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 (CWBYCTP) 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 1-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 report prepared by the Center for International Blood and Marrow Transplant Research (CIBMTR) includes both unrelated and related donor transplants facilitated by the CWBYCTP for a 3-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 1-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 1-year survival rate is calculated for each center, based on results of the censored data logistic regression.

Results are available via the CWBYCTP website (http://bloodcell.transplant.hrsa.gov/research/transplant_data/us_tx_data/index.html),[5] and a version of this report, as approved by the Health Resources and Services Administration (HRSA), is distributed to HCT centers. This information is available online at (https://www.nmdp.org/tcdirectory).[6] 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 1 unrelated or related donor transplant over the 3-year window of time for analysis.

Methods

Recipients and data

The current analysis includes first unrelated or related donor transplants performed in a 3-year time interval, with follow-up through 1 year after the last recipient underwent transplant. Beginning with the 2011 report, a rolling 3-year window of transplants is included based on the recommendation of the 2010 Center-Specific Outcomes Analysis Forum[7]. A minimum of 1-year follow-up is required for all eligible patients. All US transplant centers that performed at least 1 HCT in the time interval are considered for inclusion in the report, provided they had sufficient data with at least 1 year of follow-up available.

Typically, about 180 US transplant centers are included in the analysis, with more than 25,000 first allogeneic transplants performed by domestic transplant centers in the CWBYCTP network during this time. Occasionally, centers with quality problems involving data fields that affect survival modeling recognized during CIBMTR data quality audits are excluded from the analysis.

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, 6 months and annually post-transplant. Race was reported by recipients or by the staff at the center.

Risk factors considered

Based on recommendations developed at the CIBMTR Center Outcomes Forum,[8] 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 (as reported by centers or self-reported)
- Recipient Karnofsky / Lansky Performance Status score at transplant
- Coexisting disease (HCT Comorbidity Index [HCT-CI][9])
- Underweight: in adults, Body Mass Index (BMI) < 18.5; in pediatric patients, BMI or weight-for-age < 5 percentile
- Recipient cytomegalovirus (CMV) status
- History of mechanical ventilation
- History of invasive fungal infection
- Prior autologous transplant
- Prior solid organ transplant
- Disease and disease status / stage
- Acute myeloid leukemia (AML) European LeukemiaNet (ELN) risk group[10]
- AML transformed from myelodysplastic syndrome (MDS) or myeloproliferative neoplasm (MPN)
- Number of induction cycles to achieve first complete remission (CR1) before HCT for AML and acute lymphoblastic leukemia (ALL) patients in CR1
- Time from diagnosis to transplant for AML and ALL not in first complete remission (CR1) or primary induction failure (PIF) (used as surrogate for length of CR)
- ALL cytogenetic/molecular risk group[11]
- Other acute leukemia disease status at HCT
- MDS Revised International Prognostic Score (IPSS-R) at HCT[12]
- MDS with predisposing conditions
- CLL/PLL/other chronic leukemia disease status
- NHL and HL sensitivity to chemotherapy
- Plasma cell disorder disease status at HCT
- Year of transplant
- Donor type: matched sibling donor vs other related vs unrelated donor
- Human leukocyte antigen (HLA) matching by donor and graft type[a,13]
- Donor-recipient sex match, BM or peripheral blood stem cells (PBSC)Unrelated donor age at HCT, for BM or PBSC only

[a] For PBSC and BM 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 BM graft sources, the best available matching information at HLA-A, -B, -C, and -DRB1 was used (Weisdorf et al). For single UCB 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 UCB graft source, low/intermediate-resolution typing at HLA-A and -B, and high-resolution typing at -DRB1 only were considered. For multiple UCB 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.

- Recipient median household income based on zip code of residence

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
- History of malignancy, excluding non-melanoma skin cancer
- Therapy-related AML or MDS
- ALL molecular marker BCR-ABL at any time between diagnosis and HCT
- Del 17p in chronic lymphoblastic leukemia (CLL)
- NHL subtype
- Multiple myeloma cytogenetics risk group[14]
- Multiple myeloma Revised International Staging System (R-ISS) stage at diagnosis[15]
- Unrelated BM or PBSC donor ethnicity
- Unrelated BM or PBSC donor race
- BM or PBSC donor CMV serology
- BM or PBSC donor parity (number of pregnancies)

New or revised variables tested in the 2024 analysis

- Expanded/adapted HCT-CI for youth (malignant and non-malignant diseases)[16,17]
- Serum albumin before transplant
- Serum ferritin before transplant
- Pediatric glomerular filtration rate (ages 18 or less)
- Complex congenital heart disease (ages 18 or less)
- Prior cellular therapy (ALL, lymphoma, and myeloma)
- Measurable residual disease status for AML and ALL
- Viral infection within 60 days of HCT, disorders of immune system
- History of infection with Pneumocystis jirovecii pneumonia / Pneumocystis carinii pneumonia (immune disorders and histiocytic disorders)
- Recipients with GVHD due to maternal engraftment before transplant (immune system disorders)
- Tricuspid regurgitation jet velocity (sickle cell disease, sickle thalassemia, beta thalassemia major)
- Liver iron content (sickle cell disease, sickle thalassemia, beta thalassemia major)
- Red blood cell (RBC) transfusion dependence (beta thalassemia major)
- Iron chelation (beta thalassemia major)
- Related donor age at transplant (excluding siblings and twins)

Statistical analysis

Rationale for a fixed-effects censored data logistic regression model

One of 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, we used a fixed-effects censored data logistic regression model. The fixed-effects logistic regression model provides information about how the recipients 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 1 year.

Every effort is made to update follow-up information on each recipient. Some recipients are indeed lost to follow-up, and their final survival status at 1 year is unknown. To address this problem, the analysis only includes centers that demonstrated 90% completeness of follow-up, meaning that the 1-year status was known for at least 90% of their recipients. However, there are still some recipients for whom survival status at 1 year is incomplete, although many recipients had follow-up done just prior to 1 year. If these recipients are excluded from the Center-Specific Survival Analysis, it may bias the survival estimates. A censored data version of logistic regression based on pseudo-values[2-4] addresses this issue. This method is a generalization of logistic regression that simplifies to logistic regression (on the 1-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 individual characteristics. These predicted survival probabilities are then used to construct confidence limits for the probability of survival for all patients at a center, according to the characteristics of the patients who underwent transplant 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 4 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 1 year based on the entire sample, $\hat{S}_p(1)$. Next compute the Kaplan-Meier estimate of survival at 1 year based on the entire data set with observation *i* removed $\hat{S}_p^{(i)}(1)$. The *i*th pseudo-value is defined by $\hat{\theta}_i = n\hat{S}_p(1) - (n-1)\hat{S}_p^{(i)}(1)$.

If there is no censoring, then the *i*th pseudo-value is simply the indicator that the *i*th recipient was alive at 1 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

$$\hat{p}_i = \frac{\exp(\hat{\varphi}_i)}{1+\exp(\hat{\varphi}_i)}$$

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 1-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 1 year present.

Model building

Let ($Z_{i1},...,Z_{ip}$) 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,

$$\varphi_i = \ln \frac{\theta_i}{1-\theta_i} = \beta_0 + \sum_{l=1}^{p} \beta_l Z_{il} .$$

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.[18] 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

   $\{r_i, i = 1,...,n\}$

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 2.5th and 97.5th 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 undergone transplant at any center in the network. The observed survival rate can be compared to 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 patients as reported by the centers. If there were sufficient numbers of such patients, they were included in the multivariate modeling as a distinct category of the covariate. However, when the number of patients with data not available for a variable is too small (generally less than 20 patients) to fit the model as its own category, those patients 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).

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[c]
- Karnofsky / Lansky score at transplant
- Sorror HCT-CI[9]
- Underweight adult BMI group[b]
- Underweight pediatric BMI or weight-for-age percentile group[b]
- Recipient CMV status
- Serum albumin before transplantation
- History of mechanical ventilation
- History of invasive fungal infection[b]
- Prior autologous transplant[b]
- Prior solid organ transplant
- Prior cellular therapy for patients with lymphoma
- Disease and disease status/stage
- AML ELN risk group[10]
- AML transformed from MDS/MPN[b]
- Number of induction cycles for AML in CR1[c]
- Time from diagnosis to transplant for AML and ALL in CR2 and CR3+/relapse (used as surrogate for length of CR)
- ALL cytogenetic/molecular risk group[11]
- Number of induction cycles for ALL in CR1[b]
- MDS IPSS-R risk score at HCT[12]
- Therapy-related MDS
- MDS with predisposing condition

[b] Maintained in the model due to clinical relevance but not statistically significant

- CLL, PLL, and other chronic leukemia disease status[c]
- NHL subtype
- NHL sensitivity to chemotherapy
- HL sensitivity to chemotherapy
- Plasma cell disorder disease status
- Viral infection within 60 days of HCT, disorders of immune system
- Year of transplant[b]
- HLA matching by donor and graft type
- Donor-recipient sex match, BM or PBSC only
- Unrelated donor age at HCT, BM or PBSC only
- Related donor age at HCT, BM or PBSC only, not sibling/twin
- Recipient median household income based on zip code

The model is similar to last year, except for the following:

- Serum albumin before transplant was included
- Viral infection within 60 days of HCT, disorders of immune system was included
- Previous cellular therapy for patients with lymphoma was included
- Therapy-related MDS was included
- Related donor age (except siblings or twins) for PBSC or BM recipients was included.

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 transplant recipients at each center, actual (observed) survival at 1 year, predicted survival at 1 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 fewer 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. **Confidence limits for the prediction estimates are generally unreliable for centers whose HCT volume is ≤ 10 patients over the time period. Therefore, interpretation of performance in these centers should be considered with appropriate caution.**

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 US transplant centers performing allogeneic transplants in the online US Transplant Center Directory on http://bethematch.org. Listings are organized by state and can be found at https://www.nmdp.org/tcdirectory. 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 HRSA website https://bloodstemcell.hrsa.gov/data/donation-and-transplantation-statistics.

Because the outcome of interest is 1-year survival, at least 1 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 accepted 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 HCTs at US centers. The final model was adjusted for the risk factors listed on pages 8 and 9. . 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 the specified time period.

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