Severe acute respiratory syndrome coronavirus 2 infection in the stem cell transplant recipient — clinical spectrum and outcome

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INTRODUCTION

The emergence of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causative agent of coronavirus disease 2019 (COVID-19), has profoundly affected the care of hematopoietic stem cell transplant (HSCT) recipients. In view of the serious manifestations associated with other respiratory viral infections – such as influenza or respiratory syncytial virus (RSV) – in this and other groups of immune compromised hosts [1], it was early clear that HSCT should be considered as a risk factor for severe course of SARS-CoV-2 infection [2]. Indeed, it has been shown that patients with hematological malignancies and COVID-19 have poorer outcomes than the general population [3,4]. Ongoing immunosuppression and treatment-related toxicities resulting in immune dysregulation, mucositis or graft-versus-host disease (GvHD) would further contribute to increase the risk of complications among HSCT patients. On the other hand, the overwhelming of healthcare resources and travel restrictions imposed in most Western countries during the first months of the pandemic negatively impacted HSCT activity, particularly for allogeneic procedures [5]. A report from a large donor registry from six...
KEY POINTS
- The incidence of coronavirus disease 2019 (COVID-19) across institutional hematopoietic stem cell transplant (HSCT) cohorts vary according to regions and study periods (from 0.4% to 8.3%), although it is still unclear whether these patients face a higher risk of developing symptomatic infection as compared to the general population.
- The clinical manifestations of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection after HSCT are similar to those seen in other immunocompromised hosts, with fever, cough, upper respiratory tract symptoms, diarrhea and vomiting as the most common symptoms at presentation.
- The kinetics of SARS-CoV-2 in HSCT recipients are characterized by a more prolonged nasopharyngeal viral shedding than immunocompetent patients.
- Mortality rates are overall comparable across studies (ranging between 14.8% and 28.4%), and seem not to significantly differ from those reported for nontransplant hematological patients that required hospitalization during the first pandemic wave.
- Older recipient age, shorter time interval between transplantation and COVID-19 diagnosis, status of the underlying hematological disease and amount of immunosuppression are risk factors for mortality, whereas differences in outcomes between allogeneic and autologous procedures have been observed in most studies.

THE CLINICAL SPECTRUM OF CORONAVIRUS DISEASE 2019 IN THE HEMATOPOIETIC STEM CELL TRANSPLANT POPULATION

Since the early small, single-center case series reported during the first months of the pandemic [8,9], various large multinational cohort studies involving tens to hundreds of patients have been published over the past months [10–13,14] (summarized in Table 1), providing a comprehensive description of SARS-CoV-2 infection in both allogeneic and autologous HSCT.

Incidence and patient characteristics
Only a few studies have attempted to estimate the incidence of COVID-19 in the corresponding institutional cohorts, although reported rates greatly varied across regions and study periods (from 0.4% in 25 French centers between March and May 2020 [12] to 8.3% in a single center in Kansas through May 2021 [15]). Median age at diagnosis ranged from 47 [13] to 54.1 years [10] for allo-HSCT recipients, and was around 60 years in auto-HSCT. The median interval since transplantation differed between cohorts from 14.5 to 18.9 months for allo-HSCT and from 15.6 to 23 months for auto-HSCT recipients [11–13,14].

As shown in Table 1, the most common underlying conditions included plasma cell disorders and acute leukemia, and 35–45.8% of allo-HSCT recipients had undergone myeloablative conditioning. A proportion of patients were under immunosuppressive therapy as prophylaxis for GvHD, including corticosteroids (37.3% [10]) or regimens containing a calcineurin inhibitor, mycophenolate and sirolimus (13.6% [13] to 43.1% [11]).

Clinical features at presentation
The clinical manifestations of COVID-19 in the HSCT setting seem not to meaningfully differ from those reported for other immunocompromised hosts such as solid organ transplant (SOT) recipients, as confirmed by a recent meta-analysis [16]. Most commonly observed symptoms at presentation included fever (62.9% [17] to 78.5% [10] of patients), cough (48.1% [17] to 70.5% [14]), upper respiratory tract symptoms (27.7% [10] to 44.4% [12]), diarrhea and vomiting (7.4% [17] to 21.9% [11]), myalgia or arthralgia (15.2% [10] to 17.8% [11]), and anosmia (14.8% [17] to 42.4% [18]). Most patients (64–82%) showed pneumonia on the initial chest radiography [11,14,17,19]. Presentation was similar between allo-HSCT and auto-HSCT recipients in some [10] but not all series providing separate
| First author [ref.] | Sample size | Type of HSCT, median time to COVID-19 diagnosis | Median age at diagnosis | Main underlying conditions | Stem cell source | HLA matching | Conditioning regimen | Acute GvHD |
|---------------------|-------------|-----------------------------------------------|------------------------|---------------------------|-----------------|--------------|---------------------|-----------|
| Ljungman [10**]     | 382         | Allo-HSCT (n = 236), 15.8 months; Auto-HSCT (n = 146), 24.6 months | 54.1 years (allo-HSCT), 60.6 years (auto-HSCT) | AML (29.9%), plasma cell disorders (24.1%), NHL (16.8%), MDS/MPD (13.9%) | PB (78.8%), BM (15.7%), CB (1.7%) | Unrelated (47.0%), matched sibling (33.0%), related mismatched (14.8%) | Myeloablative (45.8%), RIC (47.0%) | No GvHD/grade 1 (55.9%), grade 2–4 (5.1%) |
| Sharma [13**]       | 318         | Allo-HSCT (n = 184), 17 months; Auto-HSCT (n = 134), 23 months | 47 years (allo-HSCT), 60 years (auto-HSCT) | Plasma cell disorders (28.3%), AML (21%), NHL (15.7%), MDS/MPD (9.1%) | PB (76.1%), BM (17.9%), CB (5.9%) | HLA-identical sibling (35.8%), matched unrelated (26.6%), haploidentical (8.7%) | Myeloablative (41.8%), RIC (55.9%) | Grade 2–4 (32.6%) |
| Pirhana [11**]      | 123         | Allo-HSCT (n = 65), 14.5 months; Auto-HSCT (n = 58), 25.9 months | 48 years (allo-HSCT), 61 years (auto-HSCT) | Plasma cell disorders (33.3%), AML (18.7%), NHL (18.7%), ALL (9.8%), MDS/MPD (9.8%) | Not reported | HLA-identical sibling (45%), unrelated (34%), haploidentical (21%) | Not reported | Not reported |
| Xhaard [12*]        | 54          | Allo-HSCT only, 15.6 months | 52.6 years | AML (38.9%), MDS/MPD (18.5%), ALL (13.0%), NHL (13.0%) | PB (79.6%), BM (18.5%), CB (1.9%) | HLA-identical sibling (38.9%), matched unrelated (35.2%), haploidentical (13.0%), unrelated (13.0%) | Myeloablative (33.3%) | 59.3% |
| Varma [14]          | 34          | Allo-HSCT (n = 20), 18.9 months; Auto-HSCT (n = 14), 13.2 months | 54 years (allo-HSCT), 59 years (auto-HSCT) | AML/ALL (47.0%), NHL (17.6%), plasma cell disorders (26.4%) | PB (80%), BM or CB (20%) | Not reported | Myeloablative (35%), RIC (65%) | 45% |

**ALL, acute lymphoblastic leukemia; Allo-HSCT, allogeneic hematopoietic stem cell transplantation; AML, acute myeloid leukemia; auto-HSCT, autologous hematopoietic stem cell transplantation; BM, bone marrow; CB, cord blood; COVID-19, coronavirus disease 2019; GvHD, graft-versus-host disease; HLA, human leucocyte antigen; MDS/MPD, myelodysplastic/myeloproliferative disorder; NHL, non-Hodgkin lymphoma; PB, peripheral blood; RIC, reduced intensity conditioning.**

*Percentages calculated on the total number of allo-HSCT recipients.
data, with higher rates of pneumonia and oxygen support requirement in the former group [11**,15]. The proportion of asymptomatic patients in these cohorts largely varied from 8.9% [10**] to 14.8% [17*] depending on the study period (first vs. second pandemic waves) and design (retrospective vs. prospective). Nevertheless, it cannot be ruled out the existence of some degree of reporting bias in studies performed during the first wave, which would have skewed the sample towards the more severe cases because of limited diagnostic capabilities in many countries.

**Cytokine release syndrome**

It has been suggested the existence of pathogenic similarities between the cytokine release syndrome (CRS) that complicates the course of severe COVID-19 and that observed in allo-HSCT recipients with acute GvHD. In fact, the term CRS was originally coined for the latter situation [20]. Indeed, a primary proinflammatory trigger – SARS-CoV-2 infection in COVID-19 or the complex interplay between conditioning regimen toxicity, engraftment syndrome and secondary infections in the allo-HSCT setting – leads in both cases to a chain of inflammatory responses mediated through damage-associated molecular patterns. This uncontrolled process disrupts the homeostasis of the immune system and ultimately results in the production of stress cytokines such as interleukin (IL)-6, lymphopenia, and events of immune dysregulation (hemophagocytic lymphohistiocytosis [HLH]) and endothelial cell damage (thrombotic microangiopathy [TMA]) [21*]. In an attempt to counter-balance this pro-inflammatory status, the frequency of CD14^+HLA-DRlow/− monocyctic-myeloid derived suppressor cells in peripheral blood is increased in both allo-HSCT [22] and COVID-19 [23], although the associated immunosuppression may facilitate in turn the occurrence of bacterial or fungal superinfection or herpesviruses reactivation [21*].

Only a few studies have provided detailed information on serum IL-6 kinetics in HSCT recipients with COVID-19 [11**,17*,19]. Piñana et al. [11**] found that IL-6 levels >50 pg/ml – present in 42.5% of evaluable patients – was associated with increased infection severity and mortality at the univariate (but not multivariate) analysis. Peak median IL-6 level in seven patients in which this cytokine was measured was 147.4 pg/ml in other cohort [17*]. Shah et al. [19] reported peak values of 108.5 and 49.5 pg/ml for 15 allo-HSCT and 13 auto-HSCT recipients, respectively. Although clearly increased in comparison to healthy subjects, these levels are far beyond those observed in critical patients with sepsis or in the setting of chimeric antigen receptor T-cell therapy, which has led some authors to question the use of the term CRS in COVID-19 [24*].

**Co-infections and superinfections**

The combined effect of ongoing immunosuppression, SARS-CoV-2-induced immune dysregulation, prolonged hospital and intensive care unit (ICU) stay and immunomodulatory therapies – such as dexamethasone or anti-IL-6 agents – may contribute to the development of infectious complications, either as co-infection at presentation or most commonly during the disease course. The incidence rates of microbiologically confirmed superimposed infections range from 13% to 25% [15,17*,19]. Most reported episodes were bacterial, with predominance of hospital-acquired pathogens such as methicillin-resistant *Staphylococcus aureus* or nonfermenting Gram-negative bacilli. Reactivation of latent viral infections (mainly Epstein–Barr virus) may also occur [19]. Some studies have observed higher serum procalcitonin levels in recipients with co-infection as compared to those free from this complication [17*]. The diagnosis of COVID-19-associated pulmonary aspergillosis (CAPA) has been only occasionally reported [15,17*,25,26], and HSCT recipients are marginally represented in case series of CAPA [27,28]. There have been also an anecdotal report of an aseptic meningitis with negative reverse transcription polymerase chain reaction (RT-PCR) testing for SARS-CoV-2 in the cerebrospinal fluid after initial clinical recovery from COVID-19, suggesting a potential pathogenic role for molecular mimicry [29].

**Severe acute respiratory syndrome coronavirus 2 kinetics**

Prolonged viral shedding from nasopharyngeal swab specimens has been long described in HSCT and SOT recipients with other respiratory tract infections, in particular influenza [30–32]. The impact of host characteristics on viral kinetics has been also proven for COVID-19, with the subsequent consequences for guiding infection control practices and discontinuation of isolation [33,34]. Persistent SARS-CoV-2 shedding for as much as 74 days was described in a 61-year-old Hodgkin lymphoma patient that had undergone auto-HSCT 6 months ago [35]. The median time to viral clearance among survivors with repeated RT-PCR testing in a large multicenter cohort was 24 days, with the longest being 210 days [10**]. Although RT-PCR positivity does not necessarily equate to ongoing infectivity, viable SARS-CoV-2 has been recovered in cell culture for more than 50 days from symptom onset in allo-HSCT recipients with low cycle thresholds (Ct) [36].
OUTCOMES OF CORONAVIRUS DISEASE 2019 IN HEMATOPOIETIC STEM CELL TRANSPLANT RECIPIENTS

Table 2 summarizes mortality and other key outcomes – rates of hospital and ICU admission and requirement for invasive mechanical ventilation (IMV), if reported – observed in the largest cohorts of adult HSCT recipients with COVID-19 published by July 2021. Mortality rates were overall comparable across studies, and mostly ranged between 18.2% [19] and 28.4% [10]. The lower mortality found by Xhaard et al. [12] (14.8%) might be explained by the younger age of their cohort and the inclusion of outpatients with milder illness. These figures are not markedly different from those observed among non-immunocompromised patients requiring hospital admission during the first pandemic wave [37,38]. A meta-analysis concluded that hospitalized HSCT recipients with COVID-19 seem similar to the general

| First author [ref.] | Sample size | Study period | All-cause mortality | Other outcomes | Risk factors for mortality or disease severity | Impact of the type of HSCT on mortality |
|----------------------|-------------|--------------|---------------------|----------------|-----------------------------------------------|----------------------------------------|
| Ljungman [10]        | 382         | March to July 2020 | 28.4%               | Attributable mortality: 25% | Oxygen therapy: 35% | Similar survival for allo-HSCT and auto-HSCT (78% vs. 72%; Pvalue = 0.8) |
| Sharma [13]          | 318         | March to August 2020 | 20.8%               | Oxygen therapy: 27% in allo-HSCT, 20% in auto-HSCT IMV: 15% in allo-HSCT, 13% in auto-HSCT | Age >50 years (aHR: 1.16–5.52) | Male gender (aHR: 3.53; 95% CI: 1.44–8.67) | Similar mortality for allo-HSCT and auto-HDCT (22% vs. 19%) |
| Piñana [11]          | 123         | March to May 2020  | 20.3%               | ICU admission: 11% in allo-HSCT, 14% in auto-HSCT | Attributable mortality: Age >70 years (aOR: 2.1; 95% CI: 1.2–3.8) Relapsed or refractory disease vs. complete/partial response (aOR: 2.9; 95% CI: 1.6–5.2) ECOG 3–4 (aOR: 2.56; 95% CI: 1.4–4.7) Neutropenia (aOR: 2.8; 95% CI: 1.3–6.1) CRP level >20 mg/dl (aOR: 3.3; 95% CI: 1.7–6.4) | No differences for auto-HSCT as compared to allo-HSCT (OR: 1.04; 95% CI: 0.43–2.5) |
| Shah [19]            | 72          | March to June 2020 | 18.2%               | Hospital admission: 44% High-flow oxygen therapy: 32% IMV: 12% | Disease severity: ≥2 vs. 0 comorbidities (HR: 5.41; 95% CI: 1.84–15.9) Infiltrates on initial imaging (HR: 3.08; 95% CI: 1–9.4) Neutropenia (HR: 1.15; 95% CI: 1.02–1.29) | Nonsignificant lower survival for allo-HSCT than auto-HSCT (60% vs. 87%) |
| Mushtaq [15]         | 58          | March to May 2020  | 16.3%               | ICU admission: 19% IMV: 11% | Disease severity: Allo-HSCT vs. auto-HSCT/CART (aOR: 3.64; 95% CI: 1.23–10.78) Higher mortality for allo-HSCT vs. auto-HSCT (28% vs. 0%; Pvalue = 0.007) |

Antimicrobial agents: viral
population in terms of disease severity and outcomes, although data from the more recent cohorts were not pooled [16]. On the other hand, mortality reported for other groups of hematological patients hospitalized during the first wave was at least comparable or higher, with 27.3% for chronic lymphocytic leukemia [39] or 33.5% for multiple myeloma [40]. Transplant recipient status was not associated with the risk of death in a large population-based registry study performed in Madrid on 697 patients with hematologic malignancies [41]. In fact, Piñana et al. [11**] found that nontransplant patients with hematological disorders such as non-Hodgkin lymphoma, chronic myeloproliferative disease or acute leukemia had actually higher mortality rates compared to HSCT recipients (32.8% vs. 20.3%, respectively).

Risk factors for poor outcome

Not unexpectedly, older age has been consistently associated with higher mortality [10**,13**], as well as shorter time from transplantation [12*,13**,17*]. The nature of underlying condition seems to exert a smaller impact than the disease status (relapsed or refractory vs. complete/partial response) at COVID-19 diagnosis, with only one study reporting higher attributable mortality in auto-HSCT due to lymphoma compared to plasma cell disorders [13**]. The presence and amount of immunosuppression – as assessed by the immunodeficiency scoring index (ISI) or the number of drugs – was also significantly correlated with higher mortality in auto-HSCT [10**,17*] or disease severity [15] in various cohorts.

The largest series reported to date was based on the collaborative effort of the European Group for Blood and Marrow Transplantation (EBMT) Infectious Diseases Working Party and the Spanish Hematopoietic Stem Cell Transplantation and Cell Therapy Group (GETH) and prospectively included 382 recipients from 22 European countries. The median age was 56.8 years and the median interval from the most recent HSCT to RT-PCR-confirmed diagnosis was 17.9 months. There was heterogeneity across countries in the proportion of patients

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**Table 2 (Continued)**

| First author [ref.] | Sample size | Study period | All-cause mortality | Other outcomes | Risk factors for mortality or disease severity | Impact of the type of HSCT on mortality |
|---------------------|-------------|--------------|---------------------|---------------|-----------------------------------------------|----------------------------------------|
| Xhaard [12*]        | 54          | March to May 2020 | 14.8% | ICU admission: 24% | Attributable mortality: Age quartile 4 (OR: 12.8, 95% CI: 1.2–137.3) | Only allo-HSCT included |
| Varma [14]          | 34          | First wave   | 20.6% | Hospital admission: 74% | All-cause mortality: Hemoglobin levels (P-value = 0.002) | Nonsignificant higher mortality for allo-HSCT than auto-HSCT (36% vs. 14%) |
| Camargo [17*]       | 28*         | March to December 2020 | 25.0% | ICU admission: 25% | All-cause mortality: Time interval from HSCT to diagnosis ≥12 months (P-value = 0.04) | Similar mortality for allo-HSCT and auto-HSCT (27% vs. 25%, P-value > 0.99) |
admitted to the ICU, which may be related to differences in available healthcare resources during the first pandemic wave. Overall, 107 patients died, yielding an all-cause mortality rate of 28.4%. The attributable mortality was slightly lower (25.2%) and the median time from confirmed infection to death was 18 days. The authors observed no significant differences in survival between autologous and allogeneic procedures, nor between recipients developing COVID-19 within the first 100 posttransplant days or beyond that point. In the multivariate analysis, older age and higher ISI acted as predictors of death, whereas better performance status exerted a protective effect. When the multivariate analysis was restricted to the allo-HSCT group, age and need for ICU admission remained associated with fatal outcome [10**].

The lack of impact on mortality of the type of transplantation (allogeneic vs. autologous) in the EBMT/GETH cohort was in accordance with most other studies [11**,13**,14,17] (Table 2) and previous experiences derived from the 2009 H1N1 influenza pandemic [42]. Although the amount of immunosuppression is usually higher in the allo-HSCT population due to the common use of myeloablative conditioning and the need of prophylaxis for GvHD, it is likely that the older age and more common presence of cardiovascular comorbidities among auto-HSCT recipients (Table 1) would act as strongest determinants of outcome, diluting potential differences between both groups.

Discrepant results, however, have been obtained from a recent single-center study on 55 HSCT recipients (32 allogeneic and 23 autologous) diagnosed with COVID-19 between March 2020 and May 2021. Most patients (62%) had undergone myeloablative conditioning. After a median follow-up of 6.1 months, all-cause mortality in the overall cohort was 16.3%, reaching 28.1% among allo-HSCT recipients. Prior grade II–IV acute GvHD, immunosuppression and allo-HSCT (compared to auto-HSCT or CAR-T therapy) were associated with the combined outcome of illness severity [15].

As previously pointed, the studies only comprising hospitalized patients during the early months of the pandemic should be taken with some caution, since the sample may be skewed towards more severe cases that were more likely to seek for medical attention and to receive a RT-PCR-based diagnosis. A prospective cohort study carried out at a single Italian center with 254 allo-HSCT recipients that were subjected to a scheduled follow-up through in-person visits or telemedicine identified 24 patients with symptoms compatible with COVID-19 in the first wave. Only six of them tested positive for SARS-CoV-2 (overall incidence of 2.4%), four of which were affected by chronic GvHD and two were receiving ruxolitinib. Despite the presence of risk factors for unfavorable outcome (male gender, age >60 years, cardiovascular comorbidities), only three patients required hospitalization and all of them completely recovered. Acknowledging the small sample size, the authors suggested that allo-HSCT should not be necessarily considered a determinant of dismal prognosis in COVID-19 [9].

Finally, the comparison of the clinical picture and outcome in allo-HSCT recipients infected with SARS-CoV-2 or seasonal human coronaviruses may be useful to contextualize the impact of COVID-19 in this population. A recent multicenter study with 402 allo-HSCT recipients included 449 episodes of upper or lower respiratory tract infection due to OC43 (37.8%), 229E (21.6%), NL63 (14.3%), and KHU1 (12.0%) coronaviruses. Hospital and ICU admission were required in only 17.8% and 2.8% of episodes, respectively. All-cause mortality was 6.9% for the overall cohort and 16.5% for those recipients with lower respiratory tract involvement [43*].

Pediatric patients

Although the available evidence is more limited, some experiences have been reported on the outcome of COVID-19 in pediatric allo-HSCT, with an overall incidence estimated at 3–4% [44,45*,46]. In the general population, children with SARS-CoV-2 infection show milder manifestations compared to adult patients [47]. A report from the Spanish Group of Pediatric HSCT identified 8 children (seven males) with a median age at diagnosis of 10 years old (range: 1–12) and leukemia or myelodysplasia as the most common underlying conditions. Clinical presentation included fever in five patients, respiratory symptoms in four, and diarrhea in the other two. Two children required ICU admission and IMV and one of them died, accounting for an overall mortality rate of 12.5%. Since primary immunodeficiencies were overrepresented in these series (more than a third of cases) as compared to the proportion of indications for pediatric allo-HSCT (about 10%), the authors suggested that impaired T-cell-mediated immunity due to the lack of thymus development may contribute to the severity of infection [45*]. A multicenter study from the United Kingdom reported the outcome of nine patients with a median age of 12 years (range: 6–16), all of them had achieved neutrophil engraftment. Clinical manifestations were variable, with fever being present in only four cases (associated to significant hypotension that required aggressive fluid resuscitation in one of them). Two patients were asymptomatic and tested as part of routine admission.
screening. Eight infants (88.9%) showed a mild disease course, whereas the remaining recipient developed CRS treated with tocilizumab, remdesivir and positive pressure respiratory support and later evolved into secondary HLH, with full recovery. Of note, two patients experienced medium-term hematologic sequelae in form of pancytopenia (with hypocellular bone marrow aspirate) and transplant-associated TMA requiring defibrotide and eculizumab therapy [44].

CONCLUSIONS AND RESEARCH GAPS

Unprecedented efforts have been made over the last year and a half to characterize the clinical course and outcomes of SARS-CoV-2 infection and its differential features in selected groups of immunocompromised patients, with particular attention having been paid to HSCT recipients [48]. As a result, we now know that symptoms at presentation in this group are overall comparable to those reported for the general population, and that the high mortality observed during the first pandemic wave seems to be driven by factors common to nontransplant patients – mainly older age – and others transplant-specific – such as the amount of immunosuppression or the status of the underlying disease. The modality of transplantation (allogeneic or autologous), on the contrary, does not influence outcomes in most published cohorts. In addition, the duration of nasopharyngeal viral shedding has been shown to be longer than in immunocompetent hosts. Unfortunately, uncertainties still persist on some critical issues. No studies to date have ascertained whether the incidence of severe COVID-19 is actually different compared to non-HSCT patients matched for age and comorbidity burden. Increased individual susceptibility may be partially outweighed by a higher compliance with preventive measures or a more stringent surveillance at early stages of infection. Beyond the fact that ongoing immunosuppression acts as a risk factor for poor outcome, the optimal adjustment of baseline therapies such as corticosteroids or calcineurin inhibitors once SARS-CoV-2 infection is diagnosed remains unknown. A multicenter study found that the rapid discontinuation of the Janus kinase inhibitor ruxolitinib in patients with myeloproliferative neoplasms and COVID-19 increased the risk of death [49*]. Although no similar data is yet available for HSCT recipients, it could hypothesized that the enhancement of SARS-CoV-2-associated CRS following the abrupt suspension of immunosuppression would also occur in these patients. Finally, and although beyond the scope of the present review, the precise role of immunomodulatory (i.e. tocilizumab [50]) or antiviral agents (i.e. remdesivir [51]) in the HSCT population should be established by means of prospective collaborative efforts, as well as the strategies to improve the immunogenicity of mRNA-based vaccines [52,53].

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Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as: ■ of special interest

■ of outstanding interest

1. Fontana L, Strasfel L. Respiratory virus infections of the stem cell transplant recipient and the hematologic malignancy patient. Infect Dis Clin North Am 2019; 33:523–544.
2. Sahu KK, Jindal V, Siddiqui AD, Cerry J. Facing COVID-19 in the hematopoietic cell transplant setting: a new challenge for transplantation physicians. Blood Cells Mol Dis 2020; 83:10439.
3. Passamonti F, Cattaneo C, Arcaini L, et al. Clinical characteristics and risk factors associated with COVID-19 severity in patients with haematological malignancies in Italy: a retrospective, multicentre, cohort study. Lancet Haematol 2020; 7:e737–e745.
4. Vjenethira A, Gong IY, Fox TA, et al. Outcomes of patients with hematologic malignancies and COVID-19: a systematic review and meta-analysis of 3377 patients. Blood 2020; 196:2881–2892.
5. Szer J, Weisdorf D, Querol S, et al. The impact of COVID-19 on the provision of donor hematopoietic stem cell products worldwide: collateral damage. Bone Marrow Transplant 2020; 55:2043–2044.
6. Mengling T, Ral G, Bernas SN, et al. Stem cell donor registry activities during the COVID-19 pandemic: a field report by DKMS. Bone Marrow Transplant 2021; 56:798–806.
7. Algazwiz A, Aljurf M, Koh M, et al. Real-world issues and potential solutions in hematopoietic cell transplantation during the COVID-19 pandemic: Perspectives from the Worldwide Network for Blood and Marrow Transplantation and Center for International Blood and Marrow Transplant Research Health Services and International Studies Committee. Biol Blood Marrow Transplant 2020; 26:2181–2189.
8. Kanellopoulos A, Ahmed MZ, Kishore B, et al. COVID-19 in bone marrow transplant recipients: reflecting on a single centre experience. Br J Haematol 2020; 190:e67–e70.
9. Lupo-Stanghellini MT, Xue E, Mastaglio S, et al. COVID-19 in recipients of allogeneic stem cell transplantation: favorable outcome. Bone Marrow Transplant 2021; 56:1–4.
10. Ljungman P, de la Cámara R, Mikulska M, et al. COVID-19 and stem cell transplantation: results from an EBMT and GETH multicenter prospective survey. Leukemia 2021; 1–10. doi: 10.1038/s41375-021-01302-5 [online ahead of print]
11. Piñana JL, Martino R, García-García I, et al. Risk factors and outcome of COVID-19 in patients with hematologic malignancies. Exp Hematol Oncol 2020; 9:21.

Multicenter retrospective study on 367 pediatric and adult patients with hematologic malignancies, including auto-HSCT and allo-HSCT recipients, with COVID-19 during the first pandemic wave in Spain, in which a poorer outcome was observed for the nontransplant group.
12. Xhaard A, Xhaard C, D’Aveni M, et al. Risk factors for a severe form of COVID-19 after allogeneic haematopoietic stem cell transplantation: a Societe Francophone de Greffe de Moelle et de Therapie cellulaire (SFGM-TC) multicentre cohort study. Br J Haematol 2021; 192:e121–e124. Multinational (France, Belgium and Switzerland) study describing risk factors for severe infection and death from COVID-19 among allo-HSCT recipients.

13. Sharma A, Bhatt NS, St Martin A, et al. Clinical characteristics and outcomes of COVID-19 in haematopoietic stem cell transplantation recipients: an observational cohort study. Lancet Haematol 2021; 8:e185–e189. Large multicentre cohort of HSCT recipients with COVID-19 revealing that older age, male gender and development of COVID-19 within the first 12 months are associated with a higher risk of mortality.

14. Varma A, Kosuri S, Ustun C, et al. COVID-19 infection in hematopoietic cell transplantation: age, time from transplant and steroids matter. Leukemia 2020; 34:2809–2812. A study revealing that patients who developed COVID-19 had a worse prognosis than those who did not.

15. Mushfaq MU, Shahdad M, Chaudhary SG, et al. Impact of SARS-CoV-2 in hematopoietic stem cell transplantation and chimeric antigen receptor T cell therapy recipients. Transplant Cell Ther 2021; 27:796.e1–796.e7. A study examining the impact of SARS-CoV-2 on hematopoietic stem cell transplantation and CAR-T therapy recipients.

16. Belkis JA, Tullius BP, Lamb MG, et al. COVID-19 in immunocompromised patients: a systematic review of cancer, hematopoietic cell and solid organ transplant patients. J Infect 2021; 82:329–338. A systematic review of COVID-19 in immunocompromised patients following allogeneic HSCT.

17. Camargo JF, Mendoza MA, Lin R, et al. Clinical presentation and outcomes of COVID-19 following hematopoietic cell transplantation and cellular therapy. Transpl Infect Dis 2021; e18625. doi: 10.1111/tid.13625. A comprehensive review of the clinical presentation and outcomes of COVID-19 following HSCT.

18. Lange A, Lange J, Jaksula E. Cytokine overproduction and immune system dysregulation in allo-HSCT and COVID-19 patients. Front Immunol 2021; 12:858896. doi: 10.3389/fimmu.2021.858896. A review of the cytokine response in COVID-19 patients and the immune system dysregulation in HSCT recipients.

19. Sever T, Kaya Z, Kirks S, et al. Thoracic air leak syndrome, pulmonary aspergillosis, and COVID-19 pneumonia after allogeneic stem cell transplantation in a child with myelodysplastic syndrome. J Pediatr Hematol Oncol 2021. doi: 10.1097/MPH.0000000000002023 [online ahead of print]. A case report of air leak syndrome and pulmonary aspergillosis in a child with myelodysplastic syndrome after HSCT.

20. Spadese M, Carforo F, Saglio F, et al. Successfully treated severe COVID-19 and cidal aspergillosis in early hematopoietic stem cell transplantation setting. Transplant Infect Dis 2021; 23:e13470. doi: 10.1111/tid.13470. A case of successful treatment of severe COVID-19 and cidal aspergillosis in a hematopoietic stem cell transplantation setting.

21. Singh S, Verma N, Kanaujia R, et al. Mortality in critically ill patients with coronavirus disease 2019-associated pulmonary aspergillosis: a systematic review and meta-analysis. Mycoses 2021; 64:1015–1027. A systematic review and meta-analysis of mortality in critically ill patients with COVID-19.

22. Chang WH, Neu KP. Incidence, diagnosis and outcomes of COVID-19-associated pulmonary aspergillosis (CAPA): a systematic review. J Hosp Infect 2021; 118:115–129. A systematic review of the incidence, diagnosis and outcomes of COVID-19-associated pulmonary aspergillosis (CAPA).

23. Bashfer F, Camargo JF, Diaz-Paez M, et al. Aseptic meningitis after recovery from SARS-CoV-2 in an allogeneic stem cell transplant recipient. Clin Med Insights Case Rep 2021; 14:1179547621100981. doi: 10.1177/1179547621100981. A case report of aseptic meningitis in a patient with SARS-CoV-2 infection.

24. Lehners N, Tabatabai J, Prifti C, et al. Long-term shedding of influenza virus, parainfluenza virus, respiratory syncytial virus and norovirus epidemiology in patients with hematological disorders. PLoS One 2016; 11:e0142858. doi: 10.1371/journal.pone.0142858. A study examining the long-term shedding of influenza and other viruses in hematopoietic stem cell transplantation recipients.

25. Rachow T, Lamk T, Kalkevich J, et al. Detection of community-acquired respiratory viruses in allogeneic stem cell transplant recipients and controls – a prospective cohort study. Transpl Infect Dis 2020; 22:e13415. doi: 10.1111/tid.13415. A study examining the detection of community-acquired respiratory viruses in allogeneic HSCT recipients.

26. de Lima CR, Mirandelli TB, Carneiro LC, et al. Prolonged respiratory viral shedding in transplant patients. Transpl Infect Dis 2014; 16:165–169. A study examining the prolonged respiratory viral shedding in transplant patients.