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INCIDENCE OF COMPLICATIONS AND METHODS FOR CORRECTION OF GRAFT-VERSUS-HOST DISEASE FOLLOWING ALLOGENEIC TRANSPLANTATION IN PATIENTS WITH ACUTE LEUKAEMIA

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Abstract. Graft-versus-host disease (GVHD) remains one of the most serious and frequent complications following allogeneic haematopoietic stem cell transplantation (allo-HSCT), particularly in patients with acute leukaemia. This study aimed to assess the incidence, clinical features, and outcomes of GVHD, as well as the effectiveness of correction methods used in a regional transplant centre in Uzbekistan. A total of 54 patients with acute myeloid or lymphoblastic leukaemia who underwent allo-HSCT between 2020 and 2023 were included. GVHD developed in 53.7% of cases, with acute GVHD occurring in 38.9% and chronic GVHD in 14.8%. The skin, gastrointestinal tract, and liver were the most commonly affected organs. Matched unrelated and haploidentical donors, as well as peripheral blood stem cell sources, were significantly associated with higher GVHD incidence. First-line corticosteroid therapy achieved a complete or partial response in 80.9% of acute GVHD cases, while steroid-refractory patients required advanced treatments such as ruxolitinib or extracorporeal photopheresis. GVHD-related mortality was 9.3%, with sepsis being the leading cause of death. These findings emphasise the need for early detection, risk-adapted prevention strategies, and improved access to second-line therapies to reduce GVHD-related complications and mortality in resource-limited settings.

Keywords: Graft-versus-host disease, allogeneic transplantation, acute leukaemia, stem cell transplant, corticosteroids, ruxolitinib, immunosuppression, Uzbekistan, transplant complications.

Introduction

Acute leukaemias, including acute myeloid leukaemia (AML) and acute lymphoblastic leukaemia (ALL), are aggressive haematological malignancies characterised by rapid proliferation of immature blood cells. Despite recent advances in chemotherapy and targeted therapies, allogeneic haematopoietic stem cell transplantation (allo-HSCT) remains the only potentially curative treatment for many patients with high-risk or relapsed/refractory disease. The procedure offers the therapeutic benefit of the graft-versus-leukaemia (GVL) effect—where donor immune cells eliminate residual malignant cells. However, this same immunological activity underlies one of the most serious post-transplant complications: graft-versus-host disease (GVHD).

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GVHD is a complex, immunologically mediated condition in which donor T-lymphocytes recognise host tissues as foreign and initiate an inflammatory attack. This condition is typically classified as either acute or chronic, based on the timing and clinical presentation. Acute GVHD (aGVHD) usually occurs within the first 100 days after transplant and primarily affects the skin, gastrointestinal tract, and liver. Chronic GVHD (cGVHD), which can develop months or even years after transplantation, resembles autoimmune disorders and can involve multiple organ systems, causing long-term morbidity and impaired quality of life. Both forms of GVHD remain major obstacles to the success of allo-HSCT and are associated with increased treatment-related mortality and reduced long-term survival.

The incidence of GVHD varies depending on several factors, including the degree of HLA matching, the source of the donor cells (bone marrow vs peripheral blood stem cells), patient age, the intensity of the conditioning regimen, and the use of prophylactic immunosuppressive protocols. Even with optimal matching, GVHD develops in 30–70% of allogeneic transplant recipients. While mild to moderate GVHD may contribute to the beneficial GVL effect, severe forms of the disease significantly compromise organ function, increase infection risk, and reduce the likelihood of disease-free survival.

Over the past two decades, numerous strategies have been developed to prevent and treat GVHD. These include pharmacological prophylaxis with calcineurin inhibitors (e.g., cyclosporine, tacrolimus) in combination with methotrexate or mycophenolate mofetil, T-cell depletion techniques, and post-transplant cyclophosphamide in haploidentical settings. In patients who develop steroid-refractory GVHD, treatment options have expanded to include biologics and targeted therapies such as ruxolitinib, extracorporeal photopheresis, and anti-IL-2 receptor antibodies. However, the efficacy of these treatments varies widely, and their availability is often limited in low- and middle-income countries, including Uzbekistan.

In clinical practice, managing GVHD requires timely recognition of early symptoms, accurate staging, risk stratification, and prompt initiation of appropriate therapy. Moreover, balancing immunosuppression to control GVHD while preserving the GVL effect and minimising infection risk is a delicate and often complex process. This is particularly important in patients with acute leukaemia, who are already highly immunocompromised due to prior chemotherapy and disease-related marrow suppression.

In Uzbekistan, allo-HSCT has become increasingly accessible in recent years, and more patients with acute leukaemia are undergoing transplantation at regional centres such as the Samarkand Regional Multidisciplinary Medical Centre. However, structured data on the incidence, severity, and management outcomes of GVHD in this population remain limited. There is a critical need to assess the frequency and nature of GVHD-related complications and to evaluate the effectiveness of locally implemented correction methods, including both first-line and salvage therapies.

This study aims to analyse the frequency of GVHD and associated complications in patients with acute leukaemia undergoing allogeneic stem cell transplantation. It also examines the treatment approaches employed at our centre, their clinical efficacy, and the challenges encountered in GVHD management. The findings are intended to guide improvements in clinical protocols and enhance transplant outcomes through better prevention, early

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detection, and tailored therapeutic strategies for GVHD in resource-constrained healthcare environments.

Methodology

This retrospective clinical study was conducted at the Blood Transfusion Unit and Haematology Department of the Samarkand Regional Multidisciplinary Medical Centre between January 2020 and December 2023. The purpose of the study was to assess the frequency, severity, and treatment outcomes of graft-versus-host disease (GVHD) in patients with acute leukaemia who underwent allogeneic haematopoietic stem cell transplantation (allo-HSCT), and to evaluate the clinical efficacy of various correction methods used in managing GVHD.

A total of 54 patients with acute leukaemia were included in the study, all of whom received allo-HSCT during the specified period. Among them, 35 were diagnosed with acute myeloid leukaemia (AML), and 19 with acute lymphoblastic leukaemia (ALL). Inclusion criteria required patients to be aged 18 or older, have a confirmed diagnosis of acute leukaemia, and have undergone allo-HSCT with complete clinical follow-up data available for at least 180 days post-transplant. Patients who received autologous transplants or had incomplete medical records were excluded from the analysis.

All patients received conditioning regimens based on their disease type and transplant risk profile. Most regimens included a combination of fludarabine, busulfan, and anti-thymocyte globulin (ATG), with adjustments based on age, comorbidities, and donor type. Donors included matched related donors (MRD), matched unrelated donors (MUD), and haploidentical donors. Peripheral blood stem cells were used in 63% of cases, and bone marrow stem cells in 37%.

GVHD prophylaxis consisted of cyclosporine or tacrolimus in combination with methotrexate or mycophenolate mofetil, initiated prior to stem cell infusion and continued post-transplant according to institutional protocols. In haploidentical transplants, post-transplant cyclophosphamide was also used as an adjunct for T-cell modulation.

Data were collected from patient medical records and included demographics (age, sex), type of leukaemia, donor type and source, conditioning regimen, GVHD prophylaxis used, time to GVHD onset, and clinical features. GVHD diagnosis was made clinically and confirmed histologically where indicated. Acute GVHD was graded based on the modified Glucksberg criteria, and chronic GVHD was assessed using the NIH 2014 consensus classification. Severity grading was based on organ involvement and functional impairment.

Management of GVHD was documented, including first-line and second-line treatment strategies. First-line therapy for acute GVHD involved systemic corticosteroids (methylprednisolone 2 mg/kg/day). In steroid-refractory cases, salvage therapies such as ruxolitinib, extracorporeal photopheresis, or combination immunosuppressants were administered depending on drug availability and patient response. Chronic GVHD was treated with prolonged immunosuppressive therapy and symptomatic management, including topical agents, ocular care, and nutritional support.

Outcomes assessed included incidence and severity of acute and chronic GVHD, response to treatment (complete, partial, or refractory), duration of immunosuppressive therapy, infection complications, overall survival, and GVHD-related mortality. The effectiveness of each therapeutic intervention was evaluated based on symptom resolution, reduction in immunosuppressive requirement, and patient quality of life during follow-up.

Statistical analysis was performed using SPSS version 26.0. Descriptive statistics summarised the baseline characteristics and GVHD incidence. Continuous variables were

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presented as means and standard deviations, and categorical variables as percentages. Group comparisons (e.g. MRD vs MUD, peripheral vs bone marrow source) were analysed using chi-square and t-tests. Kaplan–Meier survival curves were generated to estimate overall survival and GVHD-free survival, and a p-value < 0.05 was considered statistically significant.

Ethical approval for the study was obtained from the Institutional Review Board of Samarkand State Medical University. All data were anonymised, and patient confidentiality was strictly maintained. Informed consent was obtained prior to transplantation, and patients were informed that their data might be used anonymously for research purposes.

Results

This study included 54 patients with acute leukaemia who underwent allogeneic haematopoietic stem cell transplantation (allo-HSCT) between 2020 and 2023. Of the total cohort, 35 patients (64.8%) had acute myeloid leukaemia (AML) and 19 (35.2%) had acute lymphoblastic leukaemia (ALL). The median age was 39 years (range: 18–61), with a male-to-female ratio of 1.5:1. Donor types included matched related donors in 28 patients (51.9%), matched unrelated donors in 14 (25.9%), and haploidentical donors in 12 patients (22.2%). Peripheral blood stem cells were used in 34 cases (63%), and bone marrow in 20 cases (37%).

Graft-versus-host disease (GVHD) developed in 29 patients (53.7%) during the post-transplant follow-up period. Acute GVHD (aGVHD) occurred in 21 patients (38.9%), with organ involvement most commonly seen in the skin (76.2%), gastrointestinal tract (52.4%), and liver (33.3%). Among aGVHD cases, 9 (42.8%) were classified as grade I–II, and 12 (57.2%) as severe (grade III–IV). The median time to onset of aGVHD was 21 days post-transplant. Chronic GVHD (cGVHD) developed in 8 patients (14.8%), predominantly affecting the skin, oral mucosa, and eyes. Chronic GVHD typically presented after day 100, with a median onset at day 142. Limited cGVHD was observed in 5 patients, and extensive cGVHD in 3.

All patients who developed aGVHD received first-line therapy with systemic corticosteroids. A complete clinical response was achieved in 12 out of 21 patients (57.1%), partial response in 5 (23.8%), and 4 patients (19.0%) were classified as steroid-refractory. These refractory cases were treated with second-line interventions: ruxolitinib was used in 2 patients with good response; extracorporeal photopheresis was initiated in 1 patient; and combination immunosuppression (cyclosporine + mycophenolate mofetil) was used in another. Among cGVHD patients, immunosuppressive therapy achieved stable control in 6 patients, while 2 required prolonged treatment due to ongoing symptoms.

The overall survival (OS) at one year post-transplant was 81.5%, and GVHD-related mortality occurred in 5 patients (9.3%), all of whom had severe aGVHD with multi-organ involvement and infectious complications. A statistically significant association was observed between unrelated or haploidentical donors and higher GVHD incidence ($p = 0.031$), as well as between peripheral blood stem cell grafts and increased risk of cGVHD ($p = 0.044$). The median duration of immunosuppressive therapy in patients with GVHD was 5.8 months (range: 2–14 months).

Infectious complications occurred in 19 GVHD patients (65.5%), most commonly bacterial sepsis and viral reactivations (CMV and HSV). These complications contributed to prolonged hospitalisation and increased immunosuppression burden. Among patients who responded well to GVHD correction strategies, quality of life measures improved significantly during follow-up, with reduction in immunosuppressive doses and recovery of performance status.

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These results underscore that GVHD remains a frequent and clinically significant complication following allo-HSCT in acute leukaemia patients. While most cases of aGVHD responded to corticosteroids, a notable subset required advanced or prolonged interventions. Donor type and stem cell source were critical factors influencing GVHD risk and severity, and early identification combined with aggressive management improved clinical outcomes and survival rates.

Discussion

The findings of this study highlight the high frequency and clinical burden of graft-versus-host disease (GVHD) among patients with acute leukaemia undergoing allogeneic haematopoietic stem cell transplantation (allo-HSCT). With over half of the study population developing some form of GVHD, it is evident that this complication remains one of the primary barriers to achieving long-term transplant success and disease-free survival. The incidence of acute GVHD (38.9%) and chronic GVHD (14.8%) observed in this study is consistent with global reports, although the severity and outcomes are influenced by donor type, graft source, and available treatment modalities.

A key observation from this cohort is the strong association between the use of peripheral blood stem cells (PBSC) and an increased risk of both acute and chronic GVHD. This aligns with previous studies demonstrating that PBSC grafts contain a higher T-cell load compared to bone marrow, leading to more robust immune activation. Similarly, patients who received grafts from matched unrelated or haploidentical donors showed significantly higher GVHD rates compared to those with matched related donors, reinforcing the importance of HLA compatibility in mitigating post-transplant immune complications.

The response to first-line corticosteroid therapy in acute GVHD was satisfactory in more than half of the patients, reflecting current standards where steroids remain the cornerstone of treatment. However, nearly 20% of patients were steroid-refractory, necessitating second-line therapies such as ruxolitinib, extracorporeal photopheresis, or intensified immunosuppression. While these approaches provided symptomatic relief, they also increased the risk of infectious complications and extended the duration of hospitalisation. This underscores the clinical dilemma of managing GVHD aggressively while preserving immune competence and minimising secondary risks.

Chronic GVHD, although less frequent, contributed significantly to long-term morbidity. Patients with extensive cGVHD required prolonged immunosuppressive therapy and frequent outpatient visits, and often experienced reduced quality of life due to mucocutaneous involvement, fatigue, and ocular discomfort. The need for multidisciplinary care—including dermatology, ophthalmology, and psychological support—became apparent in these cases, especially when managing symptoms resistant to systemic therapy.

The GVHD-related mortality rate in this study (9.3%) reflects the severity of the disease in patients with multi-organ involvement and concurrent infections. This mortality was most pronounced in patients with severe aGVHD who did not respond to initial therapy. Sepsis, reactivation of latent viruses (notably CMV and HSV), and prolonged neutropenia contributed to the fatal outcomes. These findings highlight the importance of early diagnosis, timely initiation of therapy, and aggressive infection prophylaxis in improving survival.

Furthermore, the study illustrates the challenges faced in regional transplant centres in low- and middle-income settings. Limited access to advanced biologic therapies, donor diversity, and diagnostics hampers the early detection and optimal treatment of GVHD. However, the favourable outcomes in patients who received standard prophylaxis and responded to initial therapy indicate that a well-coordinated transplant and post-transplant care protocol can significantly reduce complications and improve quality of life.

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In conclusion, GVHD remains a common and serious complication of allo-HSCT in patients with acute leukaemia, with its incidence and outcomes closely tied to donor characteristics and stem cell source. While corticosteroids remain effective in many cases, steroid-refractory GVHD requires more advanced therapeutic approaches that may not always be accessible. Enhancing early diagnostic capacity, improving donor selection, and expanding access to modern immunosuppressive agents are essential steps to improving GVHD management in Uzbekistan. These findings provide a valuable foundation for updating national treatment protocols and guiding future research aimed at reducing the impact of GVHD in haematological transplant patients.

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