

A review on recipients of hematopoietic stem cell transplantation patients with COVID-19 infection

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Abstract: For the last few months, various geographical regions and health sectors have been facing challenges posed by the current COVID-19 pandemic. COVID-19 has led to significant disruption in the normal functioning of potentially life-saving therapies of hematopoietic cell transplant and chimeric antigen receptor therapy. As transplant physicians are gaining more information and experience regarding the undertaking of these complex procedures during the ongoing COVID-19 pandemic, we believe it is important to discuss the challenges faced, prognostic risk factors, and outcomes of COVID-19 in post-hematopoietic stem cell transplantation patients based on the available real-world data.

Keywords: COVID-19, Cancer, virus, stem cell transplantation

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Introduction

Hematopoietic stem cell transplantation (HSCT) is a highly complex procedure, which is performed with the intent to cure many hematological, oncological, and various genetic disorders. It involves multidisciplinary effort and a dedicated transplant team to perform HSCT. However, there are many factors that affect the immediate transplant outcome, long term survival, and quality of life of patients.

During the current pandemic, the risk of acquiring COVID-19 in transplant recipients has threatened the patient as well as the transplant team.¹ Uncertainty as to the transplant outcome, worsening of graft-versus-host disease, complex interaction of various anti-COVID-19 drugs and immunosuppressant agents, lack of blood products, and emotional breakdown of the patient and the treating staff are only a few of the many challenges being faced by our patients undergoing transplant and by the corresponding transplant team members.^{2,3} There are approximately more than a million transplant patients across the globe, with approximately 100,000 new transplantation additions every year. Hence there is significant

risk for these patients to acquire this coronavirus infection.⁴

International collaboration: need of the hour

Various transplantation societies across the globe have come together to unite against this deadly virus and its aftermath. International experts and renowned scientists from various subspecialties have shared their individual and institutional experiences to strengthen the data collaboration so that the rest of the world could benefit from the same.^{5,6} With regard to HSCT, the European Hematology Association, European Society for Blood and Marrow Transplantation (EBMT), American Society of Hematology, and American Society of Clinical Oncology are only a few of the various societies who have collaborated at various levels to help transplant physicians across the world.⁷ The latest updated guidelines from EBMT (Version 11 – 6 November 2020) discussed the challenges of undertaking HSCT during COVID-19, with proposed recommendations.⁸

Similarly, the Center for International Blood and Marrow Transplant Research (CIBMTR) is a

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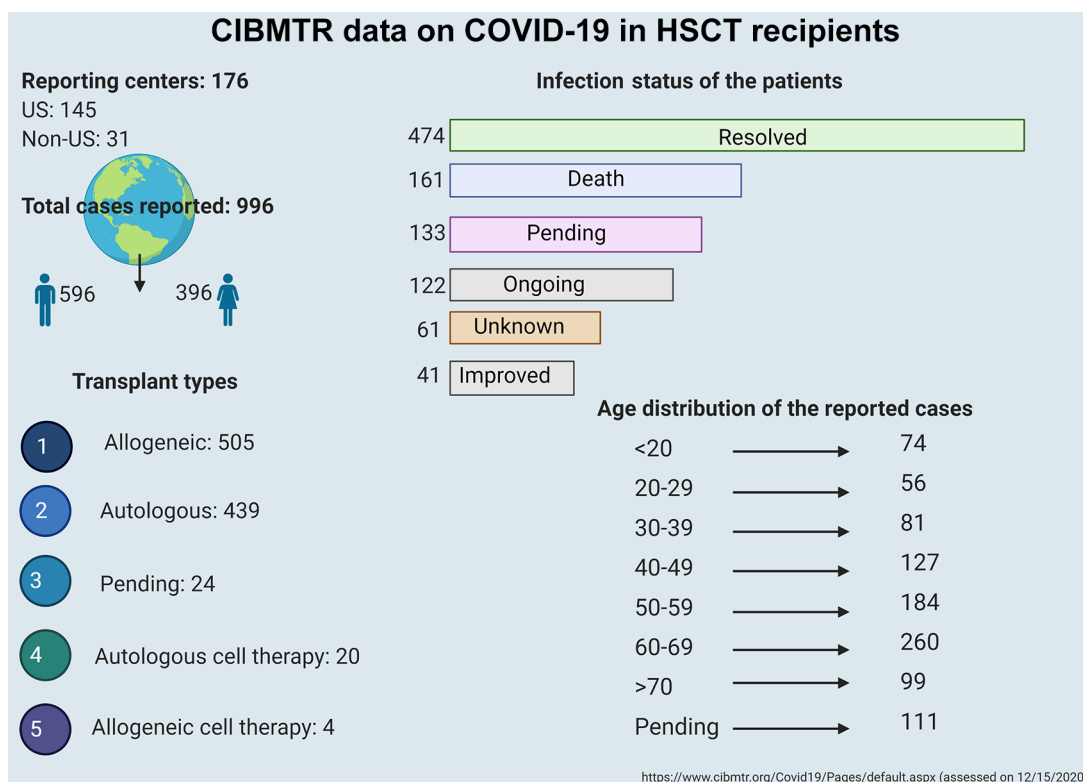


Figure 1. Descriptive representation of the reported cases of COVID-19 cases in HSCT recipients.

Adapted from CIBMTR website, assessed on 15 December 2020.

CIBMTR, Center for International Blood and Marrow Transplant Research; HSCT, hematopoietic stem cell transplantation.

research program which works in close association with the National Marrow Donor Program located at Wisconsin, USA. CIBMTR has launched a platform to gather the data from various transplant centers.⁹ Data so far (to 15 December 2020) includes 996 cases being reported from 166 transplant centers (145 US, 31 non-US). In total, there were 505 COVID-19 patients after allogeneic HSCT and 439 COVID-19 patients after autologous HSCT reported to CIBMTR. The majority of the patients were in the age group of 60–69 years. However, almost half of the patients (47.5%, 474/996) recovered from the COVID-19 infection. Almost 15% are reported to have died, with rest of the patients in various phases of treatment (pending, improved, unknown, and ongoing) (Figure 1).

Similar effort has been made by the European Reference Network (ERN Transplant Child) to gather the data on the pediatric population undergoing transplantation (both solid plus hematopoietic). A recent survey study was carried out by

Doná *et al.*¹⁰ that involved 18 centers, members of ERN Transplant Child distributed in 11 European countries. They reported 14 COVID-19 cases among pediatric transplant candidates (renal, hepatic, hematopoietic; two of each) and recipients (two renal, three hematopoietic, three hepatic) up to 14 April 2020.

Available literature

Viral load and its significance in immunocompromised patients

SARS-CoV-2 virus adherence, mode of entry, replication, and disease manifestation have been studied in detail in the last few months.¹¹ ACE2 and transmembrane protease, serine 2 (TMPRSS2) together establish a crucial step for SARS-CoV-2 virus entry to the host cell.¹² This has also been recently studied in other, different, species as well.¹³ Just like many other illnesses, COVID-19 disease has been studied for its association between viral load and infectivity/mortality.¹¹ A recent study by Pujadas *et al.*¹¹

conducted in over 1000 patients found a significant difference in the mean log₁₀ respiratory secretion viral load (5.2 copies per mL *versus* 6.4 copies per mL) in between the patients who remained alive *versus* those who had died due to COVID-19 disease. They proposed the idea that the transformation of a qualitative PCR to a quantitative assessment with viral load assessment can help in stratifying high-risk patients early in the disease course. A similar observation was noted by Magleby *et al.*¹⁴ in their 678-patient data in which they found that a high viral load independently predicted higher mortality.¹⁴ We believe that HSCT patients would certainly benefit if we could find a viral-specific quantitative prognostic parameter that can predict the COVID-19 disease course at the earliest in these immunocompromised patients. In a similar attempt, Roedl *et al.*¹⁵ published a case series of six patients with HSCT or chimeric antigen receptor T-cell therapy who required intensive care unit (ICU) level of care for COVID-19 pneumonia.¹⁵ Unlike the reports by Pujadas *et al.*¹¹ and Magleby *et al.*,¹⁴ they did not find any correlation to suggest that a high respiratory viral load at admission could correlate with high mortality. However, they did find a significant viremia in most of their critically ill patients.¹⁵ In five of six HSCT patients, the viral RNA load in plasma increased over time. Also, recent studies have found a more prolonged duration of viable SARS-CoV-2 viral shedding in immunocompromised patients as compared with immunocompetent patients.^{15,16} This could be of significant importance as a prolonged isolation may be required in such patients to prevent the spread to other health care providers, medical staff, and family members.

Who is at risk?

High-risk population. As per the available literature so far, for allogeneic HSCT, recipients who are on active immunosuppression are considered high risk for complications if they acquire COVID-19.¹⁷ This risk is regardless of their age at the time of undergoing transplantation. Similarly, for autologous HSCT, patients who are within 6 months from their transplant are at higher risk for COVID-19.¹⁸

Risk like normal population. Prolonged immunosuppression, graft-*versus*-host disease and time passed since HSCT are amongst the predisposing factors that can potentially make HSCT recipients

acquire SARS-CoV 2 infection. Allogeneic transplant recipients who are beyond 2 years since HSCT, have no graft-*versus*-host disease and off all immunosuppression have a risk level the same as that of the general population. Similarly, for autologous transplant recipients, after 6 months from HSCT, they are considered under usual risk given their immunocompetence (Figure 2).

Type of transplant and COVID-19

Various individual institutions, countries, and transplant societies have published their experience with COVID-19 infection in the HSCT setting (Table 1). Many of these studies are limited to case report/series, hence have a small sample size. These cannot be used to definitively ascertain various variables of HSCT and risk to acquire COVID-19. Based on available data, prolonged immunosuppression before HSCT, use of myeloablative regimen, and prolonged inpatient stay were associated with high risk to acquire infection. Interestingly, patients who received post-transplantation cyclophosphamide (PTCy) for graft-*versus*-host disease prophylaxis developed milder symptoms when they acquired SARS-CoV-2 infection.¹⁹

Clinical factors affecting poor outcome

Presence and number of chronic co-morbidities are one of the major risk factors for poor outcome. Even in non-HSCT patients, comorbidities such as congestive heart failure, chronic renal disorders, diabetes, chronic respiratory illnesses have been associated with poor outcome if they acquire COVID-19. Just like in any immunocompetent patient, these factors also play a significant role in post-HSCT patients as well.

Few institutional studies have been recently published across the globe reporting the clinical outcome of HSCT recipients who acquired COVID-19.^{20,23} Sharma *et al.*²⁰ studied 318 HSCT recipients diagnosed with COVID-19 reported to the CIBMTR. They found that almost half of the patients had milder form of disease severity (155/318 patients, 49%), while 14% (45/318) patients had severe disease and required mechanical ventilation. At 30th day of follow-up, overall survival was reported as 68% amongst allogeneic HSCT recipients and 67% for autologous HSCT recipients. Old age (>50 years), male sex,

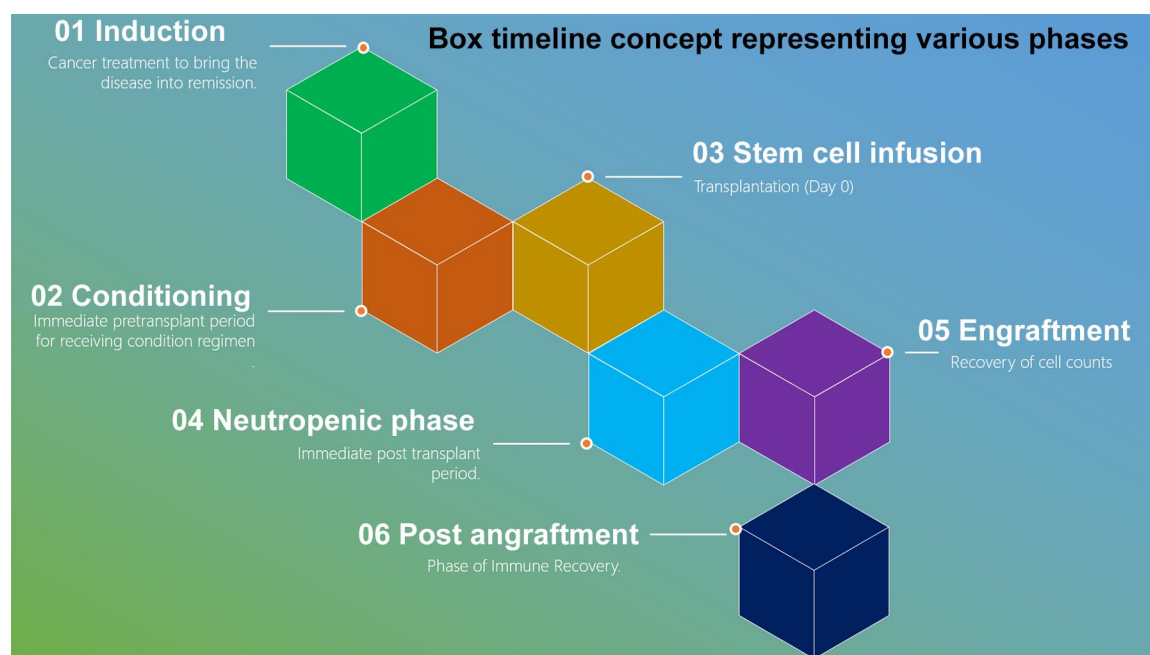


Figure 2. Various phases of hematopoietic stem cell transplantation during which patients are prone to various infections, including COVID-19.

HSCT within last 12 months had a higher mortality risk among allogeneic HSCT recipients, while patients with lymphoma had higher mortality than myeloma autologous HSCT recipients. In another study on 77 COVID-19-positive HSCT patients, Shah *et al.*²⁴ reported the number of co-morbidities, chest infiltrates, and neutropenia to be significantly associated with common endpoint outcome of a higher O₂ supplementation and mortality (Table 1).²⁴ Contrarily, Maurer *et al.*,²¹ from Dana-Farber Cancer Institute, reported a very encouraging experience from their institute.²¹ In total, 127 patients underwent cellular therapy (62 adult allo-HSCT, 38 auto-HSCT, and 27 CAR-T patients). Up to day 100 post transplant, only one of the 127 patients suffered from COVID-19 pneumonia. Unfortunately, this patient with diffuse large B-cell lymphoma who had received tisa-genelecleucel acquired SARS-CoV 2 viral infection on day 51 of infusion and ultimately died on day 121. Apart from this incident, Maurer *et al.*²¹ did not find any differences in 100-day overall survival, progression-free survival, and rates of non-COVID-19 infections when compared with patients from the pre-pandemic era. Due to these positive results, Maurer *et al.*²¹ recommended that with appropriate safeguards, cellular therapies including CAR-T cell therapy can be safely executed even during the COVID-19 pandemic.

From EBMT, Ljungman also recently shared their experience. As per the EBMT COVID-19 Registry, the society was able to collect data from 22 countries which included 382 patients (236 allogeneic, 146 autologous). Out of these, a total of 107 patients succumbed, of which COVID-19 was listed as the principal cause of mortality in 95 of patients.^{9,31} Subsequently, larger patient data were reported from collaborative effort of various hospitals in European countries.^{22,23} For instance, a collaborative study was conducted by Infectious Complications Subcommittee (GRUCINI) of the Spanish Hematopoietic Stem Cell Transplantation and Cell Therapy Group (GETH).²² This study, led by Piñana *et al.*,²² included 41 hospitals in Spain and included 367 pediatric and adult patients with hematological malignancies. It also included 65 patients of allo-HSCT and 58 patients of auto-HSCT. Surprisingly, they found that COVID-19-related mortality was higher in non-HSCT (31%) as compared with autologous stem cell transplantation (ASCT) (17%) and allo-stem cell transplantation (SCT) (18%) ($p=0.02$).

Laboratory factors affecting poor outcome

There is enough literature published so far that has confirmed thrombocytopenia, raised d-dimers, and lymphocytopenia to be associated with poor

Table 1. Recently reported studies on development of COVID-19 infection in hematopoietic stem cell transplantation patients with outcome.

Author	Cases	Allogeneic	Autologous	CAR-T cell	Primary outcome	Causes of death
Sharma <i>et al.</i> ²⁰ (CIBMTR data, worldwide data collection)	318	184	134	0	66 patients died.	COVID-19 was the cause of death in the majority of the patients (84.84%)
Maurer <i>et al.</i> ²¹ (DFCI, USA)	127	62	38	27	Only one patient (tisagenlecleucel recipient) died	Due to COVID-19 pneumonia-related complications
Piñana <i>et al.</i> ²² (GETH data, data of 41 Spanish hospitals)	123	65	58	0	25 patients died	COVID-19 was the cause of death in the majority of the patients (88.00%)
Passamonti <i>et al.</i> ²³ (The Italian Hematology Alliance, 66 Italian hospitals)	82	31	51	0	28 patients died	–
Shah <i>et al.</i> ²⁴ (MSKCC, USA)	77	35	37	5	Overall survival at 30 days was 78%	All 14 deaths were reported in patients with severe COVID-19
Yazidi <i>et al.</i> ²⁵ (Oman)	1 (Pediatric)	1	0	0	Survived	Not applicable
Rossoff <i>et al.</i> ²⁶ (USA)	1 (Pediatric)	1	0	0	Survived	Not applicable
Jarmoliński <i>et al.</i> ²⁷ (Poland)	1 (Pediatric)	1	0	0	Survived	Not applicable
Doná <i>et al.</i> ¹⁰ (Spain)	3 (Pediatric)	NA	NA	NA	100% survived	Not applicable
Sultan <i>et al.</i> ²⁸ (Egypt)	7	7	0	0	All survived	Not applicable
Malard <i>et al.</i> ²⁹ (France)	7	5	1	1	Overall survival 85%	Not mentioned
Kanellopoulos <i>et al.</i> ³⁰ (United Kingdom)	7	6	1	0	One died due to AML relapse Two died due to COVID-19 Four patients are alive	Intracranial bleed due to thrombocytopenia in the setting of AML relapse (1 patient) Pulmonary embolism (1 patient) ARDS (1 patient)
Haroon <i>et al.</i> ⁴ (Riyadh)	11	6	5	0	Overall survival 100%	Not applicable

CIBMTR, Center for International Blood and Marrow Transplant Research; DFCI, Data Farber Cancer Institute; GETH, Grupo Español de Trasplante Hematopoyético; MSKCC, Memorial Sloan Kettering Cancer Center; NA, Not available; AML, Acute Myeloid Leukemia; ARDS, Acute Respiratory Distress Syndrome.

prognosis in otherwise immunocompetent patients.^{32,33} The challenging part in extrapolating the same findings to patients suffering with cancer, especially with hematological malignancies, is that these patients already have many hematological perturbations owing to their disease pathophysiology. Hence, many times it is unrealistic to predict the disease severity in this subset of patients based on the laboratory data. HSCT patients have additional challenges to tackle, but not only limited to engraftment syndrome, delayed marrow recovery, drug induced pancytopenia, graft failure and so on.

COVID-19 in pediatric population undergoing HSCT

Data on pediatric population on COVID-19 is far more limited than in the adult population due to the lesser number of transplantations per year.³⁴ Also, the prevalence of COVID-19 is higher in the adult population when compared with children.³⁵ Hence our understanding of behavior of COVID-19 disease in the pediatric HSCT recipient population is limited to case reports. Jarmoliński *et al.*²⁷ reported a case in a 9-year-old girl of pre-B common acute lymphoblastic leukemia who developed COVID-19 disease

during the post-HSCT period. As mentioned above, Doná *et al.*¹⁰ recently reported the results from their survey involving the ERN Transplant Child members. None of the patients required ICU level of care, and no deaths were reported.

Clinically significant observations

In a case series of seven patients, Sultan *et al.*²⁸ found that despite using myeloablative conditioning regimens, they did not find any significant increased mortality secondary to COVID-19 infection. They also noted that use of PTCy for graft-versus-host disease prophylaxis was associated with mild COVID-19 symptoms. They postulated that a PTCy regimen might have a shielding role against COVID-19-related cytokine storm. Similarly, Kanellopoulos *et al.*³⁰ in their case series noted that patients with non-myeloablative conditioning and PTCy had milder symptoms despite other high-risk features like obesity and diabetes mellitus. In mouse models, PTCy has been found to expand FoxP3+CD4+T-regulatory cells which have shown to reduce pulmonary inflammation secondary to ARDS.^{36,37} Researchers have postulated that less severe COVID-19 infection in patients receiving PTCy could be due to abrogation of cytokine release syndrome (CRS) associated with COVID-19. This is like the concept of using PTCy in haplo-identical HSCT recipients to diminish the associated CRS.^{28,30}

Hence, use of non-myeloablative treatment regimen and PTCy use has been found to have a less severe clinical course if COVID-19 is acquired.^{29,30}

Patients undergoing HSCT require to be inpatients for a prolonged period. This makes them more prone to acquiring nosocomial infections. This was also found applicable for our patients with hematological malignancies who acquired SARS-CoV-2 as a part of nosocomial infection.³⁸ Kanellopoulos *et al.*³⁰ felt that all the patients in their study acquired COVID-19 disease *via* a nosocomial route. Hence it would not be unreasonable to frequently test health care providers, including the nursing staff and other transplant team members, for asymptomatic carriers of SARS-CoV-2 infection.

Conclusion

There is a scarcity of data on outcome of patients with HSCT who get infected with COVID-19.

So far, the majority of the available information is based on reports from the individual institutions. As more transplant physicians are now resuming normal functioning of their transplant units, possibilities of absolute increase in the number of transplant patients getting infected with COVID-19 is expected to rise. While our understanding about COVID-19 has improved dramatically, a special population such as HSCT patients remains at high risk and needs special attention.

Author contributions

All authors have seen the manuscript and agree to the content and data. All the authors played a significant role in the paper. KKS wrote the manuscript, gathered the data, reviewed the manuscript, and did the revision. ADS as well gave essential inputs, proofread the material, gave inputs during revision phase.

Conflict of interest statement

The authors declare that there is no conflict of interest.

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Ethical statement

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