

# The Impact of Blood Transfusion on the Efficiency of Stem Cell Transplants

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## Abstract

**Background:** While blood product transfusion is essential for managing hematologic deficits in Allogeneic Hematopoietic stem cell transplant (AHSCT) recipients, it has risks including infectious disease transmission, alloimmunization, and transfusion reactions. These risks have sparked an ongoing debate regarding the overall impact of transfusions on patient outcomes. Thus, this study aimed to evaluate the impact of Red Blood Cells (RBCs) and/or platelet transfusion on the infection incidence and overall survival in AHSCT patients. **Methods:** We performed a retrospective analysis of clinical and laboratory data of sixty adult patients with primary malignant hematological disorder who had undergone AHSCT. Participants' data were categorized into two groups; Group 1 (low transfusion group) consisted of patients receiving < 10 blood product units and Group 2 (high transfusion group) who received > 10 units. Quantitative data were expressed as mean  $\pm$  SD. The t-test of significance and Chi-square ( $\chi^2$ ) test were used, with  $p \leq 0.05$  considered significant. **Result:** A total of 60 patients' data was included. In Group 1, out of 30 patients, 13 (43.33%) developed infections. In contrast, Group 2 had 21 (70%) out of 30 patients develop infections. Group 1 had a higher survival rate (57.8%) than Group 2 (transfusion > 10 units) (46.2%) with a chi-square value = 23.56, and p-value < 0.05 indicating a statistically significant difference. **Conclusion:** The volume of blood product transfusions has a considerable impact on patient outcomes, particularly infection and survival rates. Additional long-term prospective studies and larger randomized controlled trials are needed to strengthen the evidence for determining transfusion protocols for these patients.

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## Keywords

Hematologic Neoplasms, Hematopoietic Stem Cell Transplantation, Blood Transfusion, Survival Rate

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## 1. Introduction

Hematological malignancies contribute to a significant global tumor burden. There has been a rise in the incidence of hematologic malignancies since 1990 with 1343.85 thousand cases recorded in 2019 [1], projected to reach approximately 463,493 by 2030 globally [2]. Hematological neoplasms are tumors originating from lymphatic and myeloid tissues that develop due to altered hematological functions [1] [3]. These cancers can be classified into several broadly recognized subtypes including multiple myeloma (MM), leukemia, Hodgkin lymphoma (HL), non-Hodgkin's lymphoma (NHL), and myelodysplastic syndrome (MDS) [4]. A greater degree of immunodeficiency is typically present in 50% - 80% of patients with hematologic malignancies, which frequently leads to severe morbidity and death [5] [6]. However, in the past few years, survival rates for these patients have risen substantially due to healthcare advances such as the advancement of immunotherapies, novel targeted medicines, and more efficient chemotherapeutic protocols [1].

Allogeneic Hematopoietic Stem Cell Transplantation (AH SCT) is one of the novel therapeutic approaches that has emerged as a cornerstone treatment for many high-risk hematologic malignancies. It involves the infusion of hematopoietic stem cells from a genetically similar, but not identical donor to re-establish hematopoietic function in the recipient after myeloablative or reduced-intensity conditioning regimens [7]. Therefore, this substitution of disease bone marrow by healthy donor stem cells offers the possibility of a cure or prolonged recovery [8]. Notwithstanding its therapeutic promise, AH SCT places an enormous strain on patients as well as healthcare professionals, particularly due to the potential adverse effects such as graft-versus-host disease (GVHD), infections, and transplant-related complications [9] [10]. As a result, patients frequently require supportive care to manage their severe symptoms adequately [11] [12].

Blood product transfusion is a critical component of supportive care before, during, and after the AH SCT procedure [13]. This intervention helps mitigate the negative repercussions of alloimmunization against human leukocyte antigens (HLA), regulate the immune-hematologic consequences of ABO-mismatched transplantations, and curb immunodeficiency caused by conditioning regimens [14] [15]. Thus, RBC and platelet transfusions are necessary until patients achieve stable hematopoietic recovery. While blood product transfusion is essential for managing hematologic deficits and associated complications, it has risks including infectious disease transmission, alloimmunization, and febrile nonhemolytic transfusion reactions [16]. These risks have sparked an ongoing debate regard-

ing the overall impact of transfusions on patient outcomes, particularly concerning infection incidence and overall survival [17]-[19]. This debate highlights the necessity for further research to elucidate these relationships.

Optimizing patient treatment requires balancing the risks of infection and other unfavorable outcomes with the advantages of reducing anemia and thrombocytopenia [20]. Understanding these dynamics will help clinicians make more informed judgments, ultimately improving patient outcomes and the general efficacy of AHSCT operations [21]. In this context, the aim of this study was to evaluate the impact of Red Blood Cells (RBCs) and/or platelet transfusion on the infection incidence and overall survival in patients requiring AHSCT. Understanding the relationship between transfusion practices and clinical outcomes can provide valuable insights into optimizing supportive care for these patients.

## 2. Materials and Methods

### 2.1. Study Setting and Population

This study was conducted at a university in Pune and involved sixty adult patients with primary malignant hematological disorder who had achieved complete remission and undergone AHSCT from a fully HLA-matched sibling donor.

### 2.2. Study Design

We retrospectively analyzed clinical and laboratory records to investigate the effect of the quantity of transfused blood product units on post-transplant outcomes.

### 2.3. Participant Selection Criteria

Sixty patients diagnosed with varying malignant hematological conditions such as acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), biphenotypic acute leukemia, and high-risk myelodysplastic syndrome (MDS) were enrolled in the study. The study excluded patients who had undergone ABO-mismatched AHSCT, those in relapse or partial remission, patients refractory to platelets, patients with disease relapse episodes within two months, and those who died by 100th day of post-transplantation.

### 2.4. Treatment Criteria

Before AHSCT, individuals who had severe MDS and AML underwent a conditioning regimen consisting of busulfan and fludarabine. The regimen included intravenous fludarabine at 30 mg/m<sup>2</sup> per day from day -6 to day -3, and oral busulfan at 1 mg/kg every 6 hours from day -6 to day -3. Patients with biphenotypic acute leukemia received fludarabine (30 mg/m<sup>2</sup> per day from day -6 to day -2), cytosine arabinoside (1200 mg/m<sup>2</sup> per day on days -6 and -5), busulfan (4.5 mg/kg per day on days -4 and -2), and etoposide (6 mg/kg per day from day -6

to day -2). For acute lymphoblastic leukemia, the pre-AHSCT conditioning regimen included fractionated total body irradiation (TBI) at 12 Gray over 3 days, followed by cyclophosphamide at 120 mg/kg over 2 days [19].

## 2.5. Data Grouping

Participants' data were categorized into two groups according to the number of blood products transfused. Group 1 (low transfusion group) consisted of thirty patients receiving < 10 blood product units. Group 2 (high transfusion group) consisted of thirty patients who received > 10 units.

## 2.6. Transfusion Criteria

All platelet units and red blood cells were irradiated, with red blood cells used within 28 days of irradiation. The hospital's blood bank supplied all transfused units. The transfusion threshold for one platelet apheresis unit was a platelet count of < 10,000/ $\mu$ L or active bleeding. The transfusion threshold for 2 RBC units was a hemoglobin level of 7 - 8 g/dL, or hemorrhage-induced anemia requiring maintenance of hemoglobin levels above 8 g/dL [19]. This retrospective analysis collected data from patient records within the first year post-AHSCT, including the number and type of units received (Packed RBCs or platelets), and the timing of transfusions relative to transplantation. Additionally, patient records were reviewed for infectious episodes (bacterial, viral, parasitic, or fungal) and overall survival time.

## 2.7. Statistical Analysis

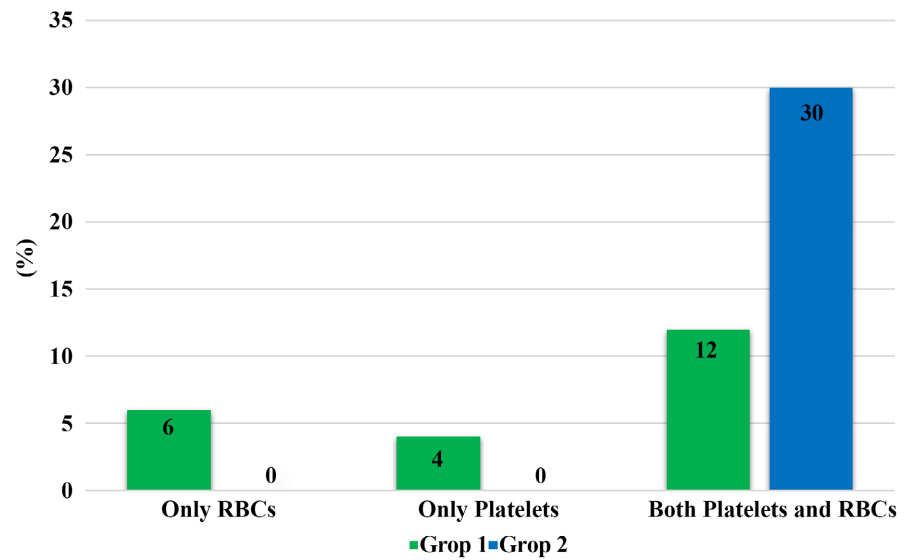
Data analysis was performed using Statistical Program for Social Science (SPSS) software. Continuous variables were represented as mean  $\pm$  SD. We utilized the t-test and Chi-square ( $\chi^2$ ) test, with p-values  $\leq$  0.05 indicating significance.

## 2.8. Ethical Considerations

The University Ethical Committee granted ethical clearance, and written informed consent was obtained from all participants. We adhered to the ethical principles outlined in the Declaration of Helsinki while conducting the study among human participants [22].

## 3. Results

A total of 60 patients' data were included; there were 33 males and 27 females between 18 and 60 years of age. The mean age of Group 1 was  $33.5 \pm 13.67$  and Group 2 was  $36.3 \pm 12.58$ . About the type of units used, 6 out of 30 patients (%) in Group 1 needed only RBCs, 4 patients (%) needed only platelet transfusion and 12 patients (%) needed both platelet and packed RBCs. In Group 2, all patients needed a transfusion of both blood components (100%) (p < 0.001) (Figure 1).



**Figure 1.** Blood component transfusion requirements in Group 1 and Group 2.

### 3.1. Impact on Infection Rate

In Group 1, out of 30 patients, 13 (43.33%) developed infections. In contrast, Group 2 had 21 (70%) out of 30 patients develop infections indicating that a higher percentage of patients in Group 2 developed infections compared to Group 1 (Table 1).

**Table 1.** Impact of blood product transfusion on infection.

Infection Category	GROUP 1 (n = 30)		GROUP 2 (n = 30)	
	Number	Percentage (%)	Number	Percentage (%)
No infection	17	56.67	9	30.00
Bacterial infection	4	13.33	6	20.00
Viral infection	5	16.67	8	26.67
Fungal infection	0	0.00	2	6.67
Bacterial and viral infection	2	6.67	3	10.00
Bacterial and fungal infection	1	3.33	2	6.67
Viral and fungal infection	1	3.33	0	0.00

### 3.2. Impact on Survival Rate

The comparison of survival rates between the two groups showed that although the median survival rate across the group was the same (median = 1.8), Group 1 (transfusion < 10 units) had a higher survival rate (57.8%) than Group 2 (transfusion > 10 units) (46.2%) with a chi-square value = 23.56, and p-value < 0.05 indicating a statistically significant difference in survival outcomes (Table 2).

**Table 2.** Impact on overall survival.

	SURVIVAL	MED	STANDARD ERROR	95% CONFIDENCE INTERVAL		CHI-SQ UARE	SIG.
				UPPER	LOWER		
Group 1	57.8%	1.8	0.25	2.45	1.39		
Group 2	46.2%	1.8	0.38	2.56	1.42	23.56	p < 0.05
Overall Survival	49.7%	1.8	0.27	2.51	1.51		

#### 4. Discussion

Allo-HSCT patients required extensive transfusion support, particularly in the first 30 days following transplant, with almost all recipients getting RBC or platelet products before engraftment [23]. However, there is a dearth of evidence about the optimal amount of blood product transfusion in allogeneic HSCT, as well as the impact of the transfusion amount on infection and survival rate [19] [24]. As a result, this single-center clinical trial was done to offer comparative data on allogeneic HSCT recipients, such as survival rate and infection incidence.

We found a greater incidence of infection in the high transfusion group than in the low transfusion group. Viral infections were the most common, followed by bacterial infection in both groups with higher incidences in the high transfusion group. The finding aligns with Nabih *et al.*'s study [19], which reported a significantly higher incidence of infection, predominantly hepatitis B and C, in the high transfusion group (60%). Similarly, one systematic review reported the incidence of cytomegalovirus in allo-HSCT to be associated with high mortality among recipients [25]. Styszczynski *et al.* [26] also found a greater overall incidence of all infections, a greater incidence of antibiotic-resistant bacteria, and a high infection fatality rate in pediatric patients receiving allo-HSCT. Gill *et al.* [27] also observed a cumulative incidence of bacterial infection of 19% and 28%, respectively, at 1 month and 12 months post-HSCT with a predominance of gram-negative bacteria among allo-HSCT patients. The higher incidence of infection reported among high transfusion allo-HSCT patients has been supported by the TRIM effect (Transfusion-related immunomodulatory effect), TA microchimerism and ILO (Iron overload) theories [19] [28] [29]. TA microchimerism refers to the presence of a small number of donor-derived cells in the recipient's circulation following a blood transfusion which can interfere with the recipient's immune system, potentially leading to immune dysregulation and increasing susceptibility to infections [30]. On the other hand, Transfusion-related immunomodulation (TRIM) encompasses various immunological changes in the recipient's body following a blood transfusion, including a state of immunosuppression that makes patients more vulnerable to infections [28]. Various studies have supported the detrimental effects of blood transfusions by the findings on RBCs and platelet storage lesions [17] [29] [31]. Platelet storage lesions can cause phenotypic shifts in platelets, triggering inflammatory reactions during transfusion. Similarly, RBCs suffer structural and functional modifications dur-

ing preservation, compromising their function and negatively impacting the endothelial, immunological, and hemostatic systems [17]. Gjaerde *et al.* [31] further reported that despite the implementation of leukocyte reduction and irradiation procedures to mitigate the immunomodulation influence of donor leukocytes in blood products, blood transfusions still negatively affected the outcomes of allo-HSCT. These procedures, while reducing some risks, do not eliminate the potential for transfusion-related complications, particularly infection. Besides, Iron overload (IOL) is a prevalent complication in hematological neoplasm patients receiving HSCT, which leads to iron-induced toxicity via producing reactive oxygen species (ROS) that harm hematopoiesis, promote clonal evolution, and cause immunosuppression, thereby increasing infection risk [19] [29]. Another microbiological study conducted in Japan reported bacteria in samples of allo-HSCT patients and concluded that the higher infection rate in high transfusion AHST patients is attributed to intensive chemotherapy-induced immunosuppression and mucosal injury, particularly in the oral cavity, which facilitates the entry of bacteria into the bloodstream. Additionally, polymicrobial infections and severe stomatitis exacerbate the risk of bloodstream infections (BSIs). These factors collectively contribute to the increased infection rates observed in this patient group [32]. Understanding these mechanisms is crucial for developing strategies to reduce infection risks, such as optimizing transfusion practices, implementing leukoreduction, and closely monitoring and managing patients' immune status post-transplantation.

Another key finding of our study is that a significantly high survival rate was noted in the low transfusion group as compared to its counterpart. This finding aligns with several previous studies. Nabih *et al.* [19] and Hosoba *et al.* [18] reported similar outcomes, suggesting that lower transfusion rates are associated with better survival. Additionally, Itonoga *et al.* [33] reported an association between a high number of RBCs transfusions prior to transplantation and poor overall survival in myelodysplastic syndrome patients aged 60 - 69 years. Furthermore, Jones *et al.* [34] found that trauma patients receiving huge, packed RBC transfusions ( $\geq 10$  units) are more likely to die within 24 hours compared to those receiving less than 10 units of RBCs. According to studies [35] [36], low blood transfusions minimize the host's exposure to foreign HLA antigens, reducing the possibility of producing antibodies against these antigens and, as a result, lowering the risk of complications such as infection, transfusion reactions, and transplant rejection. Patients' overall immunogenic burden is lowered by minimizing the number of transfusions, resulting in improved clinical outcomes. These findings underscore the potential risks associated with higher volumes and storage conditions of blood transfusions. It suggests minimizing transfusion rates, when clinically feasible, and the potential benefit of minimizing transfusion amounts and optimizing storage conditions to improve patient outcomes in allo-HSCT.

Our study reveals that the amount of blood product transfusion is a key factor in determining infection and survival rates among allo-HSCT patients. This in-

sight may be relevant for developing successful interventions to improve patient outcomes. However, our study has certain limitations. Being a single-center study, our findings may not be reproducible in other health facilities due to our smaller sample size and variations in patient characteristics, transplant procedures, and practices. Additionally, we did not assess the influence of potential confounding factors such as age, gender, pretransplant infection, and complete blood count.

Despite these limitations, our findings can nevertheless help clinicians guide patient care. Reduced infection rate in allo-HSCT patients receiving blood transfusion can be achieved through strategies like limiting RBC use, leukoreduction procedure, using single-donor products, improving pathogen testing and storage conditions, and implementing pathogen reduction technologies such as ultraviolet (UV) light-based mechanism and nucleic acid amplification technologies for screening of viruses [37] [38]. Besides, to build on our findings, more long-term prospective studies and larger randomized controlled trials are needed to investigate whether reducing the transfusion volume can decrease infection incidence rates and increase survival rates in these patients. Future studies must inquire into variations in survival and infection rates based on independent variables like age and gender, which might assist in modifying interventions for specific patient populations. Furthermore, there is a need to develop standardized transfusion protocols that may be used across several centers to reduce variability in practice and improve patient outcomes.

## 5. Conclusion

Our data indicate that the volume of blood product transfusions has a considerable impact on patient outcomes, particularly infection and survival rates. Given the association, it is crucial to consider transfusion practices while creating treatment protocols for allo-HSCT patients. Additional long-term prospective studies and larger randomized controlled trials are needed to strengthen the evidence for determining transfusion protocols for these patients.

## Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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