# Prognostic Factors Affecting Day+100 Survival in Patients Undergoing Allogeneic Haematopoietic Stem Cell Transplantation for Acute Leukaemia - A Single Centre Experience

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## ABSTRACT

**Objective:** To determine the factors affecting the first 100 days of survival in acute leukaemia patients undergoing allogeneic haematopoietic stem cell transplantation (Allo-HSCT).

**Study Design:** Descriptive study.

**Place and Duration of the Study:** Bone Marrow Transplant Centre, Rawalpindi, Pakistan, from March 2016 to February 2022.

**Methodology:** Patients with acute myeloid leukaemia (AML) or acute lymphoblastic leukaemia (ALL) in complete remission (CR) undergoing Allo-HSCT were included. Data were collected on patient demographics, diagnosis, remission status, pre-transplant analysis, donor compatibility, conditioning regimen, GVHD prophylaxis, engraftment times, post-transplant complications, mortality causes, and overall survival (OS) at 100 days.

**Results:** Among 101 transplant recipients (mean age of 24 ± 11.05 years; n = 76 males, n = 25 females), 41 had AML and 60 had ALL. Ninety patients underwent matched sibling donor (MSD)-HSCT, while 11 had haplo-identical sibling-HSCT. Patients ≤13 years had higher survival rates than older patients (94.4% *vs*. 67.5%, p = 0.03). High pre-transplant serum ferritin levels (>2500 mg/dl) predicted lower OS (48.9% *vs*. 100% in ferritin <1000 mg/dl, p <0.01). AML patients had a survival advantage over ALL patients (82.9% *vs*. 65%, p = 0.05). Early neutrophil engraftment within 14 days correlated with better survival (96.4% *vs.* 54.3%, p <0.01). Lastly, severe mucositis also adversely affected survival (60% in Grade III *vs*. 9.5% in Grade IV, p <0.01).

**Conclusion:** Identifying modifiable factors can improve long-term support and follow-up, enhancing the patient outcomes in underdeveloped nations.

**Key Words:** *Haematopoietic stem cell transplant, Day + 100 survival, Acute leukaemia, Pakistan.*

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## INTRODUCTION

Acute leukaemia incidence has risen considerably during the past few years. International Agency for Research on Cancer (IARC) statistical data showed that there were 474,519 new cases globally in the year 2020 only.[1] However, the true incidence may not be derived from this subject due to the lack of statistical data and uniform healthcare services in low- middle-income countries (LMIC).[2] Allogeneic haematopoietic stem cell transplantation (Allo-HSCT) is a potentially curative treatment.

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Survival outcomes depend on several variables, i.e., disease risk category, donor compatibility, type of conditioning regimen, graft source, stem cell dose, and post-HSCT complications[3]. In developed countries, HSCT outcomes in terms of overall survival (OS) have improved over time to 86% in the first 100 days.[4]

However, developing countries still struggle with the improvements in terms of OS being challenged by the complications of not only diseases but also the complications associated with HSCT.[5] This analysis can inform evidence-based adjustments in clinical protocols, refine patient selection criteria, and optimise management strategies. Ultimately, these improvements could lead to enhanced survival rates and clinical outcomes for transplant patients in LMICs. The aim of this study was to analyse various identifiable pre- and post-transplant factors for their statistical significance on the 100-day survival outcome to identify critical predictors of transplant success.

## METHODOLOGY

This descriptive study was executed at the Bone Marrow Transplant centre, in Rawalpindi, Pakistan, from March 2016 to February 2023.

Patients of acute myeloid leukaemia (AML) or acute lymphoblastic leukaemia (ALL), who were in complete remission (CR) and opted for HSCT, were included. Patients not in remission or who did not opt for HSCT after achieving CR were excluded from the study.

The Hospital's Ethical Committee and Review Board approved this study (Ref: IRB-018/AFBMTC/Approval/2022), and informed consent was acquired from all the participants, consistent with the Declaration of Helsinki. The data were obtained from hospital records online and from patients' files. Study data included patients' age, gender, diagnosis, disease risk stratification at diagnosis as per National Comprehensive Cancer Network (NCCN) criteria,[6,7] pretransplant remission status, transplant indication, donor compatibility, pre-transplant analysis as per European Society for Blood and Marrow Transplantation (EBMT) guidelines,[8] types of conditioning regimen, stem cells source and dose, type of graft *vs*. host disease (GVHD) prophylaxis, neutrophil engraftment time, post-transplant complications, treatment-related mortality (TRM), and OS at 100 days.

**Table I: Demographic data of acute leukaemia cases (n = 101).**

| Variables | | Number | Percentage (%) | | | Number | Percentage (%) |
|---|---|---|---|---|---|---|---|
| | Total number | 101 | 100 | | | | |
| Age groups | ≤13 years | 18 | 17.8 | Total nucleated cells (TNC) x $10^8$/l | ≤5.0 | 75 | 74.3 |
| | >13 years | 83 | 82.2 | | 5.1-10.0 | 22 | 21.8 |
| | | | | | >10.0 | 4 | 4 |
| Patient gender | Male | 76 | 75.2 | CD34 Cells x $10^6$/l | ≤3.5 | 54 | 53.5 |
| | Female | 25 | 24.8 | | >3.5 | 47 | 46.5 |
| Disease category | AML | 41 | 40.6 | GVHD prophylaxis | CSA | 13 | 12.9 |
| | ALL | 60 | 59.4 | | CSA + MTX | 82 | 81.2 |
| | | | | | CSA + MMF | 3 | 3 |
| Risk stratification | Standard | 2 | 1.9 | | CSA + MTX + MMF | 3 | 3 |
| | Intermediate | 21 | 20.7 | | | | |
| | High | 78 | 77.2 | Neutrophil engraftment days | ≤14 | 56 | 55.4 |
| | | | | | >14 | 35 | 34.6 |
| CR status | CR1 | 69 | 68.3 | | Not achieved | 10 | 9.9 |
| | CR2 | 32 | 31.7 | | | | |
| HSCT indication | Intermediate risk disease | 21 | 20.8 | Landmark achieved | Yes | 73 | 72.3 |
| | High risk disease | 35 | 34.6 | | No | 28 | 27.7 |
| | Primary refractory disease | 14 | 13.9 | Febrile neutropenia | Yes | 77 | 76.2 |
| | Relapsed disease | 31 | 30.7 | | No | 24 | 23.8 |
| Type of HSCT | MSD | 90 | 89.1 | Mucositis incidence | Yes | 91 | 90 |
| | Haplo | 11 | 10.9 | | No | 10 | 10 |
| Gender mismatch | Yes | 47 | 46.5 | Mucositis grade | Grade I | 20 | 19.8 |
| | No | 54 | 53.5 | | Grade II | 30 | 29.7 |
| Blood group mismatch | Major | 10 | 9.9 | | Grade III | 20 | 19.8 |
| | Minor | 11 | 10.9 | | Grade IV | 21 | 20.7 |
| | None | 80 | 79.2 | Gut toxicity | Mild | 16 | 15.8 |
| Pre-transplant disease status | MRD negative remission | 3 | 3 | | Moderate | 9 | 8.9 |
| | MRD positive remission | 3 | 3 | | Severe | 16 | 15.8 |
| | Morphological remission with an unknown MRD | 95 | 94.1 | | None | 60 | 59.4 |
| Pre-transplant serum ferritin (ng/ml) | ≤1000 | 7 | 6.9 | Transaminitis | Yes | 35 | 34.7 |
| | Between 1001-2000 | 35 | 34.6 | | No | 66 | 65.3 |
| | Between 2001-2500 | 12 | 11.8 | Haemorrhagic cystitis | Yes | 16 | 15.8 |
| | >2500 | 47 | 46.5 | | No | 85 | 84.1 |
| Pre-transplant HBV/HCV status | Positive | 5 | 5 | Veno-oclusive disease (VOD) | Yes | 6 | 5.9 |
| | Negative | 96 | 95 | | No | 95 | 94.1 |
| Pretransplant TB status | Positive | 5 | 5 | CMV reactivation copies (IU/ml) | ≤2000 | 5 | 4.9 |
| | Negative | 96 | 95 | | >2000 | 32 | 31.7 |
| Conditioning regimen used | MAC | 90 | 89.1 | | None | 64 | 63.4 |
| | RIC | 11 | 10.9 | Acute GVHD incidence and severity | Grade I | 12 | 11.9 |
| Stem cell source | Bone marrow (BM) | 58 | 57.4 | | Grade II | 6 | 5.9 |
| | Peripheral blood (PB) | 31 | 30.7 | | Grade III | 8 | 7.9 |
| | BM+PB | 12 | 11.9 | | Grade IV | 7 | 6.9 |
| | | | | | None | 68 | 68.4 |

**AML: Acute myeloid leukaemia; ALL: Acute lymphoblastic leukaemia; CR: Complete remission; HSCT: Haematopoietic stem cells transplant; MSD: Matched sibling donor; Haplo: Haploidentical sibling donor; MRD: Minimal residual disease; HBV: Hepatitis B virus; HCV: Hepatitis C virus; TB: Tuberculosis; MAC: Myeloablative conditioning; RIC: Reduced-intensity regimen; CSA: Ciclosporin; MTX: Methotrexate; MMF: Mycophenolate mofetil; CMV: Cytomegalovirus; GVHD: Graft vs. host disease.*

**Table II: Transplant details as per type of Allo-HSCT (MSD *vs.* Haplo) (n = 101).**

| Variable | | Matched sibling donor (MSD) n = 90 (%) | Haplo-identical sibling (Haplo) n = 11 (%) |
|---|---|---|---|
| Age groups (years) | ≤13 | 16(17.8) | 2(18.2) |
| | >13 | 74(82.2) | 9(81.8) |
| Disease category | ALL | 56(62.2) | 4(36.4) |
| | AML | 34(37.8) | 7(63.6) |
| Disease risk stratification | Standard | 2(2.2) | 0 |
| | Intermediate | 18(20) | 3(27.3) |
| | High | 70(77.8) | 8(72.7) |
| Gender mismatch | Yes | 42(46.7) | 5(45.5) |
| | No | 48(53.3) | 6(54.5) |
| Blood group mismatch | Major | 9(10) | 1(9.1) |
| | Minor | 10(11.1) | 1(9.1) |
| | None | 71(78.9) | 9(81.8) |
| Total nucleated cells (TNC) dose (x $10^8$/l) | ≤5.0 | 71(78.9) | 4(36.4) |
| | 5.1-10.0 | 18(20) | 4(36.4) |
| | >10 | 1 (1) | 3(27.3) |
| CD34 dose (x $10^6$/l) | ≤3.5 | 44(48.9) | 10(90.9) |
| | >3.5 | 46(51.1) | 1(9.1) |
| GVHD prophylaxis | CSA | 12(13.3) | 1(9.1) |
| | CSA + MTX | 75(83.3) | 7(63.6) |
| | CSA + MMF | 1(1.1) | 2(18.2) |
| | CSA + MTX + MMF | 2(2.2) | 1(9.1) |
| Neutrophil engraftment days | ≤14 | 53(58.9) | 3(27.3) |
| | >14 | 27(30) | 8(72.7) |
| Febrile neutropenia | Yes | 67(74.4) | 10(90.9) |
| | No | 23(25.6) | 1(9.1) |
| Mucositis incidence and severity | No Mucositis | 9(10) | 1(9.1) |
| | Grade I | 17(18.9) | 3(27.3) |
| | Grade II | 28(31.1) | 2(18.2) |
| | Grade III | 17(18.9) | 3(27.3) |
| | Grade IV | 19(21.1) | 2(18.2) |
| Acute GVHD incidence and severity | No GVHD | 61(67.8) | 7(63.6) |
| | Grade I | 11(12.2) | 1(9.1) |
| | Grade II | 5(5.6) | 1(9.1) |
| | Grade III | 6(6.7) | 2(18.2) |
| | Grade IV | 7(7.8) | 0 |
| CMV reactivation and copies (/ml) | ≤2000 | 27(26.7) | 1(9.1) |
| | >2000 | 23(25.6) | 9(81.8) |
| | None | 63(70) | 1(9.1) |
| Haemorrhagic cystitis | Yes | 13(14.4) | 3(27.3) |
| | No | 77(85.6) | 8(72.7) |
| Veno-oclusive disease | Yes | 6(6.7) | 0 |
| | No | 84(93.3) | 11(100) |
| Gut toxicity incidence and severity | Mild | 15(16.7) | 1(9.1) |
| | Moderate | 7(7.8) | 2(18.2) |
| | Severe | 14(15.6) | 2(18.2) |
| | None | 54(60) | 6(54.5) |
| Landmark achieved | Yes | 64(71.1) | 9(81.8) |
| | No | 26(28.9) | 2(18.2) |

***AML: Acute myeloid leukaemia; ALL: Acute lymphoblastic leukaemia; CR: Complete remission; CSA: Ciclosporin; MTX: Methotrexate; MMF: Mycophenolate mofetil; CMV Cytomegalovirus; GVHD: Graft vs. host disease.*

Neutrophil engraftment was defined as achieving absolute neutrophil count (ANC) >0.5 x $10^9$/l for three consecutive days.[9] Among post-transplant complications, oral mucositis was graded as per the World Health Organization (WHO) criteria,[10] and acute GVHD was diagnosed and graded according to EBMT criteria.[11] Febrile neutropenia was defined as a single oral temperature of >101°F, or a temperature of >100.4°F sustained over 1 hour, with an absolute neutrophil count (ANC) of < 0.5 x $10^9$/l or an ANC that is expected to decrease to <0.5 x $10^9$ over the next 48 hours.[12] Gut toxicity, haemorrhagic cystitis, and transaminitis was defined and graded as per the Common Terminology Criteria for Adverse Events (CTCAE).[13] Veno-occlusive disease (VOD) was diagnosed following the revised EBMT criteria.[14] The landmark achieved was defined as survival beyond 100 days following the initiation of the allogeneic graft infusion (DAY 0), and TRM was defined as death from any cause not attributable to disease relapse.

SPSS 25.0 was used for data analysis. Frequencies and percentages were calculated for categorical variables, whereas mean ± standard deviation was calculated for continuous variables. Survival analysis was performed using the Kaplan-Meier test, survival differences were compared with the Log-rank test, and a p-value <0.05 was considered statistically significant.

## RESULTS

A total of 101 patients underwent HSCT for acute leukaemia, including 41 (40.6%) AML and 60, (59.4%), ALL cases. The mean age of patients was 24 ± 11.05 years. Ninety (89.1%) had a matched sibling donor-HSCT, whereas 11(10.8%) had

a haplo-identical sibling-HSCT. Bone marrow harvest (BMH) was the preferred choice for stem cell source for 58 (57.4%) patients, whereas 31(30.7%) patients received stem cells from peripheral blood, and 12(11.9%) received both BMH and peripheral blood stem cells (PBSC). Recipients were given a median total nucleated cell count (TNC) dose of 4.25 x $10^8$/l (IQR 2.0 x $10^8$/l - 13.79 x $10^8$/l) and a CD34 dose of 3.5 x $10^6$/l (IQR 1.15x $10^6$/l - 8.70 x $10^6$/l). The most common post-transplant complications were mucositis (n = 91, 90%) and febrile neutropenia (n = 77, 76.2%) (Table I and II).

Using the Kaplan-Meier test, the 100-day survival was n = 73 (72.3%), and the mean survival days were 88.2 ± 2.68 days (CI 95%: 83.01-93.53). Patients ≤13 years of age had an OS of 94.4% (17/18 patients), and OS was 67.5% (56/83 patients) in the age group >13 years (p = 0.03).

**Table III: Results of statistical tests of association between day + 100 survival and study variables in acute leukaemia (n = 101).**

| Day + 100 Survival | Variable (n) | Survival percentage (%) | 95% CI | p-value |
|---|---|---|---|---|
| Age categories | ≤13 years (18) | 94.4 | 86.28-104.27 | **0.03** |
| | >13 years (83) | 67.5 | 80.79-92.84 | |
| Patient gender | Male (76) | 73.7 | 83.24-94.77 | 0.51 |
| | Female (25) | 68.0 | 69.63-94.28 | |
| Disease category | ALL (60) | 65.0 | 76.60-91.52 | **0.05** |
| | AML (41) | 82.9 | 84.87-99.03 | |
| Risk stratification | Standard (2) | 100 | | 0.71 |
| | Intermediate (21) | 71.4 | | |
| | High (78) | 71.8 | | |
| Gender mismatch | Yes (47) | 70.2 | 77.31-93.87 | 0.61 |
| | No (54) | 74.1 | 81.84-95.60 | |
| Blood group mismatch | Major (10) | 90.0 | 90.56-102.83 | 0.12 |
| | Minor (11) | 90.9 | 99.21-100.23 | |
| | None (80) | 67.5 | 77.83-90.92 | |
| Type of Allo-HSCT | MSD (90) | 71.1 | 80.60-92.37 | 0.47 |
| | Haplo (11) | 81.8 | 85.56-101.71 | |
| Conditioning regimen | MAC (90) | 71.1 | 80.60-92.37 | 0.47 |
| | RIC (11) | 81.8 | 85.56-101.71 | |
| Neutrophil engraftment day | ≤14 (56) | 96.4 | 98.59-100.26 | **<0.01** |
| | >14 (35) | 54.3 | 84.00-94.79 | |
| | Not achieved (10) | 0 | 8.52-14.87 | |
| Febrile neutropenia | Yes (77) | 71.4 | 81.48-93.35 | 0.77 |
| | No (24) | 75.0 | 74.88-98.69 | |
| Mucositis incidence and severity | Grade I (20) | 100 | | **<0.01** |
| | Grade II (30) | 100 | | |
| | Grade III (20) | 60 | | |
| | Grade IV (21) | 4.8 | | |
| | No Mucositis (10) | 100 | | |
| Gut toxicity incidence and severity | Mild (16) | 75.0 | 83.01-102.48 | 0.90 |
| | Moderate (9) | 77.8 | 65.0-104.10 | |
| | Severe (16) | 75.0 | 90.74-100.25 | |
| | No (60) | 70.0 | 76.18-91.48 | |
| Veno-oclusive disease | Yes (6) | 50 | 77.05-99.27 | 0.24 |
| | No (95) | 73.7 | 81.58-92.84 | |
| Haemorrhagic cystitis | Yes (16) | 81.3 | 86.43-100.19 | 0.39 |
| | No (85) | 70.6 | 79.95-92.30 | |
| Pre-transplant serum ferritin (mg/dl) | ≤1000 (7) | 100 | | **<0.01** |
| | 1001-2000 (35) | 94.3 | | |
| | 2001-2500 (12) | 83.3 | | |
| | >2500 (47) | 48.9 | | |
| Total nucleated cells dose (x $10^8$/l) | ≤5.0 (75) | 74.7 | | 0.17 |
| | 5.1-10.0 (22) | 59.1 | | |
| | >10.0 (4) | 100 | | |
| CD34 Cells dose (x $10^6$/l) | ≤3.5 (54) | 74.1 | 78.30-93.62 | 0.75 |
| | >3.5 (47) | 70.0 | 81.44-96.09 | |
| GVHD prophylaxis | CSA (13) | 69.2 | 88.39-100.98 | 0.98 |
| | CSA + MTX (82) | 73.2 | 79.82-92.51 | |
| | CSA + MMF (3) | 66.7 | 54.06-110.60 | |
| | CSA+MTX+MMF (3) | 66.7 | 73.99-106.00 | |
| CMV copies (IU/ml) | ≤2000 (5) | 4.9 | | 0.71 |
| | >2000 (32) | 31.7 | | |
| | None (64) | 63.4 | | |
| Acute GVHD incidence and severity | Grade I (12) | 11.9 | | 0.07 |
| | Grade II (6) | 5.9 | | |
| | Grade III (8) | 7.9 | | |
| | Grade IV (7) | 6.9 | | |
| | None (68) | 68.4 | | |

**AML: Acute myeloid leukaemia; ALL: Acute lymphoblastic leukaemia; HSCT: Haematopoietic stem cells transplant; MSD: Matched sibling donor; Haplo: Haploidentical sibling donor; MAC: Myeloablative conditioning; RIC: Reduced-intensity regimen; CSA: Ciclosporin; MTX: Methotrexate; MMF: Mycophenolate mofetil; CMV: Cytomegalovirus; GVHD: Graft vs. host disease.*

Subgroup survival analysis on disease categories showed that AML patients had an OS of 82.9% (34/41 patients) *vs*. 65% (39/60 patients) in ALL (p = 0.05). Data analysis for serum ferritin showed that pre-transplant serum ferritin levels >1000 mg/dl had adverse OS as compared to the patients with serum ferritin values ≤1000mg/dl (0/7) had 100% survival *vs*. 48.9% in patients having > 2500 mg/dl (24/47) (p <0.001). Early neutrophil engraftment ≤14 days had a better survival outcome of 96.4% (54/56) in comparison to 54.3% (19/35) in patients where neutrophil engraftment was achieved >14 days (p <0.001). The incidence and severity of mucositis also influenced survival outcomes, with 100% (10/10) survival in those with no mucositis, to 60% (12/20) in those patients with Grade III mucositis and plummeting to 9.5% (2/21) in patients having Grade IV mucositis (p <0.001 Table III).

Treatment-related mortality (TRM) was n = 28 (27.7%). Multiorgan failure secondary to septicaemia was the most frequent cause of death, i.e., n = 17 (60.7%, Figure 1).

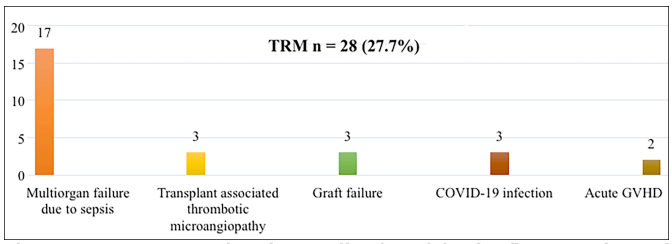


**Figure 1: Treatment-related mortality (TRM) in the first 100 days of Allo-HSCT.**

## DISCUSSION

The first 100 days post-HSCTs are critical due to patients' vulnerability to early adverse effects stemming from both compromised immune status and conditioning-related toxicities. This analysis sought to identify individuals who reached this crucial milestone and those at heightened risk of adverse outcomes to improve resource allocation in LMIC.

This study found that age significantly impacted OS. Patients ≤13 years had a better survival rate of 94.4% than patients >13 years (p = 0.03). This aspect has been well-established in a previous study by Wood *et al*.[15]

Patients proceeding to transplants generally remain transfusion-dependent for prolonged periods, leading to iron overload. A meta-analysis done by Yan *et al.* showed that higher serum ferritin levels (cut-off level >1000 mg/dl) severely affected OS and NRM in post-transplant patients.[16] The current analysis showed that patients having serum ferritin of <1000 mg/dl had 100% survival compared to patients having serum ferritin levels higher than 2500 mg/dl i.e. 48.9% (p <0.001). The rationale behind this lies in the detrimental effects of elevated serum iron, including impaired immune function and direct organ toxicity.[17]

Disease biology was found to impact survival as those patients with AML outperformed patients with ALL in terms of OS in the first 100 days. i.e., (82.9% (34/41) *vs*. 65% (39/60) (p = 0.05). Study by Natarj *et al*. from India, showed a 100-day survival for AML to be 71.3%.[18] Although a formal 100-day analysis for ALL has yet to be conducted. Ahmed *et al.* demonstrated a 3-year OS of merely 25% in high-risk cases.[19] How disease biology contributes to these outcomes was beyond the scope of this study.

Post-transplant variables were also analysed, and achievement of neutrophil engraftment in 14 days or less was found to have a statistically significant survival outcome (96.4% *vs*. 54.3%) (p <0.001). Tecchio *et al*. have previously reported that neutrophils are among the initial cells that regenerate, making them the sole cells of the immune system during the early weeks following HSCT.[20]

Additionally, mucositis was found to be statistically significant in frequency and severity. A 100 % survival was observed in patients with mild mucositis (Grade I and II) *vs.* 60% with grade III and 9.5% with Grade IV mucositis (p <0.001). This inferior outcome can be explained by an increased susceptibility to infections (direct invasive infections) supplemented by poor nutritional health in patients.[21,22]

The frequency of acute GVHD was 33 (32.6%) and while survival analysis showed inferior outcomes for patients with Grade III and IV GVHD (7.9% and 6.9%, respectively), it was not statistically significant. Similarly, CMV reactivation occurred in 37 (36.6%) of the cohort, but its effect on survival was not statistically significant. A previous study in Pakistan by Iftikhar *et al*. in 2023, showed pretransplant CMV seropositivity in 99% of recipients and donors, while the incidence of CMV reactivation was 66.1%.[23]

The limitations of this study include its retrospective design, which may introduce selection and recall biases. Additionally, the single-centred nature of the study limits the generalisability of the findings to other settings or populations. Finally, the relatively small sample size may reduce the power to detect significant associations for some variables.

## CONCLUSION

This research emphasises crucial elements that occur during the initial 100 days after HSCT, offering insights that could aid in anticipating outcomes over an extended period. While it remains challenging to pinpoint factors that can be modified to reduce hospitalisations and enhance overall survival, the study contributes additional evidence to identify patients at risk. This identification could lead to better long-term support and more vigilant follow-up for those in need.

### ETHICAL APPROVAL:

Ethical approval was obtained from the Institutional Review Board of the Armed Forces Bone Marrow Transplant Centre. (REF: IRB-018/AFBMTC/Approval/2022).

**PATIENTS' CONSENT:**
Informed consent was obtained from the patients' parents.

**COMPETING INTEREST:**
The authors declared no conflict of interest.

**AUTHORS' CONTRIBUTION:**
AS: Data analysis, drafting of the work, and critical revision.
JR, MAK: Critical revision of the manuscript for important intellectual content.
YA, UR, HK: Data collection and analysis.
All authors approved the final version of the manuscript to be published.

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