Methodology Employed for Annual Report on Hematopoietic Cell Transplant Center-Specific Survival Rates
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Introduction

The purpose of the annual report on transplant center-specific survival rates is to provide potential hematopoietic cell transplant (HCT) recipients, their families, and the general public with a comparison of survival rates among the centers in the C.W. Bill Young Cell Transplantation Program (CWWBYCTP) network. Transplant centers may use these reports for quality improvement initiatives. Reporting center-specific survival rates is a requirement of the TRANSPLANT Act of 2021, previously the Stem Cell Therapeutic and Research Act of 2005 (re-authorized in 2010 and 2015), and prior to that, the 1990 Transplant Amendments Act. Because centers vary considerably in the risk level of cases treated, a statistical model was developed to adjust for several risk factors known or suspected to influence outcome. The outcome reported is one-year overall survival, for recipients of allogeneic HCT in the United States only. No attempts are made to incorporate other outcomes, such as relapse or disease-free survival.

The first center-specific risk-adjusted comparisons were published in 1994 [1] and yearly since then. The current iteration of the report prepared by the Center for International Blood and Marrow Transplant Research (CIBMTR) includes recipients of both unrelated and related donor transplants facilitated by the CWWBYCTP for a three-year time window. The methodology for this analysis has undergone various transformations over the years. The methodology in current use has been employed since 2005, thus allowing direct comparisons over the most recent time periods. This method adjusts for risk using a censored data logistic regression model [2-4] that allows inclusion of recipients with incomplete one-year follow-up. Note that although the method has remained the same, the types of patients studied changed with the inclusion of related-donor transplants in the 2010 report, which may affect comparisons over time. A risk-adjusted one-year survival rate is calculated for each center, based on results of the censored data logistic regression.

Results are available via the CWWBYCTP website (http://bloodcell.transplant.hrsa.gov/research/transplant_data/us_tx_data/index.html), and a version of this report, as approved by HRSA, is distributed to HCT centers. This information is available online at www.bethematch.org/tcdirectory/search. Raw numbers of transplants and surviving recipients are published for each center, stratified by diagnosis and age. Each center included in the report performed at least one unrelated or related donor transplant over the three-year window of time for analysis.

Methods

Recipients and data

The current analysis includes first unrelated or related donor transplants performed in a three-year time interval, with follow-up through one year after the last recipient was transplanted. The rolling three-year window of transplants for inclusion was adopted with the 2011 report, replacing a rolling five-year window used previously. This change was based on the recommendation of the 2010 Center-Specific Outcomes Analysis Forum[5], in order to represent more current transplant center outcomes. A minimum of one-year follow-up is
required for all eligible cases. All U.S. transplant centers that performed at least one HCT in the
time interval are considered for inclusion in the report, provided they had sufficient data with
at least one year of follow-up available. Typically, about 180 U.S. transplant centers are
included in the analysis, with about 25,000 first allogeneic transplants performed by domestic
transplant centers in the CWBYCTP network during this time.

Demographics of the included cases are provided in tables for recipients of unrelated donor
transplants and recipients of related donor transplants, broken down by donor type according
to unrelated vs. baseline and follow-up data used for the analysis are provided to the CIBMTR
by the transplant centers at the time of transplant (baseline), and at 100 days, six months and
annually post-transplant, using standardized forms. Race was self-reported by recipients or by
the staff at the center.

Risk factors considered
Based on the recommendation of the Center-Specific Outcomes Analysis Forum in 2010 and
2012, variables recognized as clinically important were forced into the model regardless of
whether they were statistically significant. After careful discussion with clinical and statistical
transplant experts, the following essential risk factors were included in the model:

- Recipient age
- Recipient race (self-reported)
- Recipient Karnofsky / Lansky Performance Status score at transplant
- Coexisting disease (HCT Comorbidity Index (HCT-CI), Sorror [6])
- Low body mass index (BMI) of adults age 18 or older, or low BMI or weight-for-age
  percentile for age < 18
- Recipient cytomegalovirus (CMV) serology
- History of mechanical ventilation
- History of invasive fungal infection
- Prior autologous transplant
- Diagnosis and disease status / stage
- Acute myeloid leukemia (AML) European LeukemiaNet (ELN) risk group (Döhner et al.
  [7])
- AML transformed from myelodysplastic (MDS) / myeloproliferative (MPN) diseases
- Number of induction cycles to achieve latest complete remission (CR) before HCT for
  AML and ALL patients in CR
- Time from diagnosis to transplant for AML and acute lymphoblastic leukemia (ALL) not
  in first complete remission (CR1) or primary induction failure (PIF) (used as surrogate
  for length of CR)
- ALL cytogenetic risk group (Moorman et al. [8])
- MDS Revised International Prognostic Score (IPSS-R) at HCT (Greenberg et al. [9])
- MDS with predisposing conditions
- Resistant disease in non-Hodgkin lymphoma (NHL) and Hodgkin lymphoma (HL) only
- Plasma cell disorder disease status at HCT
- Year of transplant
- Donor type: matched sibling donor vs. other related vs. unrelated donor
• HLA matching* (Weisdorf et al [10])
• Recipient and donor gender
• Donor age (unrelated bone marrow or peripheral blood stem cells (PBSC) donors only)
• Socioeconomic status (median household income) based on zip code of residence of recipient

In addition, the following variables were believed to be of uncertain clinical relevance, and so they were included in the model only if statistically significant (p < 0.05).

• Recipient ethnicity
• Therapy related AML or MDS
• ALL molecular marker - BCR/ABL at any time between diagnosis and HCT
• T-cell lineage in ALL, Philadelphia chromosome in ALL
• Del 17p in chronic lymphoblastic leukemia (CLL)
• NHL subtype
• Multiple myeloma cytogenetics risk group (Palumbo et al. [11])
• Multiple myeloma International Staging System (ISS) stage at diagnosis
• Unrelated bone marrow (BM) or peripheral blood stem cell (PBSC) donor ethnicity
• Unrelated BM or PBSC donor race
• BM or PBSC donor CMV serology
• BM or PBSC donor parity

**Statistical Analysis**

*Rationale for a fixed effects censored data logistic regression model*

One of the CIBMTR’s goals for the transplant center-specific survival analysis is to calculate a fair and accurate predicted survival rate given a center’s recipient case mix. To do this, a fixed effects censored data logistic regression model is used. The fixed-effects logistic regression model provides information about how the recipients actually treated in a particular center would have fared had they undergone transplant at a “generic” transplant center within the CWBYCTP. This model assumes no center effect. In other words, it assumes that recipients are dying at the same uniform rate across all CWBYCTP transplant centers, after adjusting for covariates. The model also adequately accounts for recipients with incomplete follow-up at one year.

Every effort is made to update follow-up information on each recipient. Some recipients were indeed lost to follow-up, and their final survival status at one year is unknown. To address this

* For PBSC and marrow transplants, high-resolution typing at HLA-A, -B, -C, and –DRB1 was used for the cases where it was available. For the remaining patients with PBSC and bone marrow graft sources, the best available matching information at HLA-A, -B, -C, and -DRB1 was used (Weisdorf et al. (Weisdorf D, 2008)). For single cord blood transplants, high-resolution typing at HLA-A, -B, -C, and –DRB1 was used for the cases where it was available. For the remaining patients with single cord blood graft source, low/intermediate-resolution typing at HLA-A and -B, and high-resolution typing at -DRB1 only were considered. For multiple cord blood transplants, low/intermediate-resolution typing at HLA-A and -B, and high-resolution typing at -DRB1 only were considered. The match grade of the worst-matched unit was analyzed.
problem, the analysis only includes centers that demonstrated 90% completeness of follow-up, meaning that the one-year status was known for at least 90% of their transplanted recipients. However, there are still some recipients for whom survival status at one year is incomplete, although many recipients had follow-up done just prior to one year. If these recipients are excluded from the center-specific analysis, it may bias the survival estimates. A censored data version of logistic regression based on pseudo-values proposed by Andersen et al. [2], Klein and Andersen [3], and Klein et al. [4] addresses this issue. This method is a generalization of logistic regression that simplifies to logistic regression (on the one-year survival probabilities) when there is no censoring present. This regression technique is used to estimate the fixed effects and predict the recipients’ survival probabilities based on their patient characteristics alone. These predicted survival probabilities are then used to construct confidence limits for a center’s survival probability according to the characteristics of the patients transplanted at that center. The actual survival observed at that center can be compared to these intervals to assess the performance of the center. This method is described in more detail below.

**Details of fixed effects censored data logistic regression and confidence limits**
Modeling for the center-specific survival analysis can be broken down into four steps, as outlined below.

**Definition of pseudo-values**
To compute the pseudo-value for recipient $i$, first compute the pooled sample Kaplan-Meier estimate of survival at one year based on the entire sample, $\hat{S}_p(1)$. Next compute the Kaplan-Meier estimate of survival at one year based on the entire dataset with observation $i$ removed $\hat{S}_p(i)(1)$. The $i$th pseudo-value is defined by $\theta_i = n\hat{S}_p(1) - (n - 1)\hat{S}_p(i)(1)$.
If there is no censoring, then the $i$th pseudo-value is simply the indicator that the $i$th recipient was alive at one year. These pseudo-values will then be used in a regression model using a logit link, similar to a standard logistic regression model, as described in the next section. The parameters of the regression model can be estimated using generalized estimating equations (GEE), which are implemented in PROC GENMOD in SAS.

**Predicted and observed survival**
From the fitted logistic regression model, each recipient has an estimated survival rate
$$\hat{p}_i = \frac{\exp(\hat{\phi}_i)}{1 + \exp(\hat{\phi}_i)}$$
based on his or her risk characteristics. The predicted survival rate at center $j$ based on recipient characteristics $E(S_j)$ is the average of the estimated survival rates for all recipients at center $j$,
$$E(S_j) = \left(\sum_{i \in C_j} \hat{p}_i\right) \frac{1}{n_j}.$$ 
The observed one-year survival rate at center $j$ can be computed using the Kaplan-Meier estimate of survival using the recipients at center $j$. This simplifies to the sample proportion of recipients alive when there is no censoring prior to one year present.
**Model building**

Let \( (Z_{i1}, \ldots, Z_{ip}) \) denote the set of covariates in the final model for recipient \( i \). First fit a fixed effects censored data logistic regression model with no center effect,

\[
\varphi_i = \ln \frac{\theta_i}{\theta_i + \hat{\theta}_i - \hat{p}_i} = \beta_0 + \sum_{i=1}^{p} \beta_i Z_{ip}.
\]

**Confidence Limits**

Confidence limits are generated using a bootstrapping methodology. However, the bootstrap technique was modified slightly from previous years’ reports to improve the coverage probabilities of the intervals, as described in Logan et al. [12] Previously, binary outcomes were generated for each individual to simulate the confidence limits; however, a more accurate prediction interval that controls the type I error rate can be obtained by re-sampling the residuals from the general linear model instead. Define the scaled Pearson residual for patient \( i \) by

\[
r_i = \frac{\hat{\theta}_i - \hat{p}_i}{\sqrt{\hat{p}_i(1 - \hat{p}_i)}},
\]

then the bootstrap re-sampling algorithm to generate a prediction interval for center \( j \) is as follows. For \( b=1 \) to 10,000:

1. Generate \( r_i^{*b} \) for patient \( i \) by sampling with replacement from the set of residuals \( \{r_i, i = 1, \ldots, n\} \)
2. Compute the bootstrap predicted value for patient \( i \) as

\[
Y_i^{*b} = \hat{p}_i + r_i^{*b} \sqrt{\hat{p}_i(1 - \hat{p}_i)}
\]
3. Compute the predicted center outcome for center \( j \) as

\[
S_j^{*b} = \frac{1}{n_j} \sum_{i \in C_j} Y_i^{*b}.
\]

Then the 95% predicted confidence bounds for survival at center \( j \) are obtained by taking the 2.5\(^{th}\) and 97.5\(^{th}\) percentile of \( S_j^{*b} \) across the 10,000 bootstrap samples.

This confidence interval refers to the survival rate that might be observed at that center if there were no center effect and those recipients had been transplanted at any center in the network. The observed survival rate can be compared with this confidence interval to see if there is evidence of the center over-performing or under-performing the overall network.

**Handling missing data for risk factors**

Occasionally, data are not available for significant characteristics for subjects as reported by the centers. If there were sufficient numbers of such subjects, they were included in the multivariate modeling as a distinct category of the covariate. However, when the number of subjects with data not available for a variable is too small (generally less than 20 subjects) to fit the model as its own category, those subjects were imputed to the relevant highest frequency category within the variable for categorical variables, and to the median value for ordinal or numeric variables (e.g. HCT-CI).
Adjusting for the impact of the COVID-19 pandemic on outcomes of patients transplanted in 2019

HCT recipients infected with SARS-CoV-2 have been reported to have higher mortality rates than the general population. [13-15] The COVID-19 pandemic has therefore had direct negative effects on outcomes of HCT recipients. In addition, changes in HCT and centers’ standard practices and procedures in response to the pandemic may have indirect effects on HCT outcomes and may not be equally distributed across all US HCT centers. CIBMTR must carefully consider the ways these direct and indirect factors, largely beyond the control of HCT centers, may influence HCT outcomes and whether they can be adequately incorporated into the center-specific survival analysis to create a fair and unbiased representation of center outcomes. For recipients of allogeneic HCT in 2019 included in this report, the impacts of the pandemic are limited to the post-HCT period. Aside from the risk of COVID infection and related adverse outcomes, these recipients were at risk of indirect effects on outcomes related to changes in centers’ surveillance and post-HCT management practices during 2020.

Based on recommendations developed at the 2020 Center Outcomes Forum [16], we conducted an analysis of the potential impact of the COVID-19 pandemic on outcomes for the 2020 Center-Specific Survival Analysis, which utilizes follow up to one-year post transplant, to inform potential risk adjustment approaches. We analyzed three time-varying effects summarizing the potential burden of the COVID pandemic on centers, to study their impact on the hazard rate of mortality within the first year after transplant.

- **Calendar time period:** pre-COVID (before Jan. 1, 2020), vs. early in the COVID pandemic (Jan. 21-June 21, 2020), vs. later in the COVID pandemic (June 22-Dec. 31, 2020)
  - Alternative categorization of pre-COVID, Jan. 21-April 21, 2020; April 22-July 21, 2020, July 22-Oct. 21, 2020; Oct. 22-Dec. 31, 2021; was also tested.
- **Average COVID infection rates** (per 100,000 population) over the preceding 2 weeks based on the county including the zip code of the transplant center where the patient received their transplant (0 vs. >0 to 6.5 vs. >6.5), where 6.5 was approximately the median of the non-zero values in the dataset.
- **Average COVID death rates** over the preceding two weeks based on the county, including the zip code of the transplant center where the patient received their transplant (0 vs. >0 to 0.15 vs. >0.15), where 0.15 was approximately the median of the non-zero values in the dataset.

**COVID-19 adjustment methods**

To understand impacts of the COVID pandemic on the transplant center, we used the COVID infection rates and mortality rates for the county where the center is geographically located. We acquired data from The New York Times publicly available COVID data [17]. These data provide cumulative case and death counts by county daily since the first reported case in the United States on January 21, 2020. Using recent census data, these counts were transformed into two-week average case and death rates per 100,000 population based on each patient’s transplant center county. Each patient’s follow-up was broken up into two-week intervals with
two-week average case and death rates corresponding to that follow-up time period, where the values for the initial two-week interval were centered around the patient’s transplant date. The impact of COVID on the population of at-risk patients in each zip code vs. the county population was assessed and determined to be negligible.

A Cox proportional hazards model was used for all analyses, which included adjustment for all risk factors included in the 2020 Center-Specific Survival Analysis. Individual patients are the unit of analysis, mortality is the outcome of interest. Patients developing COVID infection during their first year of follow-up were censored as of the reported date of infection. Because of the large number of potential COVID effects or COVID interaction terms considered, a significance level of 0.01 was used.

Each of the three COVID factors above were analyzed both in the three category groupings described above as well as continuously with linear and quadratic terms. Because each of these three COVID variables are relatively highly correlated with one another, we looked at them one at a time added to the Cox model. Note that because all three of them are time-varying effects, we broke down each post-transplant time interval for each patient into two-week increments, coded the value of the time-varying effects at the beginning of each two-week interval, and used the start-stop method of data specification for the Cox model for time-varying effects in SAS.

We also explicitly examined interactions of each of these time-varying COVID effects with the following potential COVID effect modifier (also time-varying) factors of interest:
- Time period post-transplant (first 100 days, 100 days to 6 months, and 6 months to 1 year),
- History of acute graft-versus-host disease (GVHD) grade II-IV (no vs. yes), and
- History of chronic GVHD (no vs. yes).

**COVID-19 adjustment results**
After censoring for COVID infection in the first year after HCT, none of the three time-varying COVID effects (calendar time period, average geographic COVID infection rates, average geographic COVID death rates) had a statistically significant impact on one-year mortality. There was no effect of geographic or calendar-driven COVID incidence/mortality rates or differences in surveillance/follow-up practices associated with survival.

For those patients who underwent transplant in 2019 who did not develop COVID infection in their first year after HCT, the risk of mortality at one year is not clearly affected by the pandemic, broadly speaking. In other words, there is no evidence to support a differential impact of the pandemic on survival after HCT across the US after censoring for COVID infection in patients themselves. This analysis does not specifically address the impact of COVID infection in HCT recipients since they are censored at development of COVID infection.
Application to final Statistical Model
We have not demonstrated an independent effect of the COVID pandemic and potential impacts on care delivery upon the survival outcomes by one-year post HCT after censoring for COVID infection in recipients of HCT recipients in 2019. Therefore, we chose to use our existing logistic regression modeling approach for the center-specific survival analysis in 2021, with censoring of patients who developed COVID infection at their infection date in the first year after HCT.

Results

Patient demographics
Demographics of patients are provided in the report, by unrelated vs. related donor.

Risk factors included in final multivariate model
The results of the multivariate model are presented in a set of tables where each variable and its associated odds ratio are described, along with 95% confidence limits. Factors included in the final model are:
- Recipient age
- Recipient race**
- Karnofsky / Lansky score at transplant
- Sorror HCT-CI
- Adult BMI group
- Pediatric BMI group**
- Recipient CMV status
- History of mechanical ventilation
- History of invasive fungal infection
- Prior autologous transplant**
- Disease and disease status/stage
- AML ELN risk group
- AML transformed from MDS/MPN
- AML therapy related
- Number of induction cycles for AML and in CR1**
- Time from diagnosis to transplant for AML and ALL in CR2 and CR3+/relapse (used as surrogate for length of CR)
- ALL cytogenetic risk group**
- Philadelphia chromosome in ALL patients
- Number of induction cycles for ALL and in CR1**
- MDS IPSS-R risk score at HCT
- MDS with predisposing condition**
- NHL subtype

** Maintained in the model due to clinical relevance but not statistically significant
• Sensitivity to chemotherapy in NHL
• Sensitivity to chemotherapy in HL
• MM ISS stage at diagnosis
• Plasma cell disorder disease status
• Year of transplant
• HLA matching by donor and graft type
• Donor/recipient sex match (bone marrow or PBSC only)
• Donor age (unrelated bone marrow or PBSC donors only)
• Recipient median household income based on zip code

The model is similar to last year, except for the following:
• Recipient age grouping was adjusted in the younger groups to represent pediatric and adult cases more clearly
• Therapy-related MDS was not included in the model this year, due to no longer meeting the significance requirement
• Therapy-related AML and multiple myeloma ISS stage at diagnosis were included in the model this year due to meeting the statistical significance requirement

The Beta_0 intercept term for the model is made available in the formal report.

**Center-specific results**
Final center-specific results are presented, along with centers’ historical performance in tables, and on the public website. Numbers of transplanted recipients at each center, actual (observed) survival at one year, predicted survival at one year, 95% confidence intervals for predicted survival, and performance status are displayed for each center. Centers whose actual survival is outside the 95% confidence limits for predicted survival have a “−1” in the performance status column if performing below the confidence limit, and a “1” in the performance status column if performing above the confidence limit. Centers with a “0” in the performance status column are performing as predicted. Most centers performed as predicted with respect to overall performance in previous years. Since the censored data logistic regression model assumes no center effect, centers with smaller numbers of transplants (e.g. N = 1 or 2) will not have their predicted survival proportion regress toward the network average. Rather, the confidence limits around the predicted survival at that center will simply be much wider than those of larger centers.

Results are also displayed for centers via a visual box-plot graphic. Centers are arranged by center number, while reading from left to right across these figures. The actual survival at each center is superimposed with each box plot (using the symbol ‘•’) to give the reader an instantaneous picture of how close to under- or over-performing the center was.

Patients can find information about all U.S. transplant centers performing allogeneic transplants in the online U.S. Transplant Center Directory on [http://bethematch.org](http://bethematch.org). Listings are organized by state and can be found at [bethematch.org/tcdirectory/search](http://bethematch.org/tcdirectory/search). Along with
center outcomes, each listing includes a description of that center’s program, contact information, the number of transplants performed over a specified time period and survival statistics by patient’s age, disease type and stage for both related and unrelated donor transplants. A link to the Transplant Center Directory can also be found on the Health Resources and Services Administration (HRSA) website https://bloodstemcell.hrsa.gov/data/donation-and-transplantation-statistics.

Because the outcome of interest is one-year survival, at least one year of follow-up time is required to be included in the analysis. Data are refreshed once a year. After the report on transplant center-specific survival rates is approved by HRSA, the Transplant Center Directory is repopulated with the new data.

Summary

A fixed effects censored data logistic regression model is fitted to survival data for first unrelated and related donor hematopoietic cell transplants at U.S. centers. The model is adjusted for recipient age, recipient race, Karnofsky/Lansky score, Sorror HCT-CI, adult BMI group, pediatric BMI group, recipient CMV status, history of mechanical ventilation, history of invasive fungal infection, prior autologous transplant, disease/stage, AML ELN risk group, AML transformed from MDS or MPN, AML therapy related, number of induction cycles for AML in CR1, interval from diagnosis to transplant in ALL and AML in CR2 and CR3+/relapse, ALL cytogenetic risk group, Philadelphia positive-status in ALL, number of induction cycles for ALL in CR1, MDS IPSS-R risk score at HCT, MDS predisposing condition, CLL and other chronic leukemia disease status, NHL subtype, sensitivity to chemotherapy in NHL and HL, MM ISS stage at diagnosis, plasma cell disorder disease status, year of transplant, donor type/graft type/HLA matching, BM or PBSC donor/recipient sex match, unrelated BM or PBSC donor age at transplant, and recipient median household income. The report on transplant center-specific survival rates helps to identify centers that may have under-performed or over-performed compared to the overall network of transplant centers during this specified time period.
References