Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Perspective

COVID-19 and Hematopoietic Cell Transplantation Center-Specific Survival Analysis: Can We Adjust for the Impact of the Pandemic? Recommendations of the COVID-19 Task Force of the 2020 Center for International Blood and Marrow Transplantation Research Center Outcomes Forum

John R. Wingard[1,*], Kwang Woo Ahn[2], Christopher Dandoy[3], Miguel-Angel Perales[4], William A. Wood[5], Brent Logan[2], Marcie Riches[5], J. Douglas Rizzo[2]

[1] *Department of Medicine, University of Florida College of Medicine, Gainesville, Florida*
[2] *Medical College of Wisconsin, Center for International Blood and Marrow Transplantation Research, Milwaukee Campus, Milwaukee, Wisconsin*
[3] *Cincinnati Children's Hospital Medical Center, Department of Pediatrics, University of Cincinnati, Cincinnati, Ohio*
[4] *Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, New York*
[5] *Division of Hematology, Department of Medicine, University of North Carolina School of Medicine, Chapel Hill, North Carolina*

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A B S T R A C T

COVID-19 has significantly impacted the practice of hematopoietic cell transplantation (HCT) and likely affected outcomes of HCT recipients. Early reports document substantially higher case fatality rates for HCT recipients than seen in faced by the general population. Currently we do not have a clear picture of how much of this threat is present within the first year after HCT and how infection rates and outcomes vary with time after HCT. There are important because center-specific survival estimates for reporting purposes focus on 1-year post-HCT mortality. Transplantation centers have dramatically changed their practices in response to the pandemic. At many centers, quality assurance processes and procedures were disrupted, changes that likely affected team performance. Centers have been affected unevenly by the pandemic through time, location, and COVID-19 burdens. Assessment of center-specific survival depends on the ability to adjust for risk factors, such as COVID-19, that are outside center control using consistent methods so that team performance based on controllable risk factors can be ascertained. The Center for International Blood and Marrow Transplantation Research (CIBMTR) convened a working group for the 2020 Center Outcomes Forum to assess the impact of COVID-19 on both patient-specific risks and center-specific performance. This committee reviewed the factors at play and developed recommendations for a process to determine whether adjustments in the methodology to assess center-specific performance are needed.

CENTER-SPECIFIC OUTCOMES ANALYSIS

The CIBMTR produces an annual report on transplant center-specific survival rates to provide information to potential hematopoietic cell transplantation (HCT) recipients, their families, transplantation centers, and the general public as called for in the C.W. Bill Young Cell Transplantation Program. Reporting center-specific survival rates is a requirement of the Stem Cell Therapeutic and Research Act of 2005 (reauthorized in 2010 and 2015) and, before that, the 1990 Transplant Amendments Act. HCT center-specific outcomes have been tracked since 1994. Over the years, this analysis has become an essential tool for centers to assess the effectiveness of quality improvement endeavors. It also has become a vehicle for transparent communications to the public providing information about both expected and observed survival rates.

RISK ADJUSTMENT

Because centers vary considerably in the risk level of cases treated, the Center-Specific Survival Analysis uses a statistical model adjusting for several risk factors known or suspected to influence outcomes. The outcome reported is 1-year overall survival, for recipients of first allogeneic HCT in the United States. Methods are published annually (https://www.cibmtr.org/

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*Correspondence and reprint requests: John R. Wingard, MD, University of Florida College of Medicine, UF Health Cancer Center, PO Box 103633, Gainesville, FL 32610-3633.

E-mail address: wingajr@ufl.edu (J.R. Wingard).

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ReferenceCenter/SlidesReports/USStats/Documents/CIBMTR%20HCT%20Center%20Survival%20Report%20Methodology%20FINAL%202020-12-14.pdf). The premise underlying risk adjustment is that different centers vary in the types of diseases and characteristics of patients treated (case mix), and that such differences substantially affect outcomes. Multiple factors that affect survival have been identified and included in the statistical model. As science has evolved, new risk factors have been introduced, and others have been removed. Without adjusting for such differences, one could not determine whether a center's survival rate is driven principally by its case mix or by the skills and performance of the center's team and its practices. Furthermore, not adjusting for such risk factors might lead to an important unintended consequence of centers declining to offer transplantation to higher-risk patients to avoid less favorable outcomes.

A crucial underpinning for quality assessment is that one can assess performance associated with controllable risks related to the skill, team cohesiveness, adherence to safety standards, and maintenance of safeguards to minimize errors, independent of uncontrollable risks. Adjustments for confounding effects due to uncontrollable risks attributable to patient factors, disease factors, and other risk factors over which the center has no control are crucial.

COVID-19: A HUGE DISRUPTOR

COVID-19 arrived in the United States in early 2020. Initially, cases were concentrated mainly in several regions. Gradually the disease became distributed across the country, with asymmetric geographic infection rates and health system burdens over time. Rates of infections, hospitalizations, and deaths varied considerably and waxed and waned unpredictably at different locations. Centers have been affected unevenly by time, location, and COVID-19 burdens. At present, whether these geographic disparities in the regional impact of COVID-19 have translated to differential effects of COVID-19 on transplantation outcomes at centers is not clear. If it were determined that the effects of COVID-19 on centers were evenly distributed, then complex adjustment for this uncontrollable risk might not be needed.

INTRODUCTION

Early reports about COVID-19 indicated substantially higher morbidity and mortality in hematopoietic cell transplantation (HCT) recipients than in the general population [1-6]. Thirty-day mortality rates of 22% to 32% were seen [1,2]. Risk factors for severe COVID-19 morbidity included some of the same comorbidities (eg, male sex, older age) as in the general population but also included additional risk factors, including active immunosuppressive therapy in one study, occurrence within the first year post-transplantation in another, and comorbidities at time of infection in a third. The relative risk in patients with active graft-versus-host disease (GVHD) has been less apparent in early reports. Most cases in early reports occurred beyond 1 year post-transplantation. As of February 2021, the number of cases of COVID-19 infection during the first year post-HCT was low, but 37% of the COVID-19 infections reported to the CIBMTR occurred in that first year (unpublished data). Based on reported outcomes of other early viral infections post-HCT, it can be reasonably assumed that patients with SARS-CoV-2 infection early after HCT are more likely to have poor outcomes. This is supported by early data showing that these patients are less likely to clear the virus, which has been associated with prolonged shedding as well as with an increased risk of mutations [7]. Currently, we lack a clear picture of the magnitude of impact of COVID-19 on 1-year survival and the HCT-specific risk factors for infection and mortality.

Transplantation centers quickly recognized the threats of COVID-19 to HCT recipients and in response dramatically changed multiple transplantation practices [8,9]. These practice changes also may affect survival in ways not obvious at present (Figure 1) and can be considered indirect effects of the pandemic. Some of these changes in practice were likely to have been applied differentially across US centers based on temporal and geographic variations in pandemic intensity, the severity of disease indications, age of recipients, socioeconomic status, and type of donor (related or unrelated donor). Transplantations were delayed, necessitating the use of bridging therapies in some patients. Some transplantations were not performed, and donor stem cell products were collected in advance and frozen to ensure their availability when needed. The effects of cryopreservation on the quality of the allograft and subsequent outcomes are relatively underexplored, and several reports have raised concerns, while others were reassuring [10-12]. Evaluations of candidates for HCT were curtailed to avoid aerosolizing procedures (eg, spirometry), making risk assessment incomplete. There were fewer donors available, owing to donors grappling with their own pandemic effects, including travel restrictions, illness, and changes in employment. Compounding these issues, blood donations decreased, and the shortages necessitated changes in transfusion practices to conserve limited supplies. Hospital resources became constrained while managing the burden of COVID-19-infected patients. Availability of critical supplies, such as

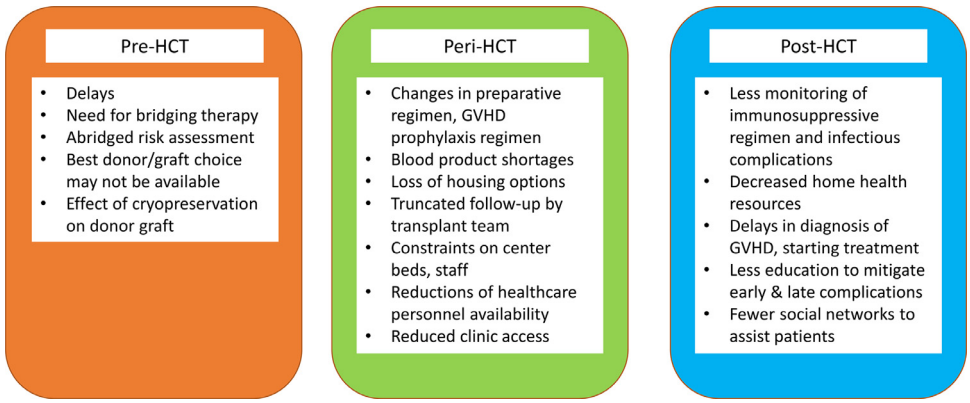

Figure 1. COVID-19 has multiple indirect effects on transplantation practices that possibly affect center-specific outcomes.

personal protective equipment, consultants for certain critical specialties (eg, Infectious Disease, Pulmonary, Nephrology), and both inpatient beds and intensive care unit beds, became constricted. Postdischarge outpatient care also changed dramatically. Clinics restricted access to implement stringent infection control measures, resulting in less oversight of ongoing care and monitoring of immunosuppressive regimens and increased infectious complications. This introduced the potential for delays in identifying and treating GVHD and less scrutiny on evaluating patient responses and the need for changes in treatment. Center initiatives to provide patient education, encourage health- promoting behaviors, and screen for early and late complications were set aside or curtailed. Communal housing was no longer safe, and finding nearby housing for patients living far from the transplant center became more challenging. As a result, patients were discharged to local care networks much sooner than considered appropriate during usual care.

The pandemic affected individuals from ethnic minorities and lower socioeconomic status to a greater degree than other populations. Centers serving large numbers of low-income patients were especially affected, because their patients had disproportionately fewer social network resources to assist with their care needs and to support and sustain themselves. The degree to which the various changes to practice described above occurred uniformly or unevenly across centers is unknown.

THE CIBMTR'S RESPONSE

Data Collection

The CIBMTR recognized the urgent need to gather data on the impact of COVID-19 on HCT outcomes and practices. Data collection systems in place in March 2020 did not collect relevant information about SARS-CoV-2 and related outcomes. The CIBMTR responded quickly to collect COVID-19-specific data by modifying data collection forms (Table 1). Questions were added to collect information on the occurrence and time of COVID-19 infection, along with granular information about COVID-19 infection, risk factors, treatments, severity of illness and outcomes, and, if death occurred, options to identify COVID-19 as a primary or secondary cause of death. Data collection was subsequently modified to capture ways in which COVID-19 necessitated changes to the transplantation plan before HCT or execution of the transplantation procedure.

Center Outcomes Forum Task Force

To increase transparency and understanding of HCT center outcomes reporting, the CIBMTR began to hold a biannual Center Outcomes Forum (COF) in 2008. The CIBMTR invites representatives of the HCT community, including transplant physicians and center directors, the American Society of Transplantation and Cellular Therapy, the Foundation for Accreditation of Cell Therapy (FACT), governmental funding agencies, patients, private payers, and statisticians to participate. The purpose is to review the current approach to center-specific outcomes reporting and to provide meaningful recommendations for future reports. Summaries of these meetings are available at http://www.cibmtr.org/Meetings/Materials/CSOA-Forum. As part of the 2020 CIBMTR COF, a task force was convened to provide guidance on how to assess the impact of COVID-19 on the evaluation of center-specific outcomes.

The fundamental question considered by the task force was whether the abrupt changes required to respond to the pandemic disrupted centers' quality measures in predictable or unpredictable ways, and did that disruption render quality assessment unreliable. More specifically, what is the magnitude of the impact of the COVID-19 pandemic on outcomes of allogeneic HCT recipients, and can the Center-Specific Analysis risk-adjustment model be modified to adequately account for the impact?

Direct Effects of COVID-19 on HCT Survival

The COVID-19 task force reviewed what was known about the direct effects of COVID-19 in individual patients and considered the various indirect effects of the pandemic on transplantation center practices. As noted, the CIBMTR developed tools to track the direct effects on individual patients, including data on the occurrence and time of onset of infection and whether COVID-19 had a direct or contributory role in death (Table 1).

Indirect Effects of COVID-19 on Transplant Centers and HCT Survival

Four categories of indirect factors on the centers that might affect center-specific performance were also identified: (1) COVID-19 burden; (2) locality of the center and patient; (3) impact of COVID-19 on center survival; and (4) indirect effects of COVID-19 burden on a center's practices.

Table 1
Changes in CIBMTR Data Collection

Data Elements	CIBMTR Form	Month Introduced
SARS-CoV-2 as infectious organism option	Forms 2100 and 4100	March 2020
Detailed COVID-19 infection and consequences	Respiratory virus post-infusion (collected on subset of allogeneic HCT recipients)	March 2020
SARS-CoV-2 as potential cause of death COVID-19 infection in recipient	Forms 2450 and 2900 Form 2450	May 2020
Patient infection base on positive COVID test, and related hospitalization or mechanical ventilation	Pre-TED, CTED	May 2020
	Pandemic impact form	August 2020
Modifications in:		
Date of HCT		
Donor selection		
Graft source		
Graft manipulation		
Preparative regimen		
GVHD prophylaxis		

COVID-19 Burden

The geographic and temporal burden of COVID-19 on the general population across the United States generally has been tracked in data collected by various entities and made publicly available using 3 parameters: infection numbers (incidence, or prevalence), hospitalizations, and deaths. These parameters generally have tracked closely together over time but not always. Testing capacity was severely limited early on and, even when testing became more readily available, it was not uniformly adopted across the United States. In addition, at various times and in different communities, divergences have been seen when infection numbers shifted disproportionately from high-risk groups such as the elderly and congregant groups to lower-risk groups such as adolescents and young adults, resulting in surges in infections without concomitant proportional increases in hospitalizations and deaths. A high infection prevalence would seem to be an excellent predictor of greater risk that an individual could become newly infected. On the other hand, higher hospitalization and death rates might be better markers of centers' constraints in accommodating patients' transplantation needs and continuity of quality measures.

Locality of the Center and Patient

However measured, the burden of COVID-19 affected HCT centers unevenly. Some centers were in communities with a high burden of COVID-19 infection, hospitalizations, and deaths, whereas others were not. However, many patients undergoing HCT live in a different community than the transplant location. Because such recipients live near the transplant center only temporarily, the burden of infection in the community of a patient's permanent residence may be more important for that individual in determining the impact of the pandemic. This may have become even more important during the pandemic as fewer housing options near the transplant center and the shift to telehealth visits accelerated timelines for many patients returning to their local community.

Impact of COVID-19 on Center-Specific 1-Year Survival Rates

The effects of COVID 19 on HCT processes and practices can be divided into categories based on the period of transplantation affected, as outlined in Figure 1. Pre-HCT factors include delays in HCT, pre-HCT workup, and so on. Peri-HCT factors include HCT procedures themselves (eg, preparative regimen, GVHD, graft type, duration of stay in proximity to the HCT center). Post-HCT factors include frequency of visits, virtual versus in person visits, frequency and quality of surveillance for complications, and risk of infection. For patients who underwent HCT in 2019, the pretransplantation decisions made and actions taken by the transplantation team and the peritransplantation management during the crucial first 100 days were not materially affected; however, patients who underwent HCT between March 2019 and December 2019 were at risk for infection as well as for effects on their transplantation care during the late phase of HCT and thus were exposed to the risk of premature death from COVID-19. From early reports of COVID-19 infections in HCT recipients, the infection appears to be less severe the later after HCT that it occurs. In contrast, all phases of HCT (pre-, peri-, and late post-HCT) were affected for most patients who underwent HCT in 2020 and are likely to be affected for all patients undergoing HCT in 2021.

The data being collated in the spring of 2021 are for patients who underwent HCT in 2019 and thus may provide only a partial picture of the pandemic effects. The broader impact may emerge only after a full year of follow-up for HCTs performed in 2020, in which all phases (pre-, peri-, and post-HCT) were affected. Transplantations performed in 2020 will not be studied until the spring of 2022. Furthermore, despite the recent introduction of vaccines, as of this writing, the pandemic continues unabated in the United States and will likely continue to impact transplant centers well into 2021. Potential approaches to analyses that include HCTs performed in 2020 and later, must account for possible impact on the pre- and peri-HCT factors, and are in development and will be informed by this year's analysis.

Indirect Effects of COVID-19 Burden on a Center's Practices

As daunting as the preceding 3 factors are, the most challenging factor to consider is how best to assess the impact of the pandemic on the team, its transplantation practices, and the center's quality measures put in place to optimize survival. It could be surmised that institutions faced with overwhelming demands of seriously ill non-HCT patients had less staff and more reassignment of work responsibilities, staff redeployments and shortages, decreased access to diagnostic procedures to evaluate comorbidities before HCT and complications after HCT, greater reductions in outpatient clinic services and access, and fewer intensive care unit beds to care for non-COVID-19 patients. Such centers with fewer resources to maintain quality measures likely responded to COVID-19 very differently than less affected centers. One surrogate marker considered for how transplantation practices were altered at a center is a drop in the number of HCTs performed; although this indicator is simple and attractive, the number of transplantations performed at a center is affected by multiple factors that have nothing to do with COVID-19, such as changes in personnel, referral patterns, and so on.

Another possible indicator considered is the responses from the patient-specific COVID-19 impact reports from the centers using revised forms rolled out by the CIBMTR to assess how COVID-19 affected the transplantation procedure for each patient. These CIBMTR form revisions were deployed in late August 2020, and their usefulness for assessing changes to the transplantation procedure prompted by the pandemic have yet to be measured. One potential shortcoming is that data were not collected prospectively in the early days of COVID-19 between March and September. However, centers were asked to provide them for all patients during this time, both retrospectively and prospectively, but how complete these data will be is unknown.

COF Task Force Recommendations

The COF task force formulated 5 recommendations (Table 2).

Recommendation 1: Expedite data collection efforts for allogeneic HCT recipients from 2019 to facilitate preliminary modeling to understand the impact of the COVID-19 pandemic on outcomes of allogeneic HCT

These data will facilitate the development of a final risk adjustment model for the Center-Specific Survival Analysis to be applied to first allogeneic HCT recipients in 2017 to 2019.

Recommendation 2: Develop a modeling approach to test the impact of COVID-19 on outcomes for recipients of HCT in 2019 and implement that approach in early 2021

The need for escalation of earlier timelines for data submission by the centers was communicated to center directors to support the needed exploratory analyses. The CIBMTR is collating the CY2019 transplantation data in the spring of 2021. The

Table 2
Working Group Recommendations to Assess and Adjust for COVID-19 Effects on Center-Specific Outcomes

1 The CIBMTR should expedite data collection efforts for allogeneic HCT recipients from 2019 to facilitate preliminary modeling to understand the impact of the COVID-19 pandemic on outcomes of allogeneic HCT.
2 Develop a modeling approach to test the impact of COVID-19 on outcomes for recipients of HCT in 2019 and to implement that approach in early 2021.
a Communicate with center directors and escalate relevant data collection efforts with centers to support earlier timelines for data submission to support these analyses.
b The preliminary modeling approach is likely to use Cox modeling to handle time-dependent covariates.
3 Use the results of the preliminary modeling of the impact of COVID-19 to design, if possible, a modified pseudovalue modeling approach for the Center-Specific Survival Analysis for the cohort of patients who underwent HCT in 2017 to 2019.
a It is important to use a consistent Center-Specific Survival Analysis model, if possible, to achieve results that are consistent with previous years and with known performance characteristics to allow year-to-year comparisons and maintain confidence in the modeling process.
b Include sections in the Center-Specific Survival Analysis report outlining the methodology and limitations of the risk adjustment for COVID-19 pandemic.
4 Develop communications for use across all relevant stakeholder groups regarding plans for Center-Specific Survival Analysis in 2021 and subsequent years to address COVID-19.
5 Continue to collaborate with SRTR and other organizations involved in public outcomes reporting to explore if and how other organizations are making assessments of the impact of COVID-19 on general acute care for geographic areas to inform this effort.

challenge faced by the statistics team is to test new models to measure both patient-specific direct effects and center-specific indirect effects of COVID-19 on center-specific survival.

The CIBMTR has traditionally used a fixed-effects censored data logistic regression model for Center-Specific Survival Analysis. A censored data version of logistic regression based on pseudovalues addresses the issue of incomplete survival status before 1 year [13-16]. This approach incorporates patient and disease variables at baseline only and does not consider time-dependent variables. The assumption is that the likelihood of post-HCT complications is largely a function of factors present before or at the time of HCT. For example, GVHD, infection, and relapse are the 3 major complications after HCT. The likelihood of GVHD is a function of the degree of matching of donor and recipient, type of graft, and type of GVHD prophylaxis. Infection risk is a function of previous infection exposure, GVHD prophylaxis, engraftment, GVHD, and center infection control measures. Relapse is a function of the type of disease, remission status, biological risk factors of the disease, and presence or absence of residual disease at the time of transplantation. These are all considered satisfactorily in the current fixed-effects model.

Several time-dependent factors are considered important to test for the 2021 analysis that includes the 2017 to 2019 cohort (Table 3). Calendar time would allow adjustment for center experience with COVID-19 changes over time in its location. The time after transplantation when COVID-19 infection occurred would be important. Based on early reports, it is reasonable to expect greater severity of illness earlier after HCT; thus, we divided HCT phases into the first 100 days, 3 to 6 months, and 6 to 12 months. Several time-dependent HCT complications should be included, especially acute and chronic GVHD. For our fundamental question evaluating the impact of COVID-19 on 1-year survival, it was judged that a time-dependent analysis might be more appropriate.

The time-dependent effects can be tested in a Cox regression model. A continuous function of time to determine potential breakpoints would be fitted. Interactions among the time-dependent covariates and interactions between the center location and the time-dependent covariates would be tested.

First, a baseline model would be built using currently known significant variables from previous years. Then time-dependent effects would be introduced in a stepwise manner to determine their function and significance of effect on outcomes. Interactions would be tested. If the impact of the time-dependent individual patient COVID-19 infection is significant, then censoring at the time of COVID-19 infection may be applied. If the need for a COVID indicator is found, then the center location rather than the patient location would be chosen to simplify the analysis.

Advantages of investigating time-dependent covariates under the Cox model include examining transplantation-related toxicities after HCT and modeling the covariates' time-varying effects on the survival (which would be important for HCTs performed in the second half of 2019).

An alternative analysis approach was also considered, involving examining year-by-year 1-year survival rates at each center (prepandemic and postpandemic). If the postpandemic outcomes were lower even after adjustments for changes in known risk factors from previous studies, then an unexplained variation would be noted. The unexplained variation could be due to a decline in team performance related or unrelated to

Table 3
Time-Dependent Effects to be Tested for the 2021 HCT Cohort Survival Analysis

• Calendar time (simple): adjusts experience of HCT centers with the pandemic, safety measures, subsequent adaptation, etc
• May be divided into periods such as March to May 2020, June to August 2020, September to December 2020
• COVID infection rates by geographic region and calendar time (using HCT center ZIP code)
• Time post-HCT: time since HCT for patients (first 100 days, 3 to 6 months, 6 months to 1 year)
• Time-dependent patient clinical status/complications after HCT (development of GVHD may increase patient risk for developing COVID and death)
• Time-dependent post-HCT COVID-19 infection status in individual patients

the effects of COVID-19. A methodology to tease out which possibility is more likely would need to be developed. In any given year, 5% to 10% of centers change from one performance category to another; this substantial baseline year-by-year variability in centers' performance will make it hard (or impossible) to separate that baseline variability from more "systematic" changes related to COVID-19.

Recommendation 3: Use the results of the preliminary modeling for the impact of COVID-19 to design, if possible, a modified censored data logistic regression modeling approach for the Center-Specific Survival Analysis for the cohort of patients who underwent HCT in 2017 to 2019

If the analysis does not suggest an impact from the pandemic, the CIBMTR will proceed with the standard regression model for the 2017 to 2019 HCT analysis. If the analysis finds an impact, the CIBMTR will need to determine whether the pseudovalue regression model analysis plan can be revised to accommodate the time-dependent effects and potential interactions. It is important to use a stable Center-Specific Survival Analysis model, if possible, to achieve results that are consistent with previous years and with known performance characteristics to allow year-by-year comparisons and maintain confidence in the modeling process.

Recommendation 4: Develop communications for use across all relevant stakeholder groups regarding plans for Center-Specific Survival Analysis in 2021 and subsequent years to address COVID-19

The Center-Specific Survival Analysis report should include sections outlining the methodology and limitations of the risk adjustment for the COVID-19 pandemic. If the analysis confirms that there is a COVID-19 impact and a pseudovalue regression model cannot be adapted, or there are too many time-variable effects, then the CIBMTR may make a recommendation to the Health Resources and Services Administration to defer specific cohorts from inclusion in the model. It may also be appropriate for the CIBMTR to include a disclaimer regarding the limitations to fully adjust for potential effects of the pandemic on the analysis and results. Because a main purpose of the Center-Specific Survival Analysis is to provide an equitable, scientifically valid performance measurement tool for use by centers for quality improvement, it is essential to acknowledge limitations that could cause misuse/misinterpretation or unreliable information to guide quality improvement activities.

Recommendation 5: Continue to collaborate with the Scientific Registry of Transplant Recipients (SRTR)

A substantial number of professional societies and other organizations in the United States analyze and publicly report procedural outcomes and are likely to be facing challenges related to the pandemic. The SRTR performs this function for solid organ transplantation outcomes in the United States under contract with Health Resources and Services Administration and is faced with a similar dilemma. The CIBMTR should explore whether other organizations are making assessments of the impact of COVID-19 on general acute care for geographic areas to inform this effort. Conversations are being shared among various stakeholders about how best to address this issue. The CIBMTR and the SRTR contractor have been sharing information about planned approaches. The payer community is closely following the CIBMTR's plans to address COVID-19 risk adjustment as payers consider modifications to their center assessments.

The FACT performs center accreditation and plays an important role in centers' corrective action plans for performance that is below expected levels. FACT processes may prove more important in the next few years, depending on the magnitude of limitations to center-specific survival analysis and public reporting. The FACT has the capability to review directly at the individual centers, something that may not be available to the payer groups, and this may be useful if the alternative analysis plan (to review the year-to-year drop in survival rates at a center and investigate each center to determine whether that is attributable to COVID-19 effects) were to be developed further.

Future Center-Specific Survival Analyses

The major theme of the COF taskforce in 2020 was to address methodologic considerations for the cohort of patients who underwent a first allogeneic HCT in 2017 to 2019 who will be analyzed in 2021. As discussed above, the impacts of COVID-19 on this cohort are limited to the post-HCT period. Subsequent cohorts of allogeneic HCT recipients in 2020 and 2021 can be anticipated to be impacted during the pre-, peri-, and post-HCT periods. Even if the analyses discussed above do not suggest an impact of COVID-19 on 1-year survival for patients who underwent HCT in 2019, it will be necessary to retest those impacts for patients who underwent HCT in subsequent years. In addition, new methodologic approaches or risk adjustment may be necessary for future cohorts that are impacted more extensively by the pandemic.

The focus of this article is center outcomes reporting and adjustment of potentially differential effects of COVID-129 across centers. Lessons learned from this analysis will be used to refine analytic and adjustment methods for research in which patients are the unit of analysis using the registry when patients who underwent HCT during the pandemic are included, as appropriate. It is likely that the pandemic will have ramifications for transplantation survival rates beyond 1 year, as is evident in the early reports of HCT survivors' experience with COVID-19 infection beyond 1 year. Furthermore, it is unclear whether COVID-19 infection in HCT survivors is associated with greater long-term COVID-19-associated morbidity than seen in the general population or lead to greater risks for HCT-associated complications, such as chronic GVHD and alloreactive lung disease as a consequence of early respiratory viral infections [17,18]. How the impact of altered patterns of health care in transplantation survivors with a greater reliance on telehealth will affect outcomes, and the timeliness of evaluation of complications and accuracy of reporting, remain unknown. The psychosocial consequences of the pandemic on HCT outcomes remain to be studied. Another implication of the pandemic that should be studied is the impacts on the outcomes of patients for whom HCT was the planned or the desired treatment but never performed; early reports suggest that the impact has differed across centers [19,20].

Further implications of the pandemic include the possibility that higher nonrelapse mortality due to COVID-19 might skew future CIBMTR research studies spanning multiple years (before and during the pandemic). Some type of adjustment for the COVID-19 effect may be necessary.

At this time, it is unclear whether the COVID-19 effects will be time-limited or will persist for multiple years. The 2 possibilities will present different modeling challenges.

CONCLUSIONS

COVID-19 has introduced an unpredictable factor that can have important implications for the measurement of center-specific outcomes. Various factors have been identified to serve as potential surrogate markers of COVID-19's impact on both patient-specific outcomes and center-specific performance. This report provides recommendations for collecting needed data to

identify data needed to determine effects and a plan for testing new statistical models to adjust for those effects.

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Conflict of interest statement: J.R.W. has received honoraria for serving on Data Safety and Monitoring Boards for Ansun, Celgene, Cidara, Merck, Shire, and ReViral. W.A.W. honoria for advisory consultations from Pfizer and Genentech. M.A.P. reports receipt of honoraria from Abbvie, Astellas, Bristol-Myers Squibb, Celgene, Incyte, Karyopharm, Kite/Gilead, Merck, Miltenyi Biotec, MorphoSys, Novartis, Nektar Therapeutics, Omeros, and Takeda; serves on data safety and monitoring boards for Cidara Therapeutics, Servier, and Medigene and on the scientific advisory board of NexImmune; has received research support for clinical trials from Incyte, Kite/Gilead, Miltenyi Biotec, and Novartis; and serves on the board of directors of Be The Match (National Marrow Donor Program), as well as on the CIBMTR Cellular Immunotherapy Data Resource Executive Committee. M.R. honoraria for advisory consultations from Jazz Pharmaceuticals, Atara Biotherapeutics; Advisory Board-BioIntelect. The other authors have no conflicts of interest to report.

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