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

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Purpose of review
Focusing on large multicenter cohorts reported over the last months, this review aims at summarizing the available evidence by July 2021 on the impact of coronavirus disease 2019 (COVID-19) on hematopoietic stem cell transplant (HSCT) recipients in terms of epidemiology, clinical features, and outcome.

Recent findings
The incidence of COVID-19 in institutional cohorts varied according to different regions and study periods from 0.4% to 8.3%. Clinical presentation was overall comparable to other immunocompromised hosts and the general population. Microbiologically confirmed superinfection occurred in 13–25% of recipients, with most episodes due to hospital-acquired bacteria and few reported cases of COVID-19-associated aspergillosis. Prolonged nasopharyngeal severe acute respiratory syndrome coronavirus 2 shedding has been demonstrated for as long as 210 days. Mortality rates were similar across studies (14.8–28.4%) and did not markedly differ from those observed in nontransplant hematological patients during the first wave. Older age and shorter time from transplantation were associated with mortality, as well as underlying disease status and amount of immunosuppression. No outcome differences were found in most studies between allogeneic and autologous procedures.

Summary
Considerable advances have been achieved in the characterization of COVID-19 in the HSCT population, although uncertainties remain in the optimal therapeutic management.

Keywords
clinical features, coronavirus disease 2019, cytokine release syndrome, hematopoietic stem cell transplantation, outcome, prognostic factors, severe acute respiratory syndrome coronavirus 2

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 immunocompromised 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 HCST 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

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Curr Opin Infect Dis 2021, 34:654–662
DOI:10.1097/QCO.0000000000000790

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.

countries revealed a decline by around 15% in the total number of stem cell products provided (particularly for bone marrow products) and by 38% in the number of newly registered donors from March to June 2020 in comparison with the preceding months [6]. In addition, initial uncertainties on the potential transmissibility of SARS-CoV-2 through stem cell products implied that exposed donors, as well as those recovering from COVID-19, should be deferred for various weeks, thus compromising the ability to perform live-saving procedures at the appropriate time [7].

More than 18 months into the pandemic, a large amount of literature has been generated on the epidemiology, clinical manifestations and determinants of outcome of COVID-19 among HSCT recipients. The present review is aimed at critically summarizing the evidence available on this issue by July 2021 as well as proposing future research avenues according to identified gaps in the current knowledge. Therapeutic strategies (either based on antiviral or immunomodulatory agents) and COVID-19 vaccines safety and effectiveness in this population will be not covered.

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, mofetil 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

Table 1. Summary of most relevant multicenter cohorts of adult HSCT recipients diagnosed with COVID-19 reported by July 2021

First author [ref.]	Sample size	Type of HSCT, median time to COVID-19 diagnosis	Median age at diagnosis	Main underlying conditions	Stem cell source[a]	HLA matching[a]	Conditioning regimen[a]	Acute GvHD[a]
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%)
Piñana [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, cordon 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.
[a]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 proinflammatory status, the frequency of $CD14^{+}HLA\text{-}DR^{low/neg}$ monocytic-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

Table 2. Main outcomes and risk factors for mortality in cohorts of adult HSCT recipients (including ≥10 patients) with COVID-19 reported by July 2021

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%	All-cause mortality: Age [per each 10-year increment] (aHR: 1.21; 95% CI: 1.03–1.43) Higher ISI group (aHR: 1.84; 95% CI: 1.02–3.33) Better performance status (aHR: 0.83; 95% CI: 0.74–0.93)	Similar survival for allo-HSCT and auto-HSCT (78% vs. 72%; *P*-value = 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	Attributable mortality in allo-HSCT: Age >50 years (aHR: 2.53; 95% CI: 1.16–5.52) Male gender (aHR: 3.53; 95% CI: 1.44–8.67) Time interval from HSCT to diagnosis ≤12 months (aHR: 2.67; 95% CI: 1.33–5.36) Attributable mortality in auto-HSCT: Lymphoma vs. plasma cell disorder (aHR: 2.41; 95% CI: 1.08–5.38)	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[a]	March to June 2020	18.2%	Hospital admission: 44% High-flow oxygen therapy: 32% IMV: 12%	Disease severity[b]: ≥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[c]	March to May 2020	16.3%	ICU admission: 19% IMV: 11%	Disease severity[d]: Allo-HSCT vs. auto-HSCT/CAR-T (aOR: 3.64; 95% CI: 1.23–10.78) Ongoing immunosuppression (aOR: 5.91; 95% CI: 1.76–19.81) Grade II–IV acute GvHD (aOR: 4.56; 95% CI: 1.10–18.86)	Higher mortality for allo-HSCT than auto-HSCT (28% vs. 0%; *P*-value = 0.007)

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) Platelet count tertile 1 (OR: 21.3; 95% CI: 1.7–267.1) Co-infection (OR: 12.0; 95% CI: 1.8–78.9) Probable pneumonia (OR: 9.9; 95% CI: 1.1–91.6) Time interval from HSCT to diagnosis quartile 4 (OR: 0.05; 95% CI: 0.01–0.7)	Only allo-HSCT included
Varma [14]	34	First wave	20.6%	Hospital admission: 74% ICU admission: 32% IMV: 23%	All-cause mortality: Hemoglobin levels (*P*-value = 0.002) LDH levels at presentation (*P*-value = 0.002) Peak LDH levels (*P*-value < 0.001) Ferritin levels (*P*-value = 0.022)	Nonsignificant higher mortality for allo-HSCT than auto-HSCT (36% vs. 14%)
Camargo [17▪]	28[e]	March to December 2020	25.0%	ICU admission: 25% RRT: 14% IMV: 21%	All-cause mortality: Time interval from HSCT to diagnosis ≤12 months (*P*-value = 0.04) ≥2 immunosuppressive drugs (*P*-value = 0.01)	Similar mortality for allo-HSCT and auto-HSCT (27% vs. 25%; *P*-value > 0.99)

aHR, adjusted hazard ratio; Allo-HSCT, allogeneic hematopoietic stem cell transplantation; aOR, adjusted odds ratio; auto-HSCT, autologous hematopoietic stem cell transplantation; CAR-T, chimeric antigen receptor T-cell; COVID-19, coronavirus disease 2019; CRP, C-reactive protein; ECOG, Eastern Cooperative Oncology Group; ICU, intensive care unit; IMV, invasive mechanical ventilation; ISI, immunodeficiency scoring index; LDH, lactate dehydrogenase; RRT, renal replacement therapy.

[a]Includes five patients that received CAR-T therapy.

[b]Disease severity defined as requiring nonrebreather or higher oxygen, or death at a lower level of oxygen.

[c]Includes three patients that received CAR-T therapy.

[d]Disease severity included moderate (evidence of lower respiratory disease/pneumonia with oxygen saturation <94% on room air), severe (oxygen saturation < 94% on room air, a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen < 300 mmHg, respiratory rate > 30 breaths/min, or lung infiltrates > 50%), or critical (respiratory failure, septic shock, multiple organ dysfunction, and/or death) categories.

[e]Includes one patient that received CAR-T therapy.

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 [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

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 latter 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].

Acknowledgements

None.

Financial support and sponsorship

This work was supported by Instituto de Salud Carlos III, Spanish Ministry of Science and Innovation (COVID-19 Research Call COV20/00181) – co-financed by European Development Regional Fund 'A way to achieve Europe'. M.F.R. holds a research contract 'Miguel Servet' (CP18/00073) from the Instituto de Salud Carlos III, Spanish Ministry of Science and Innovation.

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

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