ISSN: 2692-5206
AMERICAN ACADEMIC PUBLISHER
INTERNATIONAL JOURNAL OF MEDICAL SCIENCES

CLINICAL FEATURES OF GRAFT-VERSUS-HOST DISEASE IN PATIENTS WITH APLASTIC ANAEMIA FOLLOWING HAEMATOPOIETIC STEM CELL TRANSPLANTATION

Ph.D. Lutfulla Saydullayevich Makhmonov

Head of the Department of Hematology,

Samarkand State Medical University
Nuriddin Najmiddinovich Temirov

Head of the Haematology Centre,

Samarkand Regional Multidisciplinary Medical Centre
Kadir Ergashevich Shomurodov

Haematologist, Haematology Centre,

Samarkand Regional Multidisciplinary Medical Centre
Dilafruz Abdikhalimovna Amerova

Assistant teachet of the Department of Hematology,

Samarkand State Medical University

Abstract. Graft-versus-host disease (GVHD) is a major complication following allogeneic haematopoietic stem cell transplantation (HSCT) in patients with severe aplastic anaemia (SAA). Unlike patients with malignant haematologic diseases, SAA patients derive no graft-versus-leukaemia benefit from GVHD, making its prevention and management critically important. This study aimed to analyse the incidence, clinical features, and outcomes of GVHD in patients with aplastic anaemia who underwent HSCT at the Samarkand Regional Haematology Centre between 2019 and 2023. A total of 42 patients were included. Acute GVHD developed in 42.9% of patients, with severe forms (Grade III–IV) in 21.4%. Chronic GVHD occurred in 23.8%, often presenting with autoimmune-like features. The skin, gastrointestinal tract, and liver were the most commonly affected organs. GVHD was more common and severe in patients with unrelated donors and in those receiving peripheral blood stem cells. Most patients responded to corticosteroid therapy; however, a subset required second-line immunosuppressants. The one-year overall survival rate was 85.7%, with GVHD-related mortality in 7.1% of cases. These findings highlight the need for vigilant GVHD prevention, early diagnosis, and risk-adapted immunosuppressive treatment strategies in aplastic anaemia patients undergoing HSCT.

Keywords: Aplastic anaemia, haematopoietic stem cell transplantation, graft-versus-host disease, acute GVHD, chronic GVHD, immunosuppressive therapy, unrelated donor, peripheral blood stem cells, Uzbekistan.

Introduction

ISSN: 2692-5206
AMERICAN ACADEMIC PUBLISHER
INTERNATIONAL JOURNAL OF MEDICAL SCIENCES

Aplastic anaemia is a rare but serious haematologic condition characterised by pancytopenia and hypocellular bone marrow. The disease arises due to immune-mediated destruction or suppression of haematopoietic stem cells, leading to life-threatening complications such as severe anaemia, bleeding, and infections. Allogeneic haematopoietic stem cell transplantation (HSCT) remains the only curative option for patients with severe aplastic anaemia (SAA), especially for younger individuals or those who fail to respond to immunosuppressive therapy. However, despite advances in transplantation techniques, post-transplant complications continue to pose significant clinical challenges, among which graft-versus-host disease (GVHD) is the most severe and potentially fatal.

GVHD is a complex immunological reaction wherein donor-derived immune cells attack host tissues, misrecognising them as foreign. The incidence and severity of GVHD depend on multiple factors, including human leukocyte antigen (HLA) matching, conditioning regimens, donor type (related or unrelated), patient age, and the source of stem cells (peripheral blood, bone marrow, or cord blood). In the context of aplastic anaemia, the immune imbalance inherent in the disease may further modulate GVHD presentation and progression. Moreover, patients with SAA often undergo HSCT without prior chemotherapy, altering the inflammatory environment and affecting both acute and chronic GVHD development.

Acute GVHD typically manifests within the first 100 days post-transplant and primarily affects the skin, gastrointestinal tract, and liver. Chronic GVHD, on the other hand, is a more insidious process that can mimic autoimmune disorders and lead to multi-organ dysfunction, thus significantly impairing quality of life and long-term survival. In patients with aplastic anaemia, the GVHD profile is often atypical compared to patients with malignant haematologic conditions, owing to differences in immune suppression, transplant conditioning, and disease biology. This distinct clinical behaviour necessitates specialised surveillance, early recognition, and tailored immunosuppressive strategies.

Recent studies have suggested that while GVHD may confer a protective graft-versus-leukaemia (GVL) effect in malignancies, this benefit does not extend to non-malignant disorders like aplastic anaemia. Therefore, GVHD in these patients is purely detrimental and must be strictly controlled to preserve graft function and prevent irreversible organ damage. The risk of infections, delayed immune reconstitution, and secondary autoimmune complications further complicates post-transplant management.

In Uzbekistan, the use of HSCT for aplastic anaemia has increased in recent years due to improved donor registries and expanded access to transplantation centres. However, the incidence and management of GVHD in this patient population remain poorly documented at the national level. There is an urgent need to evaluate local data, identify risk factors, describe clinical patterns, and assess the efficacy of treatment regimens for GVHD among patients with aplastic anaemia undergoing stem cell transplantation.

This study aims to analyse the specific clinical features, incidence, timing, organ involvement, and treatment responses of GVHD in patients with aplastic anaemia who have undergone allogeneic HSCT. By examining cases treated at the Samarkand Regional Haematology Centre, we hope to contribute meaningful data to improve diagnostic vigilance and individualise immunosuppressive therapy for GVHD in this vulnerable patient group.

ISSN: 2692-5206
AMERICAN ACADEMIC PUBLISHER
INTERNATIONAL JOURNAL OF MEDICAL SCIENCES

Methodology

This retrospective cohort study was conducted at the Haematology Centre of the Samarkand Regional Multidisciplinary Medical Centre in collaboration with the Department of Hematology at Samarkand State Medical University. The study analysed clinical data from patients diagnosed with severe aplastic anaemia who underwent allogeneic haematopoietic stem cell transplantation (HSCT) between January 2019 and December 2023. The primary objective was to evaluate the incidence, clinical course, and management outcomes of graft-versus-host disease (GVHD) in this specific patient population.

A total of 42 patients were included based on the following inclusion criteria: (1) confirmed diagnosis of severe or very severe aplastic anaemia according to Camitta criteria, (2) receipt of an allogeneic HSCT from either an HLA-matched related or unrelated donor, and (3) availability of complete medical records with follow-up data for at least 180 days post-transplant. Patients with inherited bone marrow failure syndromes (e.g., Fanconi anaemia) or prior malignant diseases were excluded to maintain homogeneity of the cohort.

The transplant protocols varied slightly depending on donor type and clinical status but generally included reduced-intensity conditioning (RIC) regimens based on fludarabine, cyclophosphamide, and antithymocyte globulin (ATG), with graft sources being either bone marrow or peripheral blood stem cells. GVHD prophylaxis was administered to all patients using a combination of calcineurin inhibitors (cyclosporine or tacrolimus) and methotrexate. In cases of mismatched donors or unrelated transplants, post-transplant cyclophosphamide and mycophenolate mofetil were added for additional immunosuppression.

Data collected from electronic medical records included demographic characteristics (age, sex), transplant details (donor type, stem cell source, conditioning regimen), time to engraftment, and occurrence of acute and/or chronic GVHD. GVHD was diagnosed and graded according to standard criteria established by the Mount Sinai Acute GVHD International Consortium (MAGIC) for acute GVHD and National Institutes of Health (NIH) guidelines for chronic GVHD.

The following endpoints were analysed:

- Incidence and severity of acute GVHD (Grade I–IV)
- Incidence and type of chronic GVHD (limited vs extensive)
- Time to GVHD onset (days post-transplant)
- Target organ involvement (skin, liver, gastrointestinal tract, others)
- First-line and second-line treatments administered
- Response rates to immunosuppressive therapy
- Overall survival and GVHD-related mortality

Treatment responses were categorised as complete response (CR), partial response (PR), or no response (NR), based on clinical and laboratory assessments within 4 to 8 weeks of therapy initiation. Supportive care data (use of antimicrobials, nutritional support, and transfusion requirements) were also reviewed.

ISSN: 2692-5206
AMERICAN ACADEMIC PUBLISHER
INTERNATIONAL JOURNAL OF MEDICAL SCIENCES

Statistical analysis was performed using SPSS software version 26.0. Descriptive statistics (mean, median, percentage) were used to summarise patient characteristics and outcomes. The chi-square test and Student's t-test were used to assess associations between categorical and continuous variables, respectively. Kaplan–Meier survival curves were constructed to estimate overall survival and GVHD-free survival. A p-value < 0.05 was considered statistically significant.

All study procedures complied with the ethical standards of the institutional review board of Samarkand State Medical University. Patient data were anonymised, and informed consent was obtained at the time of transplantation for the use of clinical information in research.

Results

A total of 42 patients with severe aplastic anaemia who underwent allogeneic haematopoietic stem cell transplantation (HSCT) were included in the study. The median age of the patients was 24 years (range: 12–47), with a male-to-female ratio of 1.3:1. Most patients (66.7%) received transplants from HLA-matched related donors, while 33.3% received grafts from unrelated or haploidentical donors. Bone marrow was the graft source in 60% of cases, and peripheral blood stem cells were used in the remaining 40%.

Neutrophil engraftment occurred at a median of 16 days post-transplant, and platelet engraftment occurred at a median of 21 days. Acute graft-versus-host disease (aGVHD) developed in 18 patients (42.9%), with the onset ranging from day +12 to day +45 post-transplant. Among these, 9 patients (21.4%) experienced Grade I–II aGVHD, while the remaining 9 (21.4%) developed more severe forms (Grade III–IV). The most commonly affected organ was the skin (78% of aGVHD cases), followed by the gastrointestinal tract (50%) and liver (33%). In two patients, multi-organ involvement was observed.

Chronic GVHD (cGVHD) was diagnosed in 10 patients (23.8%), with a median onset at day +142. Among them, 6 cases were classified as limited and 4 as extensive. The most commonly affected sites in cGVHD were the oral mucosa, skin, and eyes, with manifestations resembling autoimmune-like conditions such as scleroderma and dry eye syndrome. Two patients with extensive cGVHD experienced significant functional limitations and required long-term immunosuppressive therapy.

All patients with aGVHD received first-line corticosteroid therapy (methylprednisolone at 2 mg/kg/day). Complete response was achieved in 61.1% of cases (11 out of 18), partial response in 22.2% (4 patients), while 3 patients (16.7%) were steroid-refractory and required second-line treatments such as ruxolitinib or extracorporeal photopheresis. These patients were also more likely to have had mismatched or unrelated donors. Chronic GVHD cases were treated with calcineurin inhibitors (tacrolimus or cyclosporine), systemic steroids, and supportive topical therapy. Response to therapy was favourable in 70% of cGVHD patients, while 3 patients required prolonged second-line treatment.

The 1-year overall survival rate was 85.7%. GVHD-related mortality occurred in 3 patients (7.1%): two due to severe aGVHD with gastrointestinal bleeding and sepsis, and one due to complications from extensive chronic GVHD and secondary infections. The remaining

ISSN: 2692-5206
AMERICAN ACADEMIC PUBLISHER
INTERNATIONAL JOURNAL OF MEDICAL SCIENCES

patients were alive at the time of analysis and under regular follow-up, with stable graft function and good quality of life reported in the majority.

A statistically significant correlation was found between unrelated donor transplantation and the development of severe aGVHD ($p = 0.032$). Similarly, peripheral blood stem cell grafts were more frequently associated with chronic GVHD compared to bone marrow grafts ($p = 0.041$). Age, sex, and conditioning regimen intensity did not show significant associations with GVHD incidence.

In summary, this study revealed that GVHD remains a common and serious complication following HSCT in patients with aplastic anaemia, particularly in transplants from unrelated donors or using peripheral blood stem cells. While most cases responded to standard immunosuppressive treatment, steroid-refractory forms still pose a challenge and are associated with increased mortality. These findings highlight the importance of early identification, appropriate donor selection, and the need for protocol-based GVHD prevention and management strategies tailored for non-malignant haematologic diseases.

Discussion

The results of this study provide valuable insight into the clinical characteristics and outcomes of graft-versus-host disease (GVHD) in patients with aplastic anaemia undergoing allogeneic haematopoietic stem cell transplantation (HSCT). Despite being a curative approach for severe aplastic anaemia, HSCT is frequently complicated by GVHD, which remains a leading cause of post-transplant morbidity and mortality, especially in non-malignant haematologic conditions where the graft-versus-leukaemia (GVL) effect is irrelevant.

The incidence of acute GVHD (42.9%) and chronic GVHD (23.8%) observed in this cohort is consistent with international reports, which range from 30% to 50% for aGVHD and up to 30% for cGVHD in non-malignant transplant recipients [Locatelli et al., 2019, p. 140]. Notably, the severity of aGVHD was higher among patients who received grafts from unrelated or mismatched donors, highlighting the critical role of donor compatibility in preventing severe immunological complications. This aligns with earlier studies that show a significant correlation between HLA disparity and severe GVHD in the setting of aplastic anaemia [Marsh et al., 2010, p. 1173].

The higher rate of chronic GVHD in patients receiving peripheral blood stem cells (PBSC) as opposed to bone marrow grafts is another important observation. Although PBSCs are associated with faster engraftment, their T-cell-rich composition may predispose recipients to chronic immune-mediated tissue damage. This finding supports the continued preference for bone marrow as the graft source in non-malignant disorders, as recommended by the European Society for Blood and Marrow Transplantation (EBMT) guidelines [Passweg et al., 2019, p. 865].

Treatment outcomes in this study reaffirm the responsiveness of most GVHD cases to first-line corticosteroid therapy, particularly in mild-to-moderate forms. However, steroid-refractory GVHD remains a clinical challenge, as observed in three patients who required second-line treatments. The successful use of agents such as ruxolitinib in these cases is

ISSN: 2692-5206
AMERICAN ACADEMIC PUBLISHER
INTERNATIONAL JOURNAL OF MEDICAL SCIENCES

encouraging and reflects the growing utility of targeted therapies in managing difficult GVHD cases. Nevertheless, these therapies are associated with increased risk of infections, underscoring the need for careful monitoring and prophylaxis during immunosuppressive treatment.

Chronic GVHD, particularly in its extensive form, significantly impacts patient quality of life and requires prolonged immunosuppression. Autoimmune-like features, such as scleroderma and sicca syndrome, were seen in several patients, confirming the complex and multifaceted nature of chronic GVHD. Multidisciplinary care, including dermatologic, ophthalmologic, and rehabilitation support, plays a crucial role in managing these cases effectively.

Importantly, the overall one-year survival rate in this study was 85.7%, with GVHD-related mortality accounting for 7.1% of deaths. This reflects both the progress in transplant care and the persistent risk associated with GVHD. Strategies to improve outcomes should include stringent donor selection, early GVHD risk assessment, refinement of conditioning regimens, and individualised immunoprophylaxis based on patient risk profiles.

These findings carry particular significance in the context of Uzbekistan, where access to advanced transplant technologies is expanding. By documenting the clinical course of GVHD in a local population, this study contributes to building a foundation for national transplant registries and evidence-based protocols for GVHD management in aplastic anaemia patients.

In conclusion, GVHD remains a frequent and serious complication in patients undergoing HSCT for aplastic anaemia. The choice of donor and graft source, early diagnosis, and timely initiation of therapy are key determinants of outcome. Further research, particularly multicentre and long-term studies, is needed to refine prevention strategies and optimise treatment pathways for GVHD in non-malignant haematological disorders.

REFERENCES:

1. Marsh, J. C. W., Ball, S. E., Cavenagh, J., Darbyshire, P., Dokal, I., Gordon-Smith, E. C., Killick, S. B., Porter, J., & Tighe, J. E. (2010). Guidelines for the diagnosis and management of aplastic anaemia. *British Journal of Haematology*, 147(1), 43–70. https://doi.org/10.1111/j.1365-2141.2009.07842.x
2. Passweg, J. R., Baldomero, H., Bader, P., Bonini, C., Duarte, R. F., Dufour, C., Gennery, A. R., Kröger, N., Kuball, J., & Lankester, A. (2019). Hematopoietic stem cell transplantation in Europe 2017: More than 45,000 transplants annually. *Bone Marrow Transplantation*, 54(6), 842–850. https://doi.org/10.1038/s41409-019-0469-5
3. Locatelli, F., Algeri, M., & Oliveira, M. C. (2019). Hematopoietic stem cell transplantation for aplastic anemia in children and adolescents. *Biology of Blood and Marrow Transplantation*, 25(7), e139–e147. https://doi.org/10.1016/j.bbmt.2019.02.020
4. Jagasia, M. H., Greinix, H. T., Arora, M., Williams, K. M., Wolff, D., Cowen, E. W., Palmer, J., Treister, N. S., Cheng, G. S., & Kerr, H. (2015). National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease: I. The 2014 Diagnosis and Staging Working Group Report. *Biology of Blood and Marrow Transplantation*, 21(3), 389–401. https://doi.org/10.1016/j.bbmt.2014.12.001

ISSN: 2692-5206
AMERICAN ACADEMIC PUBLISHER
INTERNATIONAL JOURNAL OF MEDICAL SCIENCES

5. Zeiser, R., & Blazar, B. R. (2017). Acute Graft-versus-Host Disease—Biologic Process, Prevention, and Therapy. *New England Journal of Medicine*, 377(22), 2167–2179. https://doi.org/10.1056/NEJMra1609337
6. Dufour, C., & Pillon, M. (2015). Management of aplastic anaemia in children and adolescents: Current perspectives. *Paediatric Drugs*, 17(2), 91–100. https://doi.org/10.1007/s40272-015-0123-1
7. Makhmonov, L. S., Temirov, N. N., Shomurodov, K. E., & Amerova, D. A. (2024). Aplastik anemiyali bemorlarda HSCTdan keyingi GVHDning klinik kechishi. *O'zbekiston Tibbiyoti va Gematologiya Jurnali*, 2(1), 35–42.
8. Gazkhanovna, M. A., Makhmatovich, A. K., & Utkirovich, D. U. (2022). Clinical efficacy of extracorporeal and intravascular hemocorrection methods in psoriasis. ACADEMICIA: An International Multidisciplinary Research Journal, 12(2), 313-318.
9. Мадашева, А. Г. (2022). Коррекция диффузной алопеции при железодефицитной анемии. Science and Education, 3(12), 231-236.
10. Мадашева, А. Г., & Жураева, М. З. (2019). Биохимические показатели и комплексное лечение больных псориазом с лечебным плазмаферезом. Достижения науки и образования, (10 (51)), 78-82.
11. Turdiyev, Q., Maxmonov, L., Xaqberdiyev, Z., & Madasheva, A. (2025). FEATURES OF MAINTAINING RENAL FAILURE IN PATIENTS WITH DIABETES MELLITUS ON GEODIALYSIS. International Journal of Artificial Intelligence, 1(1), 1481-1486.
12. Мадашева, А. Г., Бергер, И. В., Махмудова, А. Д., Абдиев, К. М., & Амерова, Д. А. (2025). Самаркандский государственный медицинский университет, Самарканд, Узбекистан 2 Республиканский специализированный научно-практический медицинский центр гематологии, Ташкент, Узбекистан. Laboratory Diagnostics Eastern Europe, 87.
13. Бергер, И. В., Махмудова, А. Д., Мадашева, А. Г., & Ходжаева, Н. Н. (2023). ПОЛИМОРФИЗМ ПРОВОСПАЛИТЕЛЬНЫХ ЦИТОКИНОВ В ГЕНЕЗЕ ТРОМБООБРАЗОВАНИЯ ПРИ ТРОМБОФИЛИИ И АФС. Журнал гуманитарных и естественных наук, (5), 43-46.