ORIGINAL ARTICLE

Incidence and clinical outcome of cytomegalovirus infection in recipients of allogenic haematopoietic stem cell transplantation; experience from a tertiary care hospital in Pakistan

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ABSTRACT

Background: Infectious complications are a major factor affecting the prognosis of HSCT recipients. Cytomegalovirus is responsible for substantial mortality in post-transplant patients. The objective of our study was to assess the frequency and outcomes of CMV infection in patients undergoing hematopoietic stem cell transplant.

Material and Methods: This retrospective study was conducted at the Aga Khan University Karachi, from January 2015 to December 2021. Quantitative PCR was done to detect CMV infection. Survival analysis was performed using the Kaplan-Meier method. Cox regression was employed to assess factors affecting survival.

Results: We included 112 patients. The frequency of CMV infection in the transplant period was 52%, with 97% of cases occurring within the first 100 days. CMV infection within 30 days occurred in 57%, between 30 and 100 days in 38% and after 100 days in 5% of patients. CMV PCR positive patients had a mean survival of 43 months (95% CI: 31.3-55.2), while CMV PCR negative patients showed an estimated mean survival of 70 months. Cox regression showed CMV positive adults with GVHD had a lower mean survival. CMV status (HR: 2.2, p-value: 0.04) and ATG use (HR: 2.3, p-value: 0.04) were associated with an increased hazard of death. No other variables were significant.

Conclusion: Overall frequency of CMV infection in our study was 52% with the majority occurring within 100 days of transplant. Adults with GVHD and patients receiving ATG had a decreased mean survival time. Understanding of factors worsening the prognosis of CMV infection is important to improve clinical practice.

Keywords: Cytomegalovirus, Allogenic stem cell transplantation, ATG, GVHD

BACKGROUND

Cytomegalovirus infection (CMVi) is a common and serious complication in CMV-seropositive recipients following allogeneic hematopoietic cell transplantation (allo-HCT).[1,2] CMVi can manifest as untreated CMV reactivation (uCMVr), clinically significant infection (cs-CMVi), or tissue invasive CMV disease (CMVd), significantly increasing the risk of bacterial and fungal infections, neutropenia, acute kidney injury due to antiviral treatment, and resulting in higher hospitalization and mortality rates, especially within the first 100 days post-transplantation.[3–5] Despite advancements in post-transplant management, allo-HCT patients remain highly vulnerable to infections due to their profoundly immunocompromised state.

Hematopoietic stem cell transplantation (HSCT), previously referred to as bone marrow transplant, has emerged over the past decades as a potentially curative treatment for various life-threatening malignant diseases and immunological disorders. Prior to stem cell infusion, patients undergo a myeloablative conditioning regimen involving high-dose chemotherapy and/or total body irradiation to eradicate malignant cells and prevent graft rejection. This regimen weakens the patient's defense mechanisms, rendering them susceptible to opportunistic infections, including multidrug-resistant organisms (MDRO), respiratory viral infections, and reactivation of human herpes viruses.[6,7]

In 2021, the European Society for Blood and Marrow Transplantation reported 47,412 HSCT procedures, with 42% being allogeneic.[8] Despite high success rates, HSCT is associated with complications such as graft-versus-host disease (GvHD) and CMV infection.[9,10] Natural killer (NK) cells, the first subset to reconstitute post-HSCT, play a crucial role in innate immunity but

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This article can be cited as: Khan ZF, Saeed N, Ashfaq D, Waqas M, Shaikh RH, Ali N. Incidence and clinical outcome of cytomegalovirus infection in recipients of allogenic haematopoietic stem cell transplantation; experience from a tertiary care hospital in Pakistan. Infect Dis J Pak. 2024; 33(4): 151-159.

DOI: https://doi.org/10.61529/idjp.v33i4.292

Receiving date: **11 Feb 2024** Acceptance Date: **03 Sep 2024**
Revision date: **03 Jul 2024** Publication Date: **30 Dec 2024**

are regulated by various receptors that influence their function. The interplay between immunosuppression and infections during the pre-engraftment neutropenic phase contributes significantly to morbidity and mortality. Dysbiosis of gastrointestinal flora, mucosal damage from indwelling devices, and prior colonization with MDROs exacerbate the risks of bloodstream infections (BSIs), pneumonia, and gastrointestinal infections.[11]

Despite significant advances in post-transplant care, CMV reactivation remains a substantial concern, occurring in 40 to 70% of cases, contributing to high morbidity and mortality rates.[12–14] HSCT-related infections occur in 13–46% of allogeneic and 5–10% of autologous transplants,[15,16] with a mortality rate of 32.7%.[17] Improved outcomes in recent years are due to less toxic conditioning protocols, advancements in human leukocyte antigen (HLA)-typing, increased donor availability, better prophylaxis and treatment of GvHD, enhanced supportive care, testing for minimal residual disease (MRD), and new prognostic models.[18] However, most deaths post-transplantation occur within the first two years,[19] and long-term survivors face increased risks of mortality due to chronic GvHD, relapse of malignant disease, infections, and secondary malignancies.[20]

Therefore, our primary objective is to conduct a retrospective study at our tertiary care hospital to assess the incidence and outcomes of cytomegalovirus infection in adult and paediatric haematopoietic stem cell transplant patients.

MATERIAL AND METHODS

This retrospective study was conducted at the Department of Oncology, Aga Khan University Hospital, Karachi, Pakistan, from January 2015 to December 2021. The study cohort consisted of adult and pediatric patients who underwent allogeneic haematopoietic stem cell transplantation (HSCT) at our tertiary care hospital and were subsequently diagnosed with cytomegalovirus (CMV) infection post-transplant. This included patients diagnosed with CMV viremia, pneumonitis, colitis, hepatitis, retinitis, or encephalitis during the post-transplantation period.

We excluded all patients with graft-versus-host disease (GVHD)-related colitis, hepatitis, or pneumonitis, patients with CMV infections not related to haematopoietic stem cell transplantation, and patients with other infectious causes, including bacterial and viral infections, in the context of haematopoietic stem cell transplantation.

The study received approval from the Ethical Review Committee (ERC) of Aga Khan University (ERC #:2023-8594-24711) and the College of Physicians and Surgeons of Pakistan (CPSP). Data collection was conducted through the electronic medical records of eligible patients, ensuring patient confidentiality. Information pertaining to demographics, transplant characteristics, CMV PCR status, and clinical outcomes was recorded in a standardized proforma.

All patients underwent assessments including physical examination, routine haematology, biochemistry testing and quantitative CMV PCR (RT-PCR). DNA is extracted from the specimen and subjected to amplification for cytomegalovirus DNA by real-time polymerase chain reaction (PCR) using the Realstar CMV PCR kit, Altona Diagnostics GmbH. The lower detection limit of the assay for CMV is 250 IU/ml and quantification range of the assay is from 1,479,108 - 250IU/ml. Diagnosis of CMV disease was based on positive CMV infection and either one of the following: the presence of appropriate symptoms (fever, and/or organ associated symptoms, such as cough/diarrhea or any other) combined with a positive CMV RT-PCR from the coherent specimen (e.g., pneumonia with positive CMV RT-PCR from bronchoalveolar lavage fluid). Plasma CMV PCR post transplantation was checked weekly from day +28 till day +100 and if positive, was checked weekly and which would continue until patients had a negative plasma CMV PCR result.

A detailed physical examination and biochemical assessment was made and results above 1000 IU/ml were taken as significant and lead to initiation of treatment with Ganciclovir or Valganciclovir.

Descriptive statistics, including medians, interquartile ranges, and percentages, were employed to summarize patient demographics (such as age and gender) and transplant characteristics (presence of GVHD, CMV status, type of transplant, etc). Survival analysis was performed using the Kaplan-Meier method, and differences in survival were assessed using the log survival function charts. We performed Kaplan-Meier survival analyses to examine the impact of CMV PCR

status, age groups, mode of transplant, gender, ATG use, and GVHD on post-transplant survival. Moreover, to investigate the effect of CMV PCR status, the patient sample was stratified by age group, gender, ATG use, and the presence of GVHD, with the impact of the CMV PCR status on the mean survival time in each of the subgroups being investigated through a Kaplan-Meier analysis. The log-rank test was used to test for significant differences in survival in our Kaplan-Meier analysis. Additionally, Cox regression analysis employed to assess for factors affecting survival, with the age group (pediatric vs. adult), gender, CMV status, ATG use, presence of GVHD, and mode of transplant (Fully-matched Allogeneic vs. Haploidentical) being taken as moderator variables. A p-value of 0.05 was taken as the cut-off for statistical significance. All analysis was carried out in IBM SPSS Statistics Version 26.

RESULTS

Our study consisted of 112 patients (table-I). The patient population included 59 adults (52.7%) and 53 pediatric patients (47.3%). The median age of the patients was 20.00 years (IQR: 24.00), ranging from 1.6 to 58 years. Gender distribution revealed 32 female patients (28.6%) and 80 male patients (71.4%).

Primary indications for transplantation were Acute Myeloid Leukemia (AML) and B-Cell Acute Lymphoblastic Leukemia (B-ALL), each accounting for 24.1% of cases. Other common indications included β-thalassemia major (16.1%), aplastic anemia (12.5%), and miscellaneous disorders which included biphenotypic leukemia, CML, CMML, Fanconi anemia, HLH, high risk MDS, myelofibrosis) (23.2%). Fully-matched allogeneic stem cell transplantation was the choice for the majority (86.6%), with 13.4% undergoing haploidentical transplants. Graft-Versus-Host Disease (GVHD) occurred in 35.7% of patients, while 64.3% did not experience any GVHD. Anti-Thymocyte Globulin (ATG) was administered to 28.6% of patients, transplant conditioning protocol. Quantitative CMV PCR (QCMV) testing revealed that 24 out of 49 tested patients had CMV levels exceeding 1000 IU/ml.

In terms of CMV serostatus, pre-transplant findings indicated that 93% of tested donors had positive CMV IgG antibodies, while none had positive CMV IgM antibodies. Among tested patients, 98% had positive CMV IgG antibodies, and 4.1% had positive CMV IgM antibodies. In the study cohort of 112 individuals, there were 58 new cases of CMV infections detected during the transplant admission period, while rest did not develop during admission, resulting in a cumulative incidence (CI) of approximately 52%.

The total person-months of observation amounted to 1,549 months, leading to an incidence rate (IR) of CMV infection, including both detected and undetected cases, of approximately 0.0375 per person-month or 0.45 per person-year.

In 52% of patients which developed CMV infection following transplantation, 58.6% of patients developed CMV infection within 30 days after transplantation, 38% between 30- and 100-days post-transplantation, and 3.4% more than 100 days after transplantation.

In our study, CMV PCR positive patients exhibited an estimated mean survival time of 43 months (95% CI: 31.3 to 55.2 months), while CMV PCR negative patients demonstrated a significantly extended estimated mean survival time of 69.5 months (95% CI: 57.3 to 81.7 months) (Figure-I).

In terms of age groups, adults had an estimated mean survival time of 50 months (95% CI: 36.8 to 62.8 months) (Figure-II), whereas pediatric patients exhibited an estimated mean survival time of 62 months (95% CI: 52 to 71.8 months) (Figure-III). However, the difference in the mean survival time between these two groups did not reach statistical significance.

Regarding the mode of transplant, complete match related transplant resulted in an estimated mean survival time of 61.6 months (95% CI: 51.4 to 71.7 months) (Figure-IV), while patients who received haploidentical stem cell transplantation had an estimated mean survival time of 39.9 months (95% CI: 20.8 to 58.9 months) (Figure-V), hence revealing no statistically significant difference in the mean survival time between these two groups.

In terms of gender, female patients displayed an estimated mean survival time of 40.5 months (95% CI: 29.3 to 51.7 months) (Figure-VI), while male patients exhibited an estimated mean survival time of 62.9 months (95% CI: 51.6 to 74.2 months) (Figure-VII). This difference, however, was not statistically significant.

For patients who did not receive ATG, the estimated mean survival time was 58.6 months (Figure-VIII) in

contrast to patients who received ATG which had mean survival time of 53 months (Figure-IX). Lastly, for patients who did not experience GVHD vs presence of GVHD the estimated mean survival time was 65 (Figure-X) and 34 months (Figure-XI) respectively.

When stratified by the age group (Table-II), those in whom CMV had been detected in the adult population had a much lower mean survival time compared to those in whom it had not been detected, while there was only a minor difference amongst the pediatric population. Patients in whom ATG was used as conditioning therapy, CMV positivity led to a much lower survival time. Similarly, CMV detection was associated with a decreased mean survival time in those who developed GVHD. On risk stratification by gender and the type of transplant, CMV detection status did not affect the duration of survival in any of the strata. We were unable to conclude regarding the statistical significance of these differences from the results of our log-rank test.

Cox regression revealed positive CMV status (HR: 2.2, 95% CI: 1.03 - 4.7, p-value: 0.04) and ATG use (HR: 2.3, 95% CI: 1.02 - 5.34, p-value: 0.04) to be associated with an increased hazard of death. On the other hand, the age group (HR: 1.43, 95% CI: 0.44 - 4.64, p-value: 0.54) gender (HR: 1.25, 95% CI: 0.63 - 2.49, p-value: 0.52) mode of transplant (HR: 0.81, 95% CI: 0.32 - 2.05, p-value: 0.66) and GVHD (HR: 0.85, 95% CI: 0.41 - 1.75, p-value: 0.66) had no significant bearing on survival.

Table-I: Basic demographic details of allogeneic stem cell transplant patients (n=112).

Variables	n (%) & median [IQR]
Age	20.0, IQR=[8.0-32.0]
Indication	
AML	27 (24.1%)
B-ALL	27 (24.1%)
β-Thalassemia Major	18 (16.1%)
Aplastic Anemia	14 (12.5%)
Miscellaneous Disorders	26 (23.2%)
GVHD	
Yes	40 (35.7%)
No	72 (64.3%)
QCMV	
Greater than 1000 (of those tested, n=49)	24 (49%)
CMV status pre-transplant	
Positive donors CMV IgG antibody (of those tested, n=43)	40 (93%)
Positive donors CMV IgM antibody (of those tested, n=42)	0
Positive patients CMV IgG antibody (of those tested, n=100)	98 (98%)
Positive patients CMV IgM antibody (of those tested, n=97)	4 (4.1%)
CMV PCR status during transplant	
Detected	58 (51.8%)
Undetected	54 (48.2%)
CMV status post-transplant	
CMV infection <30 days after transplantation	34 (58.6%)
CMV infection >30 days <100 after transplantation	22 (38.0%)
CMV infection >100 days after transplantation	2 (3.4%)

Table-II: CMV status and survival according to groups.

	Mean survival in months, (95% CI)		
Variable	**CMV Detected**	**CMV Undetected**	**p-value (log-rank test)**
Age Group			
Adults	18 (12 - 24)	58 (43 - 76)	0.129
Pediatrics	54 (39 - 69)	66(54 - 76)	0.089
Gender			
Male	45.5 (31 – 60)	71 (57.5 – 85)	0.116
Female	31 (20– 42)	45 (27 – 63)	0.552
Type of transplant			
Fully-matched Allogenic	45.3(32 – 59)	68 (55.4 – 81)	0.221

Haploidentical	Could not be estimated	Could not be estimated	-
Use of ATG			
Yes	32.3 (24.4 – 40.2)	56 (41– 71)	0.195
No	43.2 (23 – 63.6)	67 (51.2 – 82)	0.240
GVHD			
Yes	21.4 (15 – 28)	44.4 (33 – 56)	0.085
No	52 (37.2 – 67)	68 (53.5 – 82)	0.582

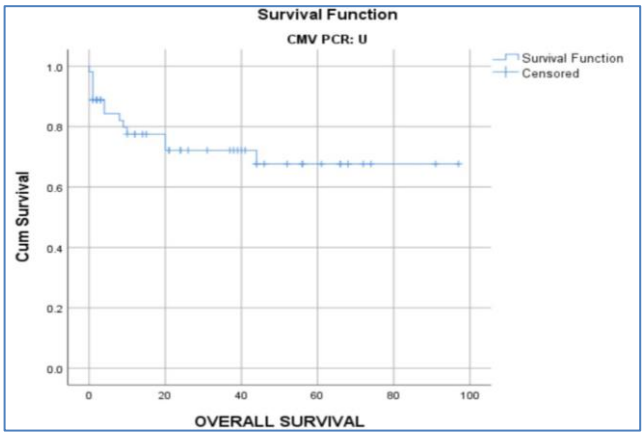

Figure-I: Survival function of CMV PCR negative patients demonstrating a mean survival time of 69.5 months (95% CI: 57.3 to 81.7 months)

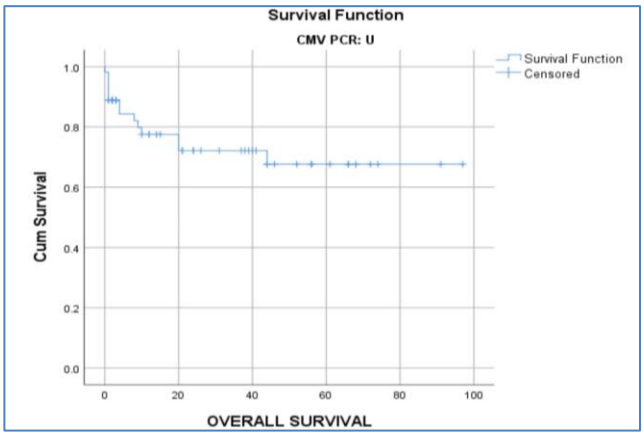

Figure-II: Survival function of adult patients with a mean survival time of 50 months (95% CI: 36.8 to 62.8 months)

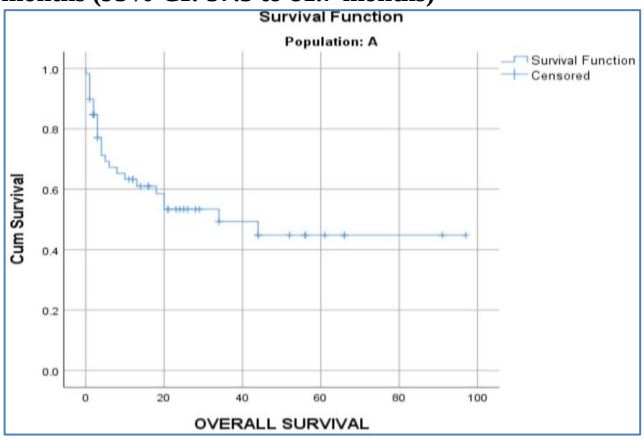

Figure-III: Survival function of pediatric patients showing a mean survival time of 62 months (95% CI: 52 to 71.8 months)

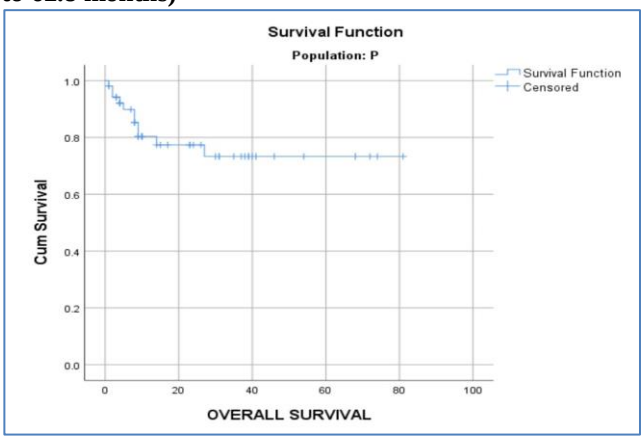

Figure-IV: Survival function for patients with fully-matched allogeneic transplant showing a mean survival time of 61.6 months (95% CI: 51.4 to 71.7 months)

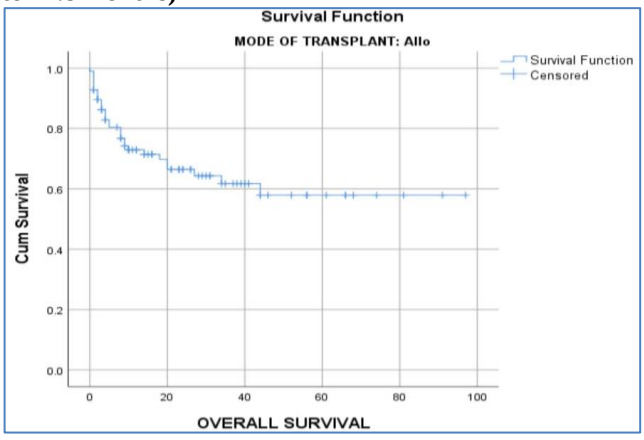

Figure-V: Survival function for patients with haploidentical transplant showing a mean survival time of 39.9 months (95% CI: 20.8 to 58.9 months)

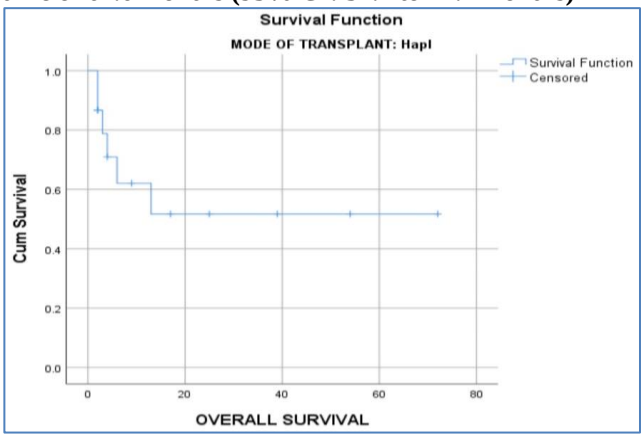

Figure-V: Survival function of female patients showing a mean survival time of 40.5 months (95% CI: 29.3 to 51.7 months).

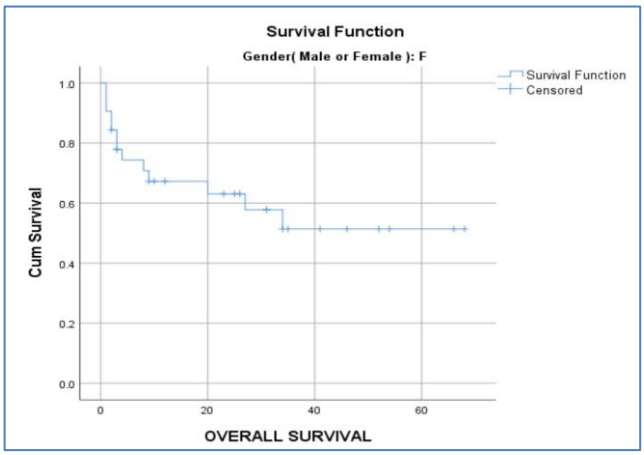

Figure-VII: Survival function of male patients demonstrating a mean survival time of 62.9 months (95% CI: 51.6 to 74.2 months)

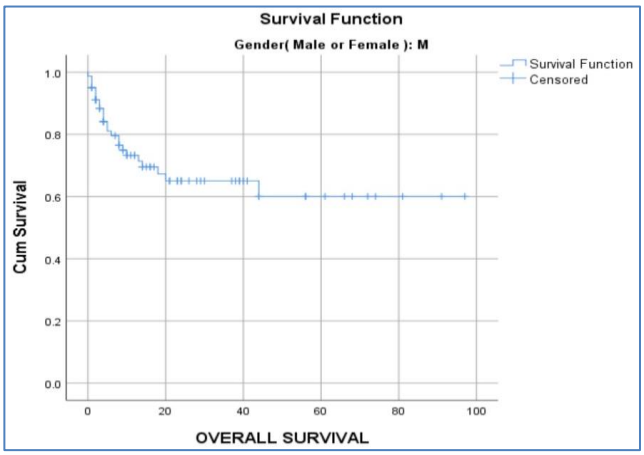

Figure-VIII: Survival function of patients who did not receive ATG demonstrating a mean survival time of 58.6 months

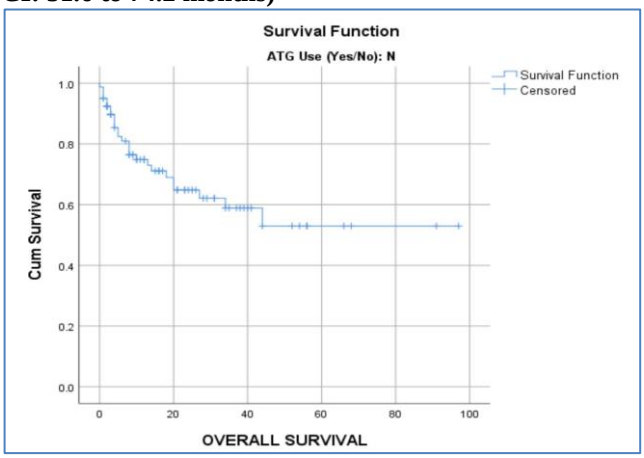

Figure-IX: Survival function of patients who used ATG showing a mean survival time of 53 months.

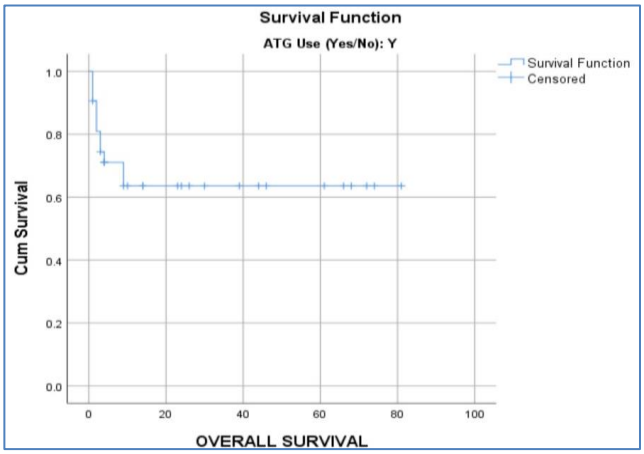

Figure-X: Survival function of patients without GVHD demonstrating a mean survival time of 65 months

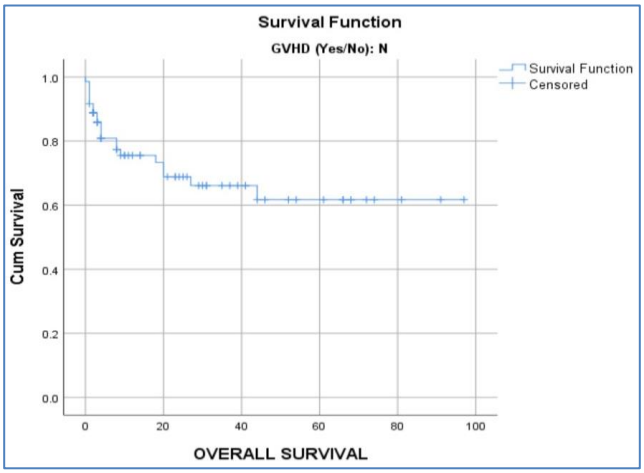

Figure-XI: Survival function of patients with GVHD showing a mean survival time of 34 months

DISCUSSION

In our study, we observed a substantial incidence of CMV infection post-HSCT, with approximately 52% of patients affected. Notably, a staggering 96.6% of these cases occurred within the early post-transplantation period, specifically within the first 100 days. This observation suggests that early CMV infection is a predominant concern following HSCT and may have significant clinical implications.

In contrast, another study from Pakistan reported a considerably lower incidence of CMV infection, with only 16% of patients (38 out of 238) experiencing CMV infection within the same post-transplantation timeframe.[21] This stark contrast in incidence rates between our study and the national research underscores potential variations in patient populations, treatment protocols, or other factors influencing the occurrence of early CMV infections post-HSCT.

In general, the incidence of post-transplant CMV disease stands at 2-3%, as reported by numerous randomized control trials,[22–24] while in actual practice, it ranges anywhere from 5-10%.[25,26] The discrepancy between the acceptable rate of CMV infections in ideal

clinical practice and the higher rates reported from lower-middle-income countries, such as in our study and other studies from Pakistan,[21] indicates that there are still gaps that have to be addressed in the context of post-transplant management in low-resource settings.

Furthermore, our findings align with a previously published study by Wu *et al*.[27], which reported that 32% of their patients developed CMV infection at a median of 23 days post-HSCT, with 89% of cases occurring within the same early post-transplantation window. The congruence between our results and Wu *et al*'s findings underscores the critical need for vigilance and proactive management in the early post-transplantation phase to mitigate the adverse effects of CMV infection, particularly within the first 100 days following HSCT.

Other studies have revealed varying incidence rates and timing of CMV infection among patients undergoing allogeneic haematopoietic cell transplantation. For instance, in a study by Rastogi *et al*, the overall incidence of CMV infection in allogeneic transplant recipients was reported at 25%, with 59 out of 239 patients experiencing CMV infection from day 0 post-transplant.[28] These findings underscore the variability in CMV infection incidence and the importance of understanding these dynamics in the context of transplantation. It is clear that CMV infection is a significant concern in the post-transplantation period, with varying incidence rates and timing across different studies, emphasizing the need for comprehensive management strategies.

In our study, we identified a notable difference in survival based on CMV PCR status. CMV PCR positive patients, considered as those who had developed CMV disease, exhibited a significantly shorter estimated mean survival time of 43 months. In contrast, CMV PCR negative patients demonstrated an extended estimated mean survival time of 70 months.

This finding is in line with Rastogi *et al*.'s results, which reported a lower survival rate for CMV disease patients compared to those without CMV disease.[28] However, it is important to note that Rastogi *et al*.'s findings did not reach statistical significance.

On the other hand, our analysis did not reveal any statistically difference in the mean survival time between adults and pediatric patients, males and females, those undergoing fully-matched allogenic and haploidentical transplants, or those receiving ATG therapy. This indicated that generally, the mean survival time was reasonable for all groups, with no single factor being associated with severely reduced survival. Similarly, the cox-regression revealed that other than CMV status, no other factors apart from ATG use had any effect on survival.

However, when stratifying the same variables and investigating the effect of CMV infection on survival, certain groups were more susceptible to the effects of CMV infection. In particular, CMV infection was associated with a decreased mean survival time amongst adults, those undergoing ATG therapy, and those with GVHD. This indicates these factors are commonly implicated in non-relapse mortality of our patients.

The use of ATG: Anti-thymocyte globulin is a regular component of conditioning chemotherapy used in transplant recipients. It is commonly used in aplastic anemia, thalassemia and few conditioning protocols for leukemias. In CMV seropositive individuals use of ATG increases the risk of CMV infection and we have seen the same finding in our cohort. GVHD is also a risk factor for CMV reactivation since use of high dose steroids leads to CMV reactivation as well.

CONCLUSION

In conclusion, CMV represents a significant cause of post-transplant morbidity and mortality, and an understanding of the factors worsening the prognosis in the context of post-transplant CMV infections is important to improve clinical practice. Overall frequency of CMV infection in our study was 52% with majority occurring in first 100 days of transplant. Adult population with GVHD and patients receiving ATG had a decreased overall mean survival time.

ACKNOWLEDGEMENTS

We would like to acknowledge the contributions of Tayyaba Muneer, Hamzah Jehanzeb, Usman Shaikh, Zehra Fadoo, Salman Naseem Adil, Munira Moosajee, and Maria Ali towards this study.

CONFLICT OF INTEREST

None

GRANT SUPPORT & FINANCIAL DISCLOSURE

Declared none

AUTHOR CONTRIBUTION

Zurrya Faseeh Khan: Main conception of the study, design the study idea, data analysis, manuscript writing, final approval, agreement to be accountable for all aspects of the work

Nabiha Saeed: Data acquisition, wrote research paper, final approval, agreement to be accountable for all aspects of the work

Dahir Ashfaq: Data acquisition, analysis, wrote research paper, final approval, agreement to be accountable for all aspects of the work

Mashal Waqas: Data acquisition, draft the work, final approval, agreement to be accountable for all aspects of the work

Reyan Hussain Shaikh: Data analysis, interpretation of data, draft the work, final approval, agreement to be accountable for all aspects of the work

Natasha Ali: Design the study idea, data analysis and interpretation, review of work critically, final approval, agreement to be accountable for all aspects of the work

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