existing regional high CMV seropositivity, the type of conditioning used for transplant and steroid use for GVHD treatment.[17] The correlation between the dose of cells infused and various transplant outcomes like GVHD, Graft Failure, relapse, OS etc. is intricate and has displayed notable diversity amongst various available studies. For instance, one study noted an elevated risk of severe aGVHD in patients undergoing allogeneic HSCT, when they received higher doses of CD3-positive and CD34-positive cells.[18] Conversely, another study observed a reduced risk of relapse and no significant impact on aGVHD or cGVHD with higher doses of nucleated marrow cells infused.[19] On the contrary, several other studies have highlighted an increased likelihood of extensive cGVHD associated with higher doses of total nucleated cells (TNC).[20] One study identified a higher total nucleated cell (TNC) dose as an independent factor linked to a higher incidence of cGVHD, reduced relapse rates, and enhanced overall survival.[21] Nevertheless, none of these studies uncovered a connection between TNC dose and the occurrence of severe acute graft-versus-host disease (aGVHD). It is worth mentioning that current study has demonstrated a statistically significant correlation between higher TNC doses and increased incidence of both acute and chronic GVHD. These findings support the fact that with a higher TNC dose, the host milieu is exposed to a higher dose of antigen-presenting cells. This in turn leads to the propagation of GVHD. One interesting area to study in our patients as a future project would be to study the incidence of GVHD in patients receiving BMH vs BMH+PBSC vs PBSC alone.[22] The graft-versus leukaemia (GVL) effect is an integral phenomenon, playing a protective role against post-transplant relapse in acute leukemias. It can confer improved Graft-versus-Host Disease (GVHD)-free, relapse-free survival (GRFS) in patients. GVL manifests concurrently with the onset of aGVHD. Consequently, at our institution, the diagnosis of Grade I/II aGVHD in post-HSCT leukemia patients is regarded as a reassuring sign. This fact has also led to the practice of tapering immunosuppression when bone marrow chimerism is falling, to induce GVHD, in other words to induce GVL effect. However, the current study did not demonstrate the protective role of GVHD or GVL as no positive correlation could be drawn between GVHD and OS. One reason could be the fact that our study included different disease groups having varying risk categories and pre-transplant treatment history. GVHD prophylaxis also varied between different disease categories. Thus, this finding needs further validation by conducting future studies on a larger cohort. The study's overall OS rate reached 48.6%, with a corresponding disease-free survival (DFS) rate of 46.5% and GRFS of 30.4%. These findings underscore the challenges of HSCT in resource-limited setting. It can be attributed to our patients being heavily treated before being taken to transplant, low socioeconomic status, under-developed healthcare infrastructure, lack of allied specialties for care, high prevalence of multidrug-resistant bugs etc.

We included cases of acute leukaemias in this study to remove the bias of the effect of disease type on GVHD. As a result of this, our cohort was small. With the progression of our transplant program and possible regional collaborations in the future, a more representative analysis can be made. Another limitation in our study is the pre-transplant clinical status of our patients which can clearly affect the OS post HSCT.[23]

CONCLUSION

Gender mismatch, CMV reactivation, mucositis and high stem cell dose are associated with increased risk of GVHD. Conditioning protocols should consider optimizing GVHD prophylaxis to reduce the incidence and severity of GVHD which is associated with significant morbidity and mortality in transplant recipients.

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Authors' Contribution

Following authors have made substantial contributions to the manuscript as under:

YA & MAK: Data acquisition, data analysis, critical review, approval of the final version to be published.

RI & AA: Study design, data interpretation, drafting the manuscript, critical review, approval of the final version to be published.

AS & MG: Conception, data acquisition, drafting the manuscript, approval of the final version to be published. Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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