



Outcomes of COVID-19 in Hematopoietic Stem Cell Transplant Recipients: Multicenter Retrospective Analysis

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Abstract COVID-19, caused by the severe acute respiratory syndrome corona virus 2 (SARS-CoV-2), was declared a pandemic by the World Health Organization on March 9, 2020. Hematopoietic stem-cell transplantation (HSCT) recipients may be highly susceptible to infection and related pulmonary complications due to nascent immune systems or organ damage from treatment-related toxicities. Poor outcomes in such group of patients were linked to older age, steroid therapy at the time of COVID-19 infection, and COVID-19 infection within a year of HSCT. We studied a cohort of 28 hematopoietic stem cell transplant recipients (male 17, M:F ratio of 1.5) with COVID-19 infection from 1st June 2020, through 31st December 2020 for outcome. Fever was the most common symptom at the time of presentation in 22 (78.5%) patients. Mortality rate at Day 28 and Day 42 was found to be 4/28 (14.3%) and 7/28 (25%) respectively. Patients within one year of HSCT and severe infection had higher day 28 mortality (with p values = 0.038)⁴. There was no relation of mortality with type of transplant.

Keywords COVID-19 · Hematopoietic stem cell transplant · Mortality rate · Infection

Introduction

Coronavirus Disease 2019 [COVID-19], caused by the severe acute respiratory syndrome corona virus 2 (SARS-CoV-2), was declared a pandemic by the World Health Organization on March 9, 2020. By February 2021, the disease has affected over 117 million people all over the world and 11.2 million people affected in India with death of 158 thousand Indian people reported.

Patients with hematological malignancies have poorer outcome with COVID-19 than the general population and patients with hematological malignancies that do not have COVID-19 [1].

Sharma. A et al. Study showed mortality rates as 32% [allogeneic] and 33% [autologous] HSCT recipients whereas Gunjan. L. Shah et al. reported mortality rate of 22% at day 30 [2, 3].

Varma. A et al. reported that poor outcomes were linked to older age, being on steroids at the time of COVID-19 diagnosis, and COVID-19 infection within a year of HSCT [4].

Patients having hematological malignancies are more prone to develop respiratory tract infections and serious complications [5]. Various studies have reported mortality rate of approximately 25–45% in patients with hematological malignancies infected with COVID-19 [6–8]. Wang. D et al. reported that patients with hematological malignancies requiring frequent visits to hospitals or clinics are at high risk of getting infected due to their immunocompromised state [9].

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Material & Methods

This was a multicenter retrospective analysis performed in four transplant centers across Delhi, India.

We studied a cohort of hematopoietic stem cell transplant recipient with COVID-19 infection from 1st June 2020, through 31st December 2020. The study was approved by the Institutional Review Board (IRB) of the Institution.

COVID-19 was classified as mild (no oxygen supplementation required with SpO₂ > 95%), moderate (supplemental oxygen required with SpO₂ [90–95%]), or severe (mechanical ventilation required with SpO₂ < 90%) [10].

Quantitative real-time reverse transcriptase-polymerase chain reaction (qRT-PCR) of nasal and/or oropharyngeal swabs was used to diagnose SARS-CoV-2 infection. Baseline demographic data was collected from electronic/manual health records and entered in a common Microsoft Excel spreadsheet format. Each of the centers anonymized their data and sent it to a centralized database. Data was centralized and analyzed by statistical methods.

Outcomes

Primary objective was to assess the + 14 and + 28 days mortality in the population. Secondary goals included determining the relationship between age, co morbidities, and severity and outcome.

Analytical Statistics

Descriptive statistics (including median, mean, and range) were used to describe the central tendency and dispersion of variables. OS curve was plotted using the Kaplan Meier method and a univariate comparison was done using log rank method. Categorical and continuous variables were analysed using a Pearson's chi square (χ) or Fisher's exact and independent *t* test to determine the potential factors for severe COVID-19 infection and day 28 mortality post COVID-19 infection. A *p* value of less than 0.05 was considered statistically significant. All statistical analysis was done using statistical package for social science software (SPSS 21, IBM SPSS Statistics for Windows, version 21.0; IBM Corp., Armonk, NY, USA).

Results

Twenty eight patients (male 17, M: F ratio of 1.5) who underwent hematopoietic stem cell transplant [HSCT] infected with SARS-CoV-2 were analyzed. Median age of this cohort is 50.5 yrs. (6–69 yrs.). Co-morbidities were

present in 14 (50%) patients. Three (10.7%) patients had 2 co-morbid conditions. Common diagnoses were Acute Myeloid Leukemia [AML] 4 (14.28%), Acute Promyelocytic Leukemia [APML] 1(3.57%), Acute Lymphoblastic Leukemia [ALL] 2 (7.14%), Chronic Myeloid Leukemia [CML] 2 (7.14%), Diffuse Large B-Cell Lymphoma [DLBCL] 1 (3.57%), Hodgkin Lymphoma [HL] 2 (7.14%), Multiple Myeloma [MM] 14 (50%), B-Thalassemia 1 (3.57%) and Severe Aplastic Anemia [SAA] 1 (3.57%). Baseline Characteristics and Clinical features of Hematopoietic Stem Cell Transplant recipients with SARS-CoV-2 infection are enlisted in Table 1.

Median number of prior lines of therapy before HSCT was 1 ranging from (1–5). Patients with Allogeneic transplant were 10 (35.7%) and autologous transplant were 18 (64.3%) patients. Three out of 10 Allogeneic HSCT recipients had GvHD.

Fifteen (53.5%) HSCT recipients were receiving maintenance therapy or immunosuppression at the time of SARS-CoV-2 infection. Median time to SARS-CoV-2 infection from HSCT is 258.5 days ranging (12–2042) days.

SARS-CoV-2 Infection

Fever was the most common symptom at the time of presentation i.e. 22 (78.5%), followed by cough 15 (53.5%) and Dyspnea 6 (21.4%). Other symptoms like Loose stools in 2 (7.14%), Anosmia in 1 (3.57%) and Sore throat in 1 (3.57%) were observed at presentation. Eleven (39.3%) patients had more than 1 symptom. Two (7.14%) patients were asymptomatic at diagnosis.

Majority of the patients were hospitalized i.e. 15 (53.5%). Median days of hospitalization were 22 days ranging (6–39) days.

Sixteen (57.1%) patients were in Mild severity while 5 (17.8%) and 7 (25%) were in Moderate and Severe category at COVID-19 diagnosis. Six of 18 (33.3%) Autologous recipients and 1 of 10 (10%) Allogeneic recipient had severe COVID-19 infection.

High Resolution Computed Tomography [HRCT] of chest was done in 13 (46.6%) patients. Five (38.4%) patients were suggestive of COVID-19 pneumonia.

Fourteen (50%) Patients received oxygen support. 13 were initially on nasal oxygen, 1 patients was directly put on HFNC who further progressed to Invasive Ventilation. Out of 13 patients, 1 progressed to NRBM, 2 progressed to HFNC and 3 progressed to Invasive Ventilation. Median duration of oxygen support was 5 days [range 0–33].

Seventeen (60.7%) patients received therapy for COVID-19 in form of antiviral drug (n = 12, 70.5%) [Remdesivir 200 mg IV on day 1 and 100 mg IV on next 4 days—(n = 10, 58.8%) and Favipiravir 1800 mg twice

Table 1 Baseline characteristics and clinical features of hematopoietic stem cell transplant recipients with COVID-19 infection

Characteristics	All (n = 28)	Allogeneic SCT (n = 10)	Autologous SCT (n = 18)
Median age in years; range	50.5 (6–69)	32.5 (6–49)	57.5 (28–69)
Male sex, n (%)	17 (60.7%)	7 (70%)	10 (55.56%)
#Median prior number lines of therapy before SCT (range)	1 (1–5)	1.5 (1–3)	1 (1–5)
Type of SCT			
Allogeneic SCT, n (%)	10 (35.7%)	NA	NA
Autologous SCT, n (%)	18 (64.3%)		
*GVHD post SCT, n (%)	3 (10.7%)	3 (30%)	–
Patient on immunosuppression at COVID diagnosis, n (%)	7 (25%)	7 (70%)	–
Relapse post SCT, n (%)	3 (10.7%)	0	3 (16.67%)
SCT recipients on Therapy at time of COVID infection, n (%)	15 (53.5%)	1 (10%)	14 (77.78%)
Median time to COVID infection from BMT in days, range	258.5 (12–2042)	157.5 (12–1384)	799.5 (90–2042)
Radiologic examination, n (%)	21 (75%)	9 (90%)	12 (66.67%)
Pneumonia	9 (32.1%)	2 (20%)	7 (38.8%)
Normal	9 (32.1%)	5 (50%)	4 (22.23%)
Other abnormality	3 (10.7%)	2 (20%)	1 (5.56%)
Severity of COVID-19 infection, n (%)			
Mild	16 (57.1%)	9 (90%)	7 (38.8%)
Moderate	5 (17.8%)	0	5 (27.7%)
Severe	7 (25%)	1 (10%)	6 (33.3%)
Hospitalisation, n (%)	15 (53.5%)	5 (50%)	10 (55.6%)
Median days of hospitalisation, range	22 (6–39)	22 (15–39)	20 (6–33)
ALC at diagnosis available, n (%)	21 (75%)	9 (90%)	12 (66.67%)
Median ALC, range	1035 (229–5406)	900 (229–3410)	1190 (560–5406)
ANC at diagnosis available, n (%)	21 (75%)	9 (90%)	12 (66.67%)
Median ANC, range	3990 (450–20,069)	3120 (450–20,069)	4560 (630–7970)
D Dimer at diagnosis available, n (%)	11 (39.3%)	4 (40%)	7 (38.8%)
Median maximum D -Dimer, range	991.6(160–15,733)	8359.3 (466.6–15,733)	640 (160–1731)
CRP values available, n (%)	11 (39.3%)	3 (30%)	8 (44.45%)
Median maximum CRP values, range	30.9 (0.6–349)	4.8 (2.4–123)	57 (0.6–349)

SCT stands for stem cell transplantation

#Prior lines of therapy is applicable for hematological malignancy

*GVHD data is applicable for allogeneic Stem Cell Transplant only

daily on day 1 followed by 800 mg twice daily for next 7 days—(n = 2, 11.7%), Tocilizumab 400 mg × 2 doses (n = 2, 11.7%), Dexamethasone doses variable from 6 mg per day for 10 days (n = 12, 42.85%) and prophylactic anticoagulants Inj Enoxaparin @ 1 mg per kg per day till discharge (n = 12, 42.85%). Convalescent Plasma Therapy [COPLA] was used in 6 (35.3%) patients with COVID-19 infection.

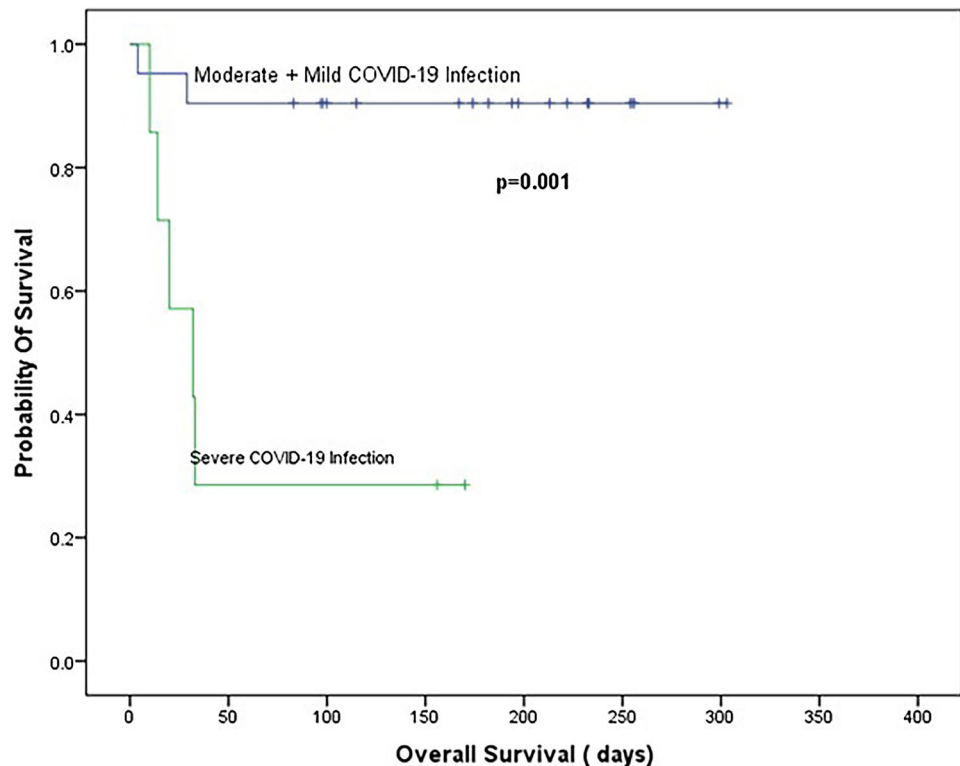
Survival

Mortality rate at Day 14 and Day 28 was found to be 3/28 (10.7%) and 4/28 (14.3%) respectively. Three patients expired beyond 28 days of follow up. Latest mortality was

seen on day + 33 of COVID-19 infection. Overall survival [OS] was 21/28 (75%). Post 28 days death is also due to COVID-19 pneumonia. Of 7 deaths, 2 patients were in mild and 5 patients were in severe category of COVID-19. Two mild patients at baseline progressed to severe disease and died during hospitalization.

Patients with Mild COVID-19 infection associated with good OS as compared to patients with Moderate and Severe COVID-19 infected patients with a highly significant $p = 0.001$. Also, patients with Severe COVID-19 infection associated with higher day 28 mortality as compared to Mild and Moderate COVID-19 infection with a significant $p = 0.038$ as depicted in Fig. 1.

Fig. 1 Overall survival probability for severe COVID-19 infection versus mild + moderate COVID-19 infection



Patients within one year of HSCT and severe infection had higher day 28 mortality (with p values = 0.038). Mortality was not significantly associated with other parameters.

Discussion

Owing to immunosuppression, patients with hematologic malignancies and those with post transplant status expected to have a higher risk of COVID-19 infection and severe disease [11].

While a Chinese study reported a two-fold elevated risk of acquiring COVID-19 in haematological malignancy patients compared to the general population, and if infected, had a greater risk of severe disease and mortality [1, 12].

Study from Italy reported a mortality ratio of 41.3 amongst 536 patients of haematological malignancies with or without COVID-19 infection [13].

A study from India reported overall mortality of COVID-19 in patients with haematological malignancies as 20% which is quite similar to our data i.e. 25% [7].

Median time from HSCT to COVID-19 Infection is reported to be 61 days (7–343 days) as compared to 258.5 days (12–2042 days) in our study [14]. Median time to COVID-19 infection is 157.5 days for Allo-HSCT compared to 799.5 days in Auto-HSCT recipients.

Majority of Autologous recipients were on maintenance treatment at the time of COVID-19 diagnosis.

Mirgh. S et al. reported a case of an elderly patient post HSCT, who received tocilizumab and recovered whereas in our study cohort only 2 patients received tocilizumab (below 60 years) and both died within 28 days of SARS COV-2 infection [15].

Rajendra. A et al. reported data of 6 HSCT patients with COVID-19 infection and showed that use of antivirals and tocilizumab can offer favourable outcomes in COVID-19 infections, whereas in our cohort majority of the patient did not received tocilizumab. Hence no such conclusion can be made as per our data [16].

Sharma. A et al. study showed the median follow-up of survivors was 21 days (IQR 8–41, range 1–93) for allogeneic HSCT recipients ($n = 184$), and 25 days (IQR 12–35, range 1–109) for autologous HSCT recipients. In our study pool, median follow-up of survivors was 272 days (range 10–406) 329.5 days (range 21–402) for allogeneic HSCT recipients ($n = 10$), and 261.5 days (range 10–406) for autologous HSCT recipients ($n = 18$) [2].

One of the Indian study reported Median length of stay for the initial hospitalization was 8 days (IQR, 5–18 days), while in our study cohort it was 8.5 days [3].

Strategies such as telemedicine, reduced clinic visits, less intensive chemotherapy and immunotherapy regimens, switching to subcutaneous or oral therapies rather than

intravenous therapies where possible, and postponing stem cell transplant procedures to a more favourable time have all been considered to reduce the risk of patient exposure to the viral infection [15].

In conclusion, patients with severe COVID-19 infection have worse outcomes irrespective of type of transplant.

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Data Availability The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declarations

Conflict of interest The authors declare that they have no conflict of interest.

Ethical Approval All authors stated that the study has been approved by the appropriate institutional review board and have been performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Informed consent Since this is a retrospective study hence no formal informed consent is required.

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