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Review Article

Secondary Impact of the Coronavirus Disease 19 Pandemic on Patients and the Cellular Therapy Healthcare Ecosystem

Jane Koo^{1,2,*}, Jeffrey J. Auletta^{3,4}, David M. Hartley^{2,5}, John Huber^{1,2}, Samantha Jaglowski⁶, Malika Kapadia⁷, Katilyn Kusnier^{1,2}, Leslie Lehmann⁷, Joseph Maakaron⁸, Kasiani C. Myers^{1,2}, Ahna Pai^{2,9}, Loretta Parker¹⁰, Rachel Phelan¹¹, Christine Sper¹, Seth J. Rotz¹², Christopher E. Dandoy^{1,2}

¹ Division of Bone Marrow Transplantation and Immune Deficiency, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio

² Department of Pediatrics, University of Cincinnati, College of Medicine, Cincinnati, Ohio

³ Center for International Blood and Marrow Transplant Research, Milwaukee, Wisconsin

⁴ Hematology/Oncology/BMT and Infectious Diseases, Nationwide Children's Hospital, Columbus, Ohio

⁵ James M. Anderson Center for Health Systems Excellence, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio

⁶ Division of Hematology-Oncology and Transplantation, Department of Pediatrics, Ohio State University Medical Center, Columbus, Ohio

⁷ Division of Pediatric Oncology, Dana-Farber/Boston Children's Cancer and Blood Disorders Center, Department of Pediatrics, Harvard University Medical School, Boston, Massachusetts

⁸ Division of Hematology, Oncology, and Transplantation, Department of Medicine, University of Minnesota, Minneapolis, Minnesota

⁹ Department of Behavioral Medicine & Clinical Psychology, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio

¹⁰ Division of Hematology/Oncology, Department of Pediatrics, The University of Oklahoma College of Medicine, Oklahoma City, Oklahoma

¹¹ Division of Pediatric Hematology, Oncology, Blood and Marrow Transplantation, Department of Pediatrics, Medical College of Wisconsin and Children's Wisconsin, Milwaukee, Wisconsin

¹² Department of Pediatric Hematology, Oncology, and Blood and Marrow Transplantation, Cleveland Clinic Children's Hospital, Cleveland, Ohio

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Transplant Associated Learning Network Team (TALNT): Members of the Transplant Associated Learning Network Team:

Lisa Beatty; Division of Pediatric Oncology, Dana-Farber/Boston Children's Cancer and Blood Disorders Center, Department of Pediatrics, Harvard University Medical School, Boston, MA. E-mail: Lisa_Beatty@dfci.harvard.edu

Neel Bhatt, MBBS, MPH; Clinical Research Division, Fred Hutchinson Cancer Research Center, Seattle, WA E-mail: nbhatt@fredhutch.org

Robyn Blacken BSN, RN; Affiliation(s): Division of Pediatric Oncology, Dana Farber/Boston Children's Cancer and Blood Disorders Center, Boston, MA, USA; Email: Robyn.Blacken@childrens.harvard.edu

Kathy Demmel, University of Cincinnati College of Medicine, Department of Pediatrics; Division of Bone Marrow Transplantation and Immune Deficiency, Cincinnati, OH. Kathy.Demmel@cchmc.org

Therese Dodd, BA, MBA, RN, CPHQ, FNAHQ; Affiliation(s): Sarah Cannon Transplant & Cellular Therapy Network, Nashville, TN; Email: Therese.Dodd@SarahCannon.com

Laura Flesch, DNP, APRN-CNP, FNP; Affiliation(s): University of Cincinnati College of Medicine, Department of Pediatrics; Division of Bone Marrow Transplantation and Immune Deficiency, Cincinnati, OH. Email: Laura.Flesch@cchmc.org

Rita Jakubowski DNP; Department of Medical Oncology/ Hematopoietic and Cellular Therapy Service; Icahn School of Medicine/Mount Sinai Medical Center, New York, New York. Email: rita.jakubowski@mountsinai.org

Mark Juckett, MD; Division of Hematology, Oncology, and Transplantation; Department of Medicine; University of Minnesota. Email: juck0001@umn.edu

Nicole Liberio MD; Division of Pediatric Hematology, Oncology, Blood and Marrow Transplantation, Department of Pediatrics, Medical College of Wisconsin and Children's Wisconsin, Milwaukee, WI. Email: nliberio@mcw.edu

Mark Mueller; University of Cincinnati College of Medicine, Department of Pediatrics; Division of Bone Marrow Transplantation and Immune Deficiency, Cincinnati, OH. Email: Mark.Mueller@cchmc.org

Sagar Patel, MD; Huntsman Cancer Institute, University of Utah; Salt Lake City, Utah; Email: Sagar.Patel@hci.utah.edu

Veronika Polishchuk, MD; Division of Hematology, Oncology, and Bone and Marrow Transplant, Nationwide Children's Hospital, Department of Pediatrics, Ohio State University, OH, USA. Email: Veronika.Polishchuk@nationwidechildrens.org

Audrey Sigmund, Divisions of Hematology and Medical Oncology, The Ohio State University, Columbus, OH; Email: Audrey.Sigmund@OSUMC.edu

Sarah Tarquini Ph.D.; Dana-Farber Boston Children's Cancer and Blood Disorders Center; Email: Sarah_Tarquini@dfci.harvard.edu

*Correspondence and reprint requests: Jane Koo, Bone Marrow Transplantation and Immune Deficiency, Cancer and Blood Diseases Institute, Cincinnati Children's Hospital Medical Center, 3333 Burnet Ave, MLC 11027, Cincinnati, OH 45229-3039.

E-mail address: jane.koo@cchmc.org (J. Koo).

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A B S T R A C T

The Coronavirus disease 2019 (COVID-19) pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has significantly impacted global health and healthcare delivery systems. To characterize the secondary effects of the COVID-19 pandemic and mitigation strategies used in the delivery of hematopoietic stem cell transplantation (HSCT) care, we performed a comprehensive literature search encompassing changes in specific donor collection, processing practices, patient outcomes, and patient-related concerns specific to HSCT and HSCT-related healthcare delivery. In this review, we summarize the available literature on the secondary impacts the COVID-19 pandemic on the fields of HSCT and cellular therapy. The COVID-19 pandemic has had numerous secondary impacts on patients undergoing HSCT and the healthcare delivery systems involved in providing complex care to HSCT recipients. Institutions must identify these influences on outcomes and adjust accordingly to maintain and improve outcomes for the transplantation and cellular therapy community.

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INTRODUCTION

The Coronavirus disease 2019 (COVID-19) pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has profoundly impacted global health and healthcare delivery systems. As of May 2022, more than 500 million cases of COVID-19 have been reported worldwide, resulting in more than 5 million deaths. More than 80 million cases have been diagnosed in the United States, resulting in more than 1 million deaths [1,2]. Patients with hematologic malignancies and nonmalignant disorders who require cellular therapy and hematopoietic stem cell transplantation (HSCT) or receiving cellular therapy are at even greater risk of complications and unfavorable outcomes when infected with COVID-19 [3–5]. Transplantation centers worldwide have been challenged by the COVID-19 pandemic causing disruption of healthcare services for HSCT recipients. In many cases, delayed transplantation or cellular therapy is not a viable option given the patient's medical needs; as a result, providing HSCT and administering cellular therapies like chimeric antigen receptor (CAR) T cells have continued despite the health and logistical challenges associated with the COVID-19 pandemic [6].

Recent analyses have described the primary impacts of COVID-19 on HSCT recipients, showing decreased overall survival (OS) in both allogeneic HSCT (allo-HSCT) and autologous HSCT (auto-HSCT) recipients following a COVID-19 diagnosis [7,8]. In addition, new variants of concern, including Delta and Omicron, are continuing to emerge, but less has been published on the secondary effect of COVID-19 on HSCT-related healthcare delivery and mitigation strategies in the context of these new variants [6]. Therefore, we conducted a systematic review to evaluate the secondary effects of the COVID-19 pandemic on HSCT.

In this review, we summarize the pandemic's secondary impacts/effects on transplantation-specific issues, including donor eligibility, selection, graft availability, and selection. We also examine the influence of the COVID-19 pandemic on patient-related care and healthcare delivery problems and offer potential areas of additional investigation in these areas. Finally, we discuss mitigation strategies to address challenges faced by patients, providers, and healthcare systems.

METHODS

A literature search using PubMed and Google Scholar was conducted on February 15, 2022, and updated on May 15, 2022, using the following search terms: "hematopoietic stem cell transplantation," "bone marrow transplant," "coronavirus disease 2019," "COVID-19," "severe acute respiratory syndrome coronavirus 2," "SARS-CoV-2" or "impact," "mitigation," or "delay" or "workers," "cryopreservation," "healthcare delivery," and "chimeric antigen receptor T cell." No filters or publication time limits were applied to the search. Our search identified 22 articles on this topic. Studies were excluded if the study focused only on the COVID-19-related clinical outcomes of HSCT

recipients. Because of this review's specific focus, clinical outcomes studies were excluded that described morbidity- and mortality-related outcomes in pediatric and adult HSCT and cellular therapy recipients or described the clinical spectrum of COVID-19 infection in this patient population. A total of 22 of these studies were excluded. All search results were imported to the EndnoteX9.0 reference manager, and all duplicates were removed. Based on each manuscript's methods and main findings, articles were categorized as relevant to (1) prioritization of transplantation and cancer care, (2) patient-related factors, and (3) healthcare delivery issues.

SECTION 1: CHANGES TO TRANSPLANTATION AND CELLULAR THERAPY DELIVERY DURING THE COVID-19 PANDEMIC**Patient Access to Transplantation and Cellular Therapy**

In the uncertainty of the early part of the pandemic, transplantation centers needed to balance performing life-saving transplantation procedures with the risk of exhausting needed healthcare resources. Transplantation centers began designing algorithms to guide the temporary deferral of transplantation based on a patient's underlying diagnosis, interrupting patient care for nonmalignant diseases like hemoglobinopathies and primary immunodeficiencies [9–11]. Table 1 summarizes the types of practice changes occurring at centers worldwide, and Figure 1 details the timeline of the collected reports on the secondary effects of the COVID-19 pandemic on HSCT [12]. Of note, most of the analysis was done on patients at the beginning of the pandemic, and there are little data on the impact of more recent variants on the healthcare delivery system (eg, Omicron variant).

The Fred Hutchinson Cancer Center/Seattle Cancer Care Alliance published their approach, outlining the triage process for allo- and auto-HSCT in adult patients. They also categorized primary disease indications based on urgency and defined which patients should proceed to transplantation immediately and which patients could be delayed. Patients with high-risk hematologic malignancies generally proceeded to HSCT without delay based on their algorithm. In contrast, those with stable, lower-risk hematologic malignancies, myeloproliferative disorders, and nonmalignant diseases were delayed. Additionally, some nonurgent patients who had already started pre-transplantation baseline evaluation were discharged to their local oncologists to receive maintenance chemotherapy in anticipation of beginning transplantation at a later date [13]. During the first 3 months of the pandemic in the Pacific Northwest, between March 6 and May 31, 2020, only 27% of planned allo-HSCTs and 58% of planned auto-HSCTs were performed as planned, with 43% of patients being redirected to nontransplantation oncology care.

Memorial Sloan Kettering Cancer Center analyzed the impact of treatment delays related to COVID-19 on patients initially scheduled to undergo cellular therapy. Prospective

Table 1
Changes During the COVID-19 Pandemic Impacting Transplantation and Cancer Care Procedures

Study and Year	Population	Transplantation Center	Transplant Type	Study Design	Summary of Findings
Passweg et al., 2022 [54]	Adult and pediatric patients	EBMT	Allo-HSCT and auto-HSCT	Data survey collection	Reduction of total HSCT procedures by 6.5%. Allo-HSCT procedures declined by 5.1%, and auto-HSCT procedures reduced by 7.5%. These changes were most significant in nonmalignant disorders for allo-HSCT and autoimmune diseases for auto-HSCT. EBMT still observed a 64% increase in CAR T cell therapies in 2020.
Ueda Oshima et al., 2021 [13]	Adult patients	Fred Hutchinson Cancer Center/ Seattle Cancer Care Alliance	Allo-HSCT and auto-HSCT	Summary of COVID-19 experience	Developed an algorithm to prioritize patients for HSCT with the greatest anticipated benefit (>20% expected long-term survival rate). Urgent allo-HSCT procedures included high-risk AML in CR1, AML, ALL >CR1 and secondary AML. Allo-HSCTs that were either delayed or considered for delay included myeloproliferative disorders, MDS, and standard- and intermediate-risk leukemias. Urgent auto-HSCTs included aggressive lymphomas. Auto-HSCTs for multiple myeloma, low-grade lymphoma, and autoimmune diseases were delayed.
Nawas et al., 2021 [14]	Adult patients with hematologic malignancies and solid tumors	Memorial Sloan Kettering Cancer Center	Allo-HSCT, auto-HSCT, and CAR T cell therapy	Evaluated 85 patients who experienced a delay of HSCT or CAR T cell during the initial COVID-19 pandemic	Only 66% of planned procedures occurred during this period; 5 patients died during the delay. Progression of disease (42%) was the most common reason for not proceeding with allo-HSCT and good disease control in plasma cell dyscrasias (75%) for auto HSCT.
Liu, et al., 2021 [55]	Adult patients	Duke University Health System	HSCT recipients	Summary of home care delivery encounters	Described changes to healthcare delivery practices through the use of home care encounters using frequent visits from advanced care providers and transplantation nurses
Perreault et al., 2021 [56]	Adult patients	Yale-New Haven Health	Both HSCT recipients and non-HSCT recipients	Evaluated 45 patients who met the criteria for home-based IVIG infusion	Twenty-seven patients (60%) agreed to home-based IVIG infusion. There were no infusion-related complications, and 24 patients (92%) had no concerns about receiving IVIG and/or s.c. Ig at home. There was a cost savings of \$12,877, with decreased clinic infusion visits and 106 hours of additional available infusion chair time per month.

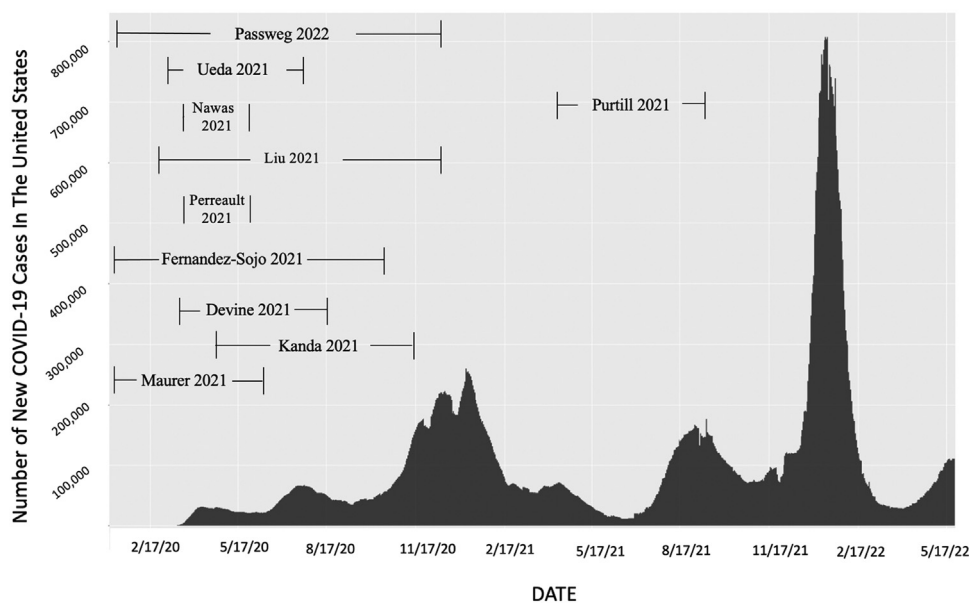


Figure 1. Timeline of reported cases regarding secondary effects of COVID-19: seven-day moving average of new cases of COVID-19 in the United States. The citations demonstrate the time period represented by the period of data collection for the included studies.

data were collected between March 19, 2020, and May 11, 2020. It included all patients scheduled for cellular therapy admission or undergoing their initial evaluation with the plan to admit for cellular therapy. This cohort comprised 85 patients, including 42 (49.4%) scheduled to undergo auto-HSCT, 36 (42.4%) scheduled for allo-HSCT, and 7 (8.2%) scheduled for CAR T cell therapy. At the time of the analysis, only 56 patients (66%) had received their planned therapy, including 53 (62%) scheduled for auto-HSCT, 57 (67%) for allo-HSCT, and 73 (86%) for CAR T cell therapy. Disease control was the most widely cited reason for not proceeding with auto-HSCT or CAR T cell therapy; conversely, the most common reason for deferring allo-HSCT was the progression of primary disease [14].

Finally, a cross-sectional survey performed by the Cellular Therapy and Immunobiology Working Party of the European Group for Blood and Marrow Transplantation (EBMT) that 14 of 49 centers (29%) had at least 1 patient in whom CAR T cell therapy was delayed. The most cited reasons for delay included reduced access to intensive care units, decreased on-site medical providers, and patient bed capacity [15]. Further studies are needed to determine how delayed transplantation might have led to the loss of transplantation opportunities, reduced likelihood of successful transplantation, and adverse patient outcomes.

Donor Considerations

The pandemic has had a considerable influence on donor selection and availability. Guidelines from the American Society of Transplantation and Cellular Therapy and the EBMT recommend testing patients for SARS-CoV-2 before starting their preparative regimens [6,16]. In addition, these guidelines state that donors with SARS-CoV-2 detected in a respiratory sample are ineligible to donate, and that any donor who had close contact with a person diagnosed with COVID-19 should be excluded from donating for at least 28 days [16]. The low risk of viral transmission in donor products was demonstrated as the pandemic advanced and donor criteria loosened [17].

Because international flight restrictions and other COVID-19-related transport issues may hamper timely delivery of fresh allogeneic stem cell products, on March 30, 2020, the National Marrow Donor Program (NMDP) required that all unrelated donor cell products be cryopreserved before the initiation of the recipients' preparative regimen. Understandably, centers reported decreased hematopoietic progenitor cell (HPC) collection and processing procedures during the initial year of the pandemic, along with a dramatic increase in the cryopreservation of HPC products even from related donors [13,18–21].

At the Dana-Farber Cancer Institute, outcomes of 127 adult cellular therapy recipients treated during the initial COVID-19 surge were compared with historical controls treated before the pandemic, and notable changes in donor selection, donor screening, and cryopreservation practices were observed. Changes included more in-depth donor health history screening, explicitly asking for COVID-19 exposure or symptom. In addition, a shift toward unrelated domestic donors secondary to restrictions on international travel occurred [21]. No delay was observed in the median time from donor workup request to the day of transplantation in the COVID-19 period compared with the pre-COVID-19 period. In accordance with the NMDP, all unrelated donor peripheral blood mononuclear cell (PBMC) products were cryopreserved [21].

Conversely, the Italian experience has been markedly different, with the literature reporting only mild decreases in the number of auto-HSCT procedures (-15% reduction) and a

minimal reduction in the number of allo-HSCT procedures (only a 2.4% reduction) [19].

In addition to decreased PBMC collection rates, the practice of the collection and utilization of cord blood (CB) units changed. The possibility of vertical transmission (in utero, mother-to-child) of SARS-CoV-2 has been suggested, but the data are quite limited [22]. Yet, because of the COVID-19 pandemic and the fear of possible vertical transmission, CB donation decreased, leading to a reduction of CB inventories worldwide [23]. For example, the French Cord Blood Bank Network observed a 45% decrease in CB collection practices and a 24% decrease in international unit exchange with the American Cord Blood Bank compared with prepandemic years [24].

Additionally, concerns arose about whether granulocyte colony-stimulating factor (G-CSF) as part of HPC mobilization in COVID-19-positive donors would lead to a hyperinflammatory syndrome and put donors at risk. No adverse events or hyperinflammatory symptoms were reported in related donors who tested positive for SARS-CoV-2 and concurrently received G-CSF during mobilization. Additionally, none of the 3 patients who received these stem cell products subsequently had detectable SARS-CoV-2 [20]. In contrast, the use of G-CSF in the setting of neutropenia has been shown to worsen clinical status in some cancer patients with SARS-CoV-2 [25].

Patient Considerations

Recommendations from the NMDP and EBMT in 2020 included that transplantation centers should secure and cryopreserve grafts before starting conditioning regimens. This change in practice resulted in studies evaluating patient outcomes using cryopreserved or fresh stem cell grafts. The impact on patient outcomes has varied in different analyses. Table 2 summarizes previously reported studies evaluating the effects in HSCT recipients who received cryopreserved grafts. The largest study analyzing clinical outcomes included a recent Center for International Blood and Marrow Transplant Research (CIBMTR) analysis evaluating 7397 patients [26].

Multivariate analysis showed no difference in engraftment rates, survival, and nonrelapse mortality (NRM) with cryopreservation of bone marrow (BM) grafts. However, cryopreservation of related donor PBSC grafts was associated with decreased platelet recovery and increased incidence of grade II–IV and grade III–IV acute graft-versus-host disease (GVHD) compared with recipients of fresh PBSC grafts. Additionally, cryopreservation of unrelated PBSC grafts was associated with delayed neutrophil and platelet engraftment, elevated risk for NRM and relapse, and decreased OS and progression-free survival (PFS). Multivariate analysis showed that cryopreservation was associated with inferior OS [26,27].

These results were a marked change from an earlier CIBMTR analysis that demonstrated no differences in OS, relapse, progression, engraftment, and rates of clinically significant acute GVHD in patients with hematologic malignancies who underwent transplantation with cryopreserved grafts versus those who received fresh grafts [28]. Conversely, other centers saw no immediate impact on their patient outcomes secondary to changes in stem cell collection and cryopreservation practices; for example, Dana-Farber Cancer Institute saw no differences across all allo-HSCT recipients in terms of 100-day OS, PFS, non-COVID-19 infections, and other transplantation-related complications, including graft failure and GVHD. None of the recipients contracted COVID-19 during the first 100 days post-HSCT [21]. In a study of a smaller cohort, no differences in OS, rate of acute GVHD at day 100, or neutrophil/platelet recovery were observed among 32 patients who

Table 2
Summary of Outcomes Secondary to Change in Cryopreservation Practices During the COVID-19 Pandemic

Study and Year	Population	Transplant Type	Primary Diagnosis	Study Design	Summary of Findings
Hsu et al., 2021 [26]	Pediatric and adult patients	Allo-HSCT	Hematologic malignancies	CIBMTR analysis of 7397 total patients comparing outcomes of HSCT recipients who received fresh or cryopreserved allogeneic BM or PBSC grafts	Multivariate analysis showed no significant increased risk of delayed engraftment, relapse, nonrelapse mortality, or survival with cryopreservation of related donor PBSC grafts was associated with delayed platelet engraftment and increased risk of grade II-IV and grade III-IV aGVHD. Cryopreservation of unrelated PBSC grafts is associated with delayed neutrophil engraftment, increased NRM, and decreased PFS and OS.
Hamdanai et al., 2020 [28]	Adult patients	Allo-HSCT	Hematologic malignancies	CIBMTR analysis of 274 patients comparing outcomes of allo-HSCT recipients who received cryopreserved PBSC grafts and post-transplantation cyclophosphamide to allo-HSCT recipients of fresh grafts	No difference in 1-year and 2-year OS between patients who received cryopreserved or fresh grafts. Matched pair regression analysis showed cryopreservation of graft was not associated with higher mortality. There were no differences between the two groups in neutrophil, platelet engraftment, grade III-IV aGVHD, NRM, and relapse/progression. Lower rates of cGVHD and disease-free survival in patients who received cryopreserved grafts.
Eapen et al., 2020 [30]	Pediatric and adult patients	Allo-HSCT	Severe aplastic anemia	Compared outcomes of allo-HSCT recipients with severe aplastic anemia who received cryopreserved grafts compared with 194 allo-HSCT recipients who received fresh grafts	Higher 1-year overall mortality was higher among patients who received cryopreserved grafts than those who received fresh grafts. There were no differences in the incidence of aGVHD and cGVHD
Fernandez-Sojo et al., 2021 [29]	Adult patients	Allo-HSCT	Hematologic malignancies	Matched case-control cohort study of 32 patients who underwent allo-HSCT who received cryopreserved grafts compared to 32 patients who received fresh grafts	No difference in time to neutrophil and platelet engraftment, donor chimerism, rates of aGVHD at day 100, OS, and PFS.
Devine et al., 2021 [57]	Pediatric and adult patients	Allo-HSCT	Hematologic malignancies and nonmalignant diseases	Analysis of outcomes of 959 and 2499 recipients of cryopreserved and fresh BM or PBSC grafts	No difference in OS at day 100 and day 180 between the groups. Slight delays in neutrophil and platelet recovery in the cryopreserved group. No difference in primary graft failure by day 28 between the groups.
Kanda et al., 2021 [58]	Pediatric and adult patients	Allo-HSCT	Hematologic malignancies and nonmalignant diseases	Retrospective, a single-cohort study of 112 patients from the Japan Marrow Donor Program analyzing HSCT recipients of unrelated BM or PBSC cryopreserved grafts	Neutrophil engraftment at day 28 was 91.1% and was not different between recipients of cryopreserved grafts and recipients of fresh grafts. There was a trend toward a shorter time to neutrophil recovery in recipients of cryopreserved PBSC grafts.
Jacob et al., 2021 [59]	Adult patients	Allo-HSCT	Hematologic malignancies	Single-center analysis of 64 patients who underwent allo-HSCT with cryopreserved or fresh CD34 ⁺ -selected grafts	No difference in 2-year OS, relapse-free survival, the cumulative incidence of relapse, and cumulative incidence of NRM at 2 years between recipients of cryopreserved grafts and recipients of fresh grafts. Also no difference in the incidence of grade II-IV GVHD.
Maurer et al., 2021 [21]	Adult patients	Auto-HSCT, Allo-HSCT, and CAR T cell therapy	Hematologic malignancies (2 patients with aplastic anemia)	A retrospective analysis comparing 127 cell therapy recipients treated during the COVID-19 pandemic and 142 cell therapy patients treated before the pandemic	No differences in OS at day 100, PFS, rates of non-COVID-19 infections, neutrophil and platelet recovery, graft failure, or aGVHD in allo-HSCT recipients. No differences in the incidence of neurotoxicity and cytokine release syndrome in CAR T cell recipients.
Novitzky-Basso et al., 2022 [27]	Adult patients	Allo-HSCT	Hematologic malignancies and non-malignant diseases	Analysis comparing outcomes of 483 patients who received allo-HSCT at Princess Margaret Cancer Centre	Patients who received cryopreserved grafts had reduced survival, lower incidence of cGVHD, delayed neutrophil engraftment, and higher rate of

(continued)

Table 2 (Continued)

Study and Year	Population	Transplant Type	Primary Diagnosis	Study Design	Summary of Findings
				who received cryopreserved or fresh PBSC grafts	graft failure. There was no difference in the incidence of aGVHD or relapse between cryopreserved graft recipients and fresh graft recipients.
Purtill et al., 2021 [60]	Pediatric and adult patients	Allo-HSCT	Hematologic malignancies and nonmalignant diseases	Comparison analysis of 191 allo-HSCT recipients who received cryopreserved or fresh grafts from the Australian Bone Marrow Transplant Recipient Registry	Similar outcomes between COVID era and pre-COVID era with respect to post-thaw CD34 viability, neutrophil recovery, and graft failure. However, problems with 29% of products in the form of damage during transit, low cell dose, inadequate labeling, missing representative samples, or missing documentation. These problems were critical in 7 cases (4%). At the last follow-up, 22 products (12%) had not been infused.

aGVHD indicates acute graft-versus-host disease.

underwent unrelated donor HSCT with either cryopreserved or fresh PBSC grafts [29].

However, when looking more closely at specific disease categories, the lack of differences in outcomes is not universal. For example, patients with certain nonmalignant diseases had worse outcomes with the changes in cryopreservation practices during the pandemic. Specifically, in patients with aplastic anemia, higher rates of graft failure and 1-year overall mortality were seen in HSCT recipients who received cryopreserved grafts compared with those who received noncryopreserved grafts, even when adjusted for sex, baseline performance scores, other comorbidities, cytomegalovirus serostatus, and ABO blood group match [30]. Careful subanalyses of HSCT recipients of specific disease groups are warranted, as the experience with aplastic anemia patients shows that cryopreservation might not lead to the best outcomes for this patient cohort.

Large-scale studies are needed to examine the long-term impact of the changes in stem cell collection and processing implemented during the COVID-19 pandemic. Comparing data following the onset of COVID-19 compared with the 3 months immediately before onset of the pandemic demonstrated that the NMDP was able to convert patient cycles (from initiation of the preliminary donor search to graft infusion) at nearly the same or a higher rate over a similar or shorter period. Furthermore, despite travel restrictions and interruptions to domestic courier services, graft products were delivered to transplantation centers at a similar rate as before the onset of the COVID-19 pandemic [31]. In contrast, the DKMS reported a 15.9% reduction in donors worldwide, with a consequent decreased number of bone marrow product donations. Cryopreservation of stem cell products became the new temporary standard owing to COVID-19-related travel restrictions and donor availability. Recruitment of donors also declined significantly because the DKMS stopped public offline donor recruitment, resulting in a 40% decrease in new donors during the pandemic [32]. Similar struggles with bone marrow donor recruitment were seen in other countries, including Poland [33].

Similar trends were published by the World Marrow Donor Association in their most recent Global Trends Report, which details the impact of the COVID-19 pandemic on unrelated HSC donations. A total of 103 donor registries and CB banks from 61 countries participated in the 2020 Global Trends Report, which noted that HSC donations from unrelated donors (both PBSC and BM stem cell sources) diminished by

3.5% from 20,330 in 2019 to 19,623 in 2020, compared with an average annual growth rate of +3.9% from 2015 to 2019. Not surprisingly, the 3.5% decrease includes a 29% reduction in BM donations and a 2.6% increase in PBSC donations, resulting in a drop in the BM share of unrelated HSC donations from 19.3% in 2019 to 14.2% in 2020 [34]. The reasons cited for such marked changes in donation practices included disrupted courier use from increased travel restrictions, decreased donor availability, donor selection practice changes, and prioritization of patients with more acute diseases.

SECTION 2: IMPACT ON RESEARCH AND CANCER-RELATED THERAPY DURING THE COVID-19 PANDEMIC

Cancer Care and Clinical Trial Enrollment

The COVID-19 pandemic drastically disrupted the conduct and management of cancer patients enrolled in clinical trials. With the onset of the pandemic, centers observed an apparent decline in the numbers of new cancer diagnoses, likely reflecting access to care issues and patient avoidance of care for fear of contracting COVID-19 [35]. In addition, several studies demonstrated a reduction in National Cancer Institute (NCI)-sponsored cancer trials along with overall clinical trial enrollment [36]. Similar reductions in cancer clinical trials were noted worldwide, as one Italian center saw an 84.5% reduction in patient clinical trial enrollment [35].

To mitigate the significant impact on clinical research, the National Cancer Institute and the US Food and Drug Administration (FDA) issued guidance on provide flexibility to ensure that patients participating in clinical trials were exposed to as minimal risk as possible during the COVID-19 pandemic [37,38]. Such clinical trial changes included implementing remote and electronic consent and telehealth visits. Many sites temporarily paused enrollment owing to local, state, sponsor, or institutional restrictions intended to prevent the spread of COVID-19 [39]. In response to the rapidly growing number of patients in need of a hospital bed, research staff and resources were redirected toward providing medical care for the influx of COVID-19 patients. In addition, many academic institutions paused routine clinical research activities and prioritized clinical trials focusing on COVID-19 therapies [40].

In Seattle, phase 1 and 3 HSCT trials were halted temporarily, and only phase 2 trials with potential benefits for patients were allowed to continue enrollment. All study visits were transitioned to telehealth, and any other ancillary studies were paused [13]. A similar reduction in clinical research

activity was observed at Memorial Sloan Kettering Cancer Center during the peak of the pandemic [14]. Small clinical trials focused on HSCT recipients also were negatively impacted by the pandemic [41,42]. Future studies analyzing the long-term effect of the pandemic on clinical research, clinical trial enrollment, and patient outcomes are needed.

SECTION 3: ADJUSTMENTS TO TRANSPLANTATION AND CELLULAR THERAPY HEALTHCARE DELIVERY SERVICES DURING THE COVID-19 PANDEMIC

Access to Care

In the early post-transplantation period, patients required close monitoring, given their elevated risk of developing acute toxicities and complications during this time. To mitigate the spread of COVID-19 within the HSCT patient population, the EBMT and other transplantation organizations released guidelines for all HSCT/cellular therapy recipients to avoid unnecessary clinic visits and reduce exposure to SARS-CoV-2 [43].

When clinically appropriate and feasible, telemedicine visits were substituted for in-person visits [44] and patient referrals for transplantation consultation [13]. Telehealth visits were piloted at Memorial Sloan Kettering Cancer Center, specifically in patients undergoing HSCT in outpatient and inpatient settings, with 27 telehealth visits conducted with 25 patients. Out of a total of 54 provider assessments, 7 providers (13%) were unable to complete a component of the physical examination. Notably, 81% of the patients (out of 25) were either satisfied or very satisfied with the telemedicine sessions, with some overall satisfaction rates higher among patients than among providers [45]. Additional studies evaluating the success and limitations of telemedicine are needed, as most have been limited to pilot studies assessing feasibility among HSCT recipients.

Aside from testing the feasibility of incorporating telehealth into the overall care of HSCT patients, the use of telemedicine has allowed increased access to survivorship care for HSCT recipients regardless of socioeconomic background. At a single center in Kansas, the implementation of telehealth visits increased access to medical care in 2020 compared with 2019, irrespective of patient sex, neighborhood income, and driving distance to the center [46]. Data showed that telehealth procedures could be done in clinically appropriate circumstances and potentially increase patient satisfaction rates. However, larger-scale studies are needed to confirm these observations and to evaluate the use of telehealth on overall outcomes.

Digital technologies allowing medical providers to monitor a patient's clinical status in real time were used following discharge. The SMARTCOVID19 study allows clinicians to use a telehealth platform to collect patient vital signs and physical and psychological data daily over a 2-week period following discharge. Only 12 of 21 patients eligible for the trial were able to enroll and complete this study, with technological barriers the most frequent limiting factor in the study. However, among the 12 patients who enrolled, high adherence rates and reasonable patient satisfaction with the system were observed [47]. Similarly, pilot studies monitoring cardiovascular risk factors in adult transplant recipients have shown good compliance among participating patients [48].

Blood Product Shortages

Blood donation was affected by pandemic-associated cancellations of blood donation drives and interruptions in blood registry services due to travel restrictions and staff sickness. Because of measures promoting social distancing, many schools and universities were forced to close during the initial

part of the pandemic, leading to a dramatic decrease in the number of blood donations in the United States [49]. As a result of decreased donations, blood product shortages arose. Hospitals responded by accepting an inventory of blood units from nonaffected areas of the country and developing a triage system that prioritized blood use for specific patients [13]. The Worldwide Network for Blood and Marrow Transplantation and the CIBMTR Health Services and International Studies Committee jointly produced an expert opinion on supportive care guidelines for HSCT patients. The guidelines recommended lowering the threshold for blood product transfusion at the beginning of HSCT and minimizing blood loss by using prevention strategies like minimizing blood draws or treatment with tranexamic acid if clinically feasible [6].

Emotional Exhaustion for Patients and Healthcare Workers

Healthcare workers worldwide have risen to the huge demands and stressors of treating COVID-19 patients, potentially at the cost of their own physical health and mental well-being. Although recognition of the mental health impact of COVID-19 on healthcare workers has been increasing, little attention has been given to understanding the impact of working on a pandemic from the healthcare worker's perspective. Although at the beginning of the pandemic, healthcare workers strove to treat COVID-19 patients with purpose and forged collaborations across health systems to promote improvement in healthcare delivery practices, a heavy workload quickly impacted the psychosocial well-being of frontline workers. A meta-analysis of healthcare workers' experiences found that working with colleagues and peers provided a unique source of moral support; however, themes of burnout from increased workloads and ethical and professional dilemmas quickly became prominent [50].

HSCT is associated with many psychological stressors and unique issues differing from those related to other chronic diseases and therapies, such as anxiety related to different stages of HSCT care, sleep disruptions, and post-traumatic stress reactions from medical events and treatments [51]. Therefore, patients undergoing HSCT require psychological support and pharmacologic interventions [52]. However, the stresses of undergoing HSCT therapy were exacerbated during the COVID-19 pandemic, with limited psychosocial support from patients' families. Many hospitals adopted strict no visitor policies during the initial wave of the COVID-19 pandemic making an already-difficult hospitalization more difficult for families and patients to endure. Therefore, experts recommended monitoring for detrimental psychological effects on HSCT patients and survivors [6]. Similarly, ensuring the mental health and well-being of an overtaxed healthcare provider group became equally important.

Only one study specifically evaluated the emotional and mental issues that arose in HSCT medical staff during the initial part of the COVID-19 pandemic. In this study, 398 nurses working in HSCT centers across northern Italy were evaluated to define the prevalence of physical issues, sleep disorders, and burnout symptoms and look for correlations with COVID-19 geographical incidence. Ultimately, COVID-19 incidence did not influence the nurses' overall burden of symptoms in the HSCT setting. However, moderate levels of emotional exhaustion, depersonalization, and decreased sleep quality across all territories were observed [53].

Staffing Issues

One of the major responses hospitals and health systems implemented was the suspension of elective procedures to

save capacity, supplies, and staff to treat COVID-19 patients. As a result of suspending nonemergent procedures, health systems lost a large portion of their annual revenue, which forced them to make cost reductions an immediate priority. In the United States, many hospital systems furloughed thousands of employees in an effort to remain financially stable during the COVID-19 pandemic. Additionally, operational changes to ensure adequate infrastructure to maintain and continue patient care were critical during the pandemic. Some transplantation centers created backup coverage systems in the event of absences due to illness or exposure to ensure sufficient ancillary, nursing, and physician staffing. Physicians who were at higher risk from COVID-19-related illnesses were diverted from clinical-based activities to telehealth consultation services. To accommodate the high influx of patients during the pandemic, outpatient transplant nursing staff were reassigned to assist with screening and triage services for the hospitals [13].

DISCUSSION

It is obvious the COVID-19 pandemic has significantly impacted global health and healthcare delivery systems. In this review, we have summarized the specific secondary impacts caused by COVID-19 on the field of HSCT and cellular therapy. These secondary impacts have affected the prioritization of transplantation-related practices and cancer care for patients worldwide. The major changes that we observed are decreases in overall donor recruitment and collections, increases in cryopreservation practices, and prioritization of HSCT for acute diseases. Although the outcomes for some disease groups were not impacted by such changes in practices, subanalyses of certain disease groups have shown that the outcomes are not generalizable for all groups of patients.

Changes to patient-related issues include decreased clinical trial enrollment and access to care. To follow social distancing rules, healthcare systems and hospitals began implementing unique practice changes, such as increasing telehealth visits and homecare visits, to ensure patients were still receiving the necessary care.

Finally, we also reviewed changes in healthcare delivery issues, including blood product shortages, vaccine hesitancy in patients and their families, staffing issues, and emotional burn-out and exhaustion for healthcare workers. The COVID-19 pandemic revealed vulnerabilities of the HSCT and cell therapy ecosystems, such as blood product and staffing shortages. And although a majority of the studies focused on the initial year of the pandemic, these studies are highly applicable to later and future states of the pandemic and also future global health crises. The lessons and changes developed from the initial part of the COVID-19 pandemic laid the foundational framework to make the appropriate healthcare delivery and infrastructure changes required to continue to provide care to this unique set of patients. Our experience during the COVID-19 pandemic can help guide preparations and hopefully circumvent such problems. And given the huge impact on the psychosocial well-being of healthcare and other frontline workers, this pandemic has taught us that further infrastructure to support and maintain their well-being during such health crises is crucial. In addition, although these studies are small and data are limited, this information can help provide a backbone for augmenting such practices in the future if similar health crises arise.

The COVID-19 pandemic has required a multifaceted approach to address system- and patient-level needs. In this regard, Ardura et al. [11] proposed a holistic approach to

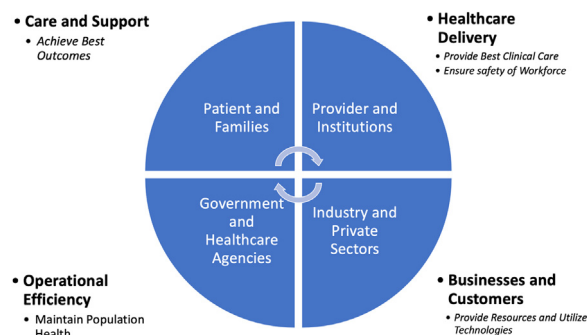


Figure 2. Holistic care model for patients and healthcare providers during the COVID-19 pandemic. Adapted from Ardura et al. [11].

addressing the complex nature of healthcare delivery during the COVID-19 pandemic. This approach requires that healthcare delivery systems be able to rapidly address and respond to changes; have access to and interpret consistent and accurate messaging from government agencies; reallocate and repurpose available resources at the local, regional, and national levels; and engage informed communities (Figure 2) [11].

The COVID-19 pandemic has had numerous secondary impacts on patients undergoing HSCT and the healthcare delivery systems involved in providing complex care to transplantation recipients. Institutions and providers must recognize these influences on outcomes and adjust accordingly to maintain and improve outcomes for the HSCT community. The system-level impact of COVID-19 resulted in lessons learned and potential applications for future challenges requiring the holistic response of the cell therapy ecosystem.

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