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Pre-Transplant Risk Factors Associated With Poor Outcomes in Adolescents and Young Adults Undergoing Allogeneic Hematopoietic Stem Cell Transplantation

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Pre-Transplant Risk Factors Associated With Worse Outcomes in Adolescents and Young Adults Undergoing Allogeneic Hematopoietic Stem Cell Transplantation

A thesis submitted in partial satisfaction

of the requirements for the degree Master of Science in Clinical Research

by

Brian Friend

2018

ABSTRACT OF THE THESIS

Pre-Transplant Risk Factors Associated With Worse Outcomes in
Adolescents and Young Adults Undergoing
Allogeneic Hematopoietic Stem Cell Transplantation

by

Brian Friend
Master of Science in Clinical Research
University of California, Los Angeles, 2018
Professor Robert M. Elashoff, Chair

Adolescents and young adults (AYAs) undergoing allogeneic hematopoietic stem cell transplantation (HSCT) have unique risk factors and poor outcomes when compared to children, but this population has not been well-studied. We sought to examine the prevalence of various risk factors in AYAs undergoing allogeneic HSCT and determine which factors had the greatest impact on overall survival (OS) and non-relapse mortality. This was accomplished by retrospectively collecting data on 241 patients who received their first allogeneic HSCT at UCLA between 2005-2015. Few of the comorbidities included in the hematopoietic stem cell transplantation – comorbidity index (HCT-CI) were prevalent in this population, with a history of pulmonary disease being most common. We demonstrated that compared to a baseline model, adding the HCT-CI did not improve the ability predict OS, while substituting just three important comorbidities including a history of pulmonary disease, infection, and prior malignancy resulted in a significant improvement in model performance.

The thesis of Brian Friend is approved.

David Elashoff

Gary J. Schiller

Robert M. Elashoff, Committee Chair

University of California, Los Angeles

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1. INTRODUCTION

Every year, across the United States nearly 2,000 adolescents and young adults (AYAs), defined as those aged 15-39 years old, undergo allogeneic hematopoietic stem cell transplantation (HSCT).[1] While this patient population is relatively healthy, AYAs have unique comorbidities and significantly poorer outcomes following allogeneic HSCT when compared to children less than fifteen years old, but there have been few studies in this setting. Several models in adults have been developed to help predict outcomes in patients undergoing allogeneic HSCT including the hematopoietic stem cell transplantation – comorbidity index (HCT-CI).[2] This index may not be appropriate for use in AYAs given that most of the comorbidities are age-related and the prior validation studies for the HCT-CI included patients with a median age of greater than forty years.[3]

Allogeneic HSCT is a potentially curative procedure for many hematologic diseases, however post-transplant complications such as opportunistic infection, graft-versus-host disease (GVHD), and organ dysfunction often result in substantial morbidity and mortality.[4] In recent years, there has been increasing interest in trying to better understand the patient and treatment factors that may predispose to poorer outcomes in allogeneic HSCT. Recognizing these adverse determinants has allowed for the development of models such as the HCT-CI, that can reliably predict which patients are at highest risk of mortality, specifically non-relapse mortality (NRM).[2] This model has since been validated in multiple prospective studies[5-7] and has provided a significant clinical impact, as physicians may address high-risk patients differently in an attempt to increase their likelihood of survival.

While allogeneic HSCT is thought to be more tolerable in younger patients resulting in better outcomes when compared to adults, this has not been the case for AYAs. These patients have significantly worse outcomes than younger pediatric patients following allogeneic HSCT, with most deaths the result of complications from transplant. One study demonstrated a 2-fold

increase in NRM for patients aged 13-30 years old with acute lymphoblastic leukemia compared to patients < 13 years old.[8] Similar differences have also been seen in patients transplanted for acute myelogenous leukemia.[9] The reasons why AYAs are thought to have worse outcomes when compared to children are not entirely clear but may include differences in tumor biology,[10] access to care including clinical trials,[11] and psychosocial issues such as noncompliance.[12]

Although AYA patients have inferior outcomes following allogeneic HSCT when compared to children less than fifteen years old, there have been limited studies examining the risk factors for this population. This includes one small, retrospective study that tested the utility of the HCT-CI in AYAs and demonstrated that it was useful in predicting outcomes for these patients. However, as these younger patients have fewer comorbidities than older adults, only four of the fifteen variables included in the original HCT-CI study were found to have greater than 10% prevalence.[3] In fact, most of the comorbidities included in the HCT-CI are age-related, suggesting that this index is less useful for this younger patient population.[2]

Besides the fact that most of the risk factors that comprise the HCT-CI are not frequently seen in AYAs, additionally, this population has unique comorbidities. Psychosocial issues such as noncompliance and lack of family support are particularly common in this age group, and are known to contribute to poor outcomes.[12] The recognition of these dimensions led to the development of the psychosocial assessment of candidates for transplantation (PACT) scale, a tool that was initially designed to evaluate psychosocial issues in patients prior to solid organ transplantation.[13] More recently, this instrument has shown utility in predicting outcomes in patients undergoing allogeneic HSCT.[14,15]

Given the limited studies and distinctive domains present in AYA patients undergoing allogeneic HSCT, we sought to examine the risk factors seen specifically in this population, and to determine which of these comorbidities were associated with inferior outcomes. We then utilized these findings to develop several multivariable models to show which factors were most important in predicting outcomes in this younger patient population.

2. METHODS

2.1 Study population

A retrospective study was performed that included 241 patients aged 15-39 years who underwent their first allogeneic HSCT for any diagnosis at our institution between January 2005 and December 2015. The study was IRB-approved prior to data collection. A variety of conditioning regimens were used, but most patients received a myeloablative regimen. In addition, several regimens were utilized for GVHD prophylaxis.

Disease risk was assigned based on both disease type and staging according to the classification outlined in the disease-risk index (DRI) for malignant diseases.[16] Patients with nonmalignant disease were considered low risk. In cases when cytogenetics were either not performed or unavailable, the patient was determined to have disease of intermediate risk, as was done in the development of the original index.[16]

2.2 Comorbidity data

We collected data on the comorbidities from the original HCT-CI study through review of the medical record. These risk factors were defined as in Sorror's initial study unless otherwise specified below.[2] The comorbidity "Body Mass Index" was scored differently for patients under age eighteen than on the HCT-CI, as obesity is defined as a Body Mass Index at or above the 95th percentile of a certain age and sex for pediatric patients. The three cardiovascular comorbidities were combined into a single cardiovascular component given the rarity of this risk factor in this population. We also examined data on other possible risk factors in the AYA population including a novel psychosocial variable.

2.3 Psychosocial data

The psychosocial component was initially considered a binary variable. This variable was marked as “positive” if the patient described any of the following issues and at least one had a significant impact on his/her well-being: emotional distress, lack of support, care of young children, transportation, financial concerns including insurance and housing, noncompliance, substance abuse, or cultural issues related to language barrier and citizenship status. Psychosocial issues were also measured more uniformly using the PACT scale, that includes multiple subscores and an overall numerical rating that suggests how likely a provider would be to recommend a particular patient for HSCT.[13]

Two reviewers analyzed the “Psychosocial Assessment” conducted for each patient blinded to outcome and decided whether a patient was “positive” for the psychosocial variable (as described above) and concluded a PACT score for each patient. Discrepancies were resolved through discussion, and PACT scores were averaged when agreement could not be reached.

2.4 Outcomes

The primary outcomes for this study were overall survival (OS) and NRM. OS and NRM were calculated from date of transplantation to the time of the event. NRM was defined as death after transplant that was not preceded by disease progression or relapse. Patients who proceeded to a second transplant were censored at the time of the second transplant. The number of days to engraftment was also determined and used as a covariate in the analysis. Neutrophil engraftment was defined as an Absolute Neutrophil Count of 500 cells/μl for three consecutive days. Platelet engraftment was defined as a platelet count of 20,000/mm^3 unsupported by platelet transfusion.

2.5 Sample size

The sample size calculation demonstrated that 246 patients would provide 87% power to detect hazard ratios of at least 1.5 associated with a comorbidity in the Cox proportional hazards regression model, assuming a two-sided 0.05 level of significance. Five patients were later excluded as they did not meet the inclusion criteria. Prior studies had identified hazard ratios for pulmonary and hepatic disease of 3.7 and 3.9, respectively,[2] suggesting that this study would have sufficient power to detect comorbidity effects on survival. Additionally, this sample size was sufficient to include 6-10 covariates in the Cox model based on recommendations suggesting that 10-15 events are necessary per variable in the model.[17]

2.6 Statistical analysis

Overall survival curves were estimated using the Kaplan-Meier method. Cumulative incidence curves and probabilities for NRM were calculated by using relapse mortality as a competing risk for NRM. The predictors of OS were evaluated using the Cox proportional hazards model and those of NRM were investigated using the Fine and Gray competing risk regression model taking into account the competing risk of relapse mortality. Both methods adjusted for covariates. The proportional hazard and corresponding subhazard assumption was assessed using Schoenfeld residuals.

For both OS and NRM analyses we created a sequence of survival models. Model 1 included patient- and transplant-related factors only. Model 2 was comprised of the variables from Model 1 and the HCT-CI score. Model 3 included patient- and transplant-related factors as in Model 1 and the comorbid conditions. Model 4 consisted of the variables from Model 1, the comorbid conditions, and the psychological component, including the binary variable and PACT score. Final models were selected using the backwards procedure for variable selection and $p < 0.15$ as the retention criterion.

The prediction ability for each model was assessed using Harrell's C-statistic, both unvalidated and then validated through 10-fold cross-validation. Pairs of nested models were compared using the likelihood ratio (LR) test. In addition, to compare prediction accuracy for pairs of non-nested models and validated nested models, the function rcorrp.cens was used as implemented in the R software. The function computes U statistics for testing whether predictions of one model are significantly more concordant than those of another model.[18] Missing values were singly imputed using regression imputation for the purpose of the multivariable analysis. The results of the imputed analysis were compared to the complete case analysis through a sensitivity analysis.

3. RESULTS

3.1 Patient characteristics

Our population of AYAs at UCLA was diverse, as 63% of patients were described as non-White including 44% of patients who were described as Hispanic (Table 1). The median age was 27 years and there was a male predominance (59%) in our patients. Most patients (73%) had a diagnosis of leukemia, with the most common diagnosis being acute lymphoblastic leukemia. Lymphoma and nonmalignant disease comprised the other main diagnostic groups. A substantial proportion (27%) of patients were considered high-risk based on the DRI. The source of stem cells was mixed, with peripheral blood (42%) being most common, though umbilical cord blood was also used considerably (24%). Median time to engraftment was nineteen days.

Age (years), median (range)	27 (15-39)
Gender, no. (%) Male Female	 142 (59) 99 (41)
Race/Ethnicity, no. (%) Caucasian Hispanic African American Asian	 88 (37) 107 (44) 14 (6) 32 (13)
Diagnosis, no. (%) Leukemia Lymphoma Nonmalignant	 168 (72) 32 (13) 38 (16)
Disease Risk Index, no. (%) Low Intermediate High	 42 (17) 133 (55) 66 (27)
Sibling-match, no. (%) Yes No	 128 (53) 113 (47)
HLA mismatch, no. (%) 0 1 2 3	 177 (73) 44 (18) 19 (7.9) 1 (0.4)
Cell source, no. (%) Bone marrow Peripheral blood Cord blood	 80 (33) 102 (42) 59 (24)
Conditioning, no. (%) Myeloablative Reduced intensity conditioning Nonmyeloablative	 224 (93) 7 (2.9) 10 (4.2)
Engraftment (days), median (range)	19 (9-67)

Table 1. Patient characteristics.

3.2 Comorbidities

Of all the comorbidities scored on the HCT-CI in our study, the only risk factors to have a prevalence of greater than 10% were pulmonary, hepatic, cardiac, infectious, psychiatric, and obesity (Table 2). Among all of the comorbidities that were investigated, the pulmonary risk

factor was observed most frequently (54%) in our AYA patients. The median HCT-CI score was two (range 0-9).

A novel psychosocial variable was also very common, with a prevalence of 35%. With the addition of this variable, the median number of comorbidities was two (range 0-6). Financial concern (23%) was the most widespread challenge of the psychosocial issues. The use of the PACT scale demonstrated that only four percent of patients would have been considered “poor” candidates for allogeneic HSCT.

Comorbidity	No. (%)	Unadjusted HR, OS (95% CI)	p-value	Unadjusted HR, NRM (95% CI)	p-value
Pulmonary disease (moderate, severe)	86 (36) 43 (18)	1.37 (0.89-2.10) 1.87 (1.14-3.06)	0.1535 0.0133	1.26 (0.73-2.17) 1.97 (1.07-3.64)	0.4093 0.0308
Psychosocial variable	83 (35)	0.97 (0.62-1.50)	0.8846	0.85 (0.47-1.51)	0.5699
Obesity	58 (24)	1.04 (0.40-2.72)	0.9305	1.93 (0.45-8.38)	0.3795
Hepatic disease (moderate, severe)	45 (19) 10 (4.2)	0.93 (0.57-1.52) 1.80 (0.83-3.90)	0.7761 0.1345	1.03 (0.56-1.92) 1.06 (0.33-3.41)	0.9222 0.9195
Psychiatric disturbance	35 (15)	1.45 (0.90-2.33)	0.1226	1.71 (0.98-2.97)	0.0569
Cardiac disease	30 (12)	1.09 (0.63-1.88)	0.7525	1.20 (0.60-2.38)	0.6101
Infection	24 (10)	1.88 (1.11-3.19)	0.0194	1.23 (0.57-2.64)	0.6029
Prior malignancy	11 (4.6)	1.91 (0.89-4.10)	0.0989	1.92 (0.73-5.05)	0.1848
Diabetes mellitus	10 (4.2)	0.51 (0.16-1.62)	0.2554	0.3 (0.04-2.28)	0.2449
Cerebrovascular disease	6 (2.5)	0.27 (0.04-1.94)	0.1938	0.50 (0.08-3.30)	0.4697
Inflammatory bowel disease	3 (1.2)	NR	NR	NR	NR
Rheumatologic disease	3 (1.2)	NR	NR	NR	NR
Peptic ulcer disease	3 (1.2)	NR	NR	NR	NR
Renal disease	2 (0.8)	NR	NR	NR	NR

Table 2. Prevalence of various comorbidities and univariate analysis for NRM and OS. NR = not reported.

3.3 Outcomes

OS for this population at 1, 3, and 5 years was 63%, 53%, and 48%, respectively (Figure 1A). Median OS was 4.5 years with a median follow-up time was 603 days post-transplant. NRM at 1, 3, and 5 years was 26%, 29%, and 30%, respectively (Figure 1B). Recurrence of primary disease was responsible for 41% of deaths while 59% of patients died from NRM. A majority (54%) of deaths due to NRM were caused by infections.

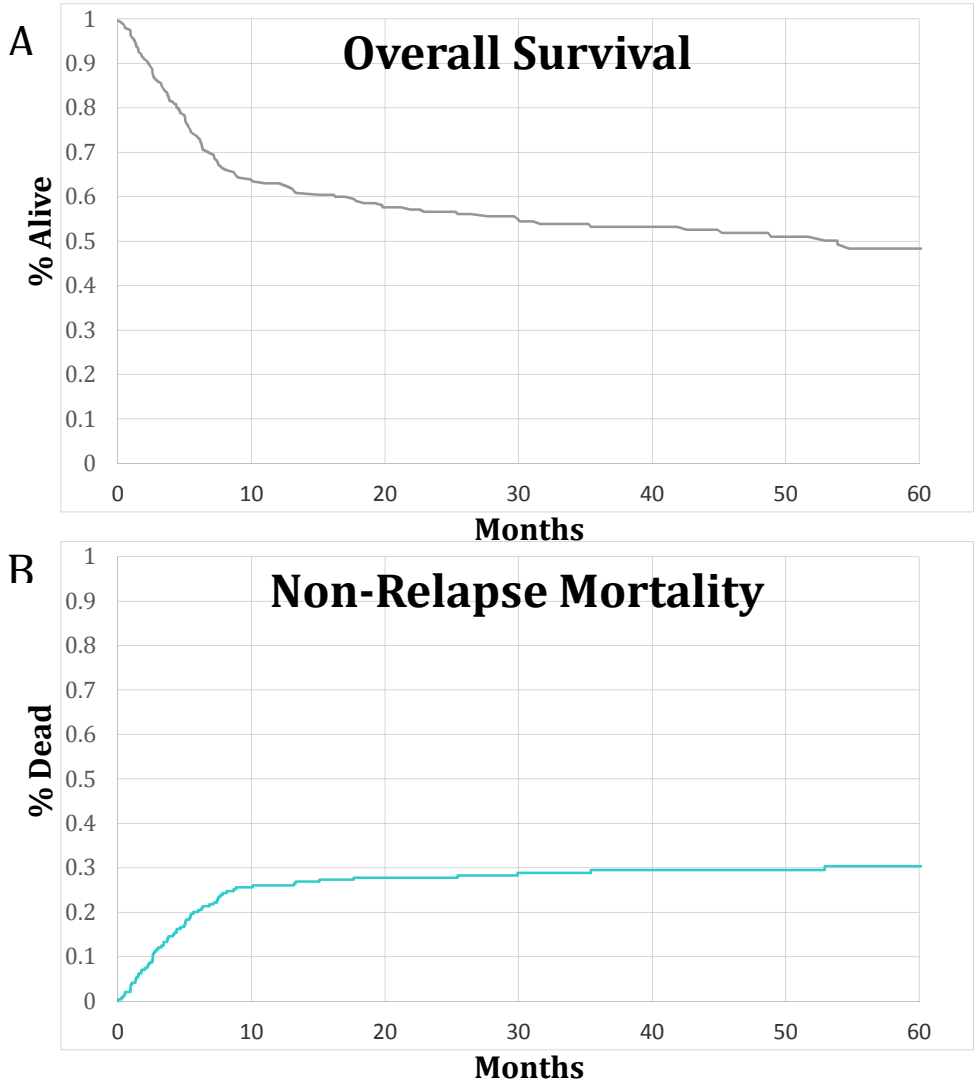


Figure 1. Patient outcomes at 1, 3, and 5 years after allogeneic HSCT. (A) Kaplan-Meier curve for overall survival. (B) Cumulative incidence of non-relapse mortality.

3.4 Univariate and multivariable analyses

In univariate analysis, a history of severe pulmonary disease was associated with worse OS (HR 1.87, p = 0.01) and increased NRM (HR 1.97, p = 0.03). Other comorbidities that appeared to be important included a history of infection, as this was associated with poorer OS (HR 1.88, p = 0.01), while a history of prior psychiatric disease trended towards higher NRM (1.71, p = 0.06). However, the psychosocial variable was not correlated with worse OS (HR 0.97, 95% CI 0.62-1.50) (Table 2).

For our multivariable analysis, Model 1 served as a reference to construct subsequent models for both OS (C-statistic = 0.672) and NRM (C-statistic = 0.707). After variable selection, both Model 1s included race/ethnicity, degree of HLA mismatch, and day of engraftment. The model for OS also included DRI while the model for NRM applied recipient CMV status (Table 3-4). Conditioning regimen did not meet the proportional subhazard assumption, however this variable was not significantly associated with outcomes in most of the models and was thus excluded. Notably, African Americans had worse OS (HR 2.39, p = 0.025) and increased NRM (HR 2.37, p = 0.043).

Compared to Model 1, Model 2 did not demonstrate a significant improvement in the prediction of OS (LR, p = 0.082), nor did it improve discrimination (C-statistic = 0.683). However, a HCT-CI score of three or greater was associated with worse OS (HR 1.81, p = 0.038). On the other hand, the inclusion of HCT-CI score in the model for NRM was not significant and the concordance statistic was essentially unchanged (C-statistic = 0.706). Model 3 for OS included a history of pulmonary disease (moderate and severe), infection, and prior malignancy, all of which were correlated with poorer survival. This model was significantly better in predicting OS as compared to Model 1, as evidenced by its significantly greater LR (p < 0.001) and slightly higher C-statistic, 0.703. Validated C-statistics calculated following 10-fold cross validation revealed a similar difference in model performance, (Model 1, C-statistic = 0.626 [95% CI 0.573-0.679]; Model 3, C-statistic = 0.654 [95% CI 0.601-0.706]) though this was not significant (p =

0.110). Still, Model 3 did not significantly outperform Model 2 (concordance, p = 0.170). Patients with at least two comorbidities were shown to have worse OS (HR 2.45, p = 0.01) with five-year OS approaching 40%, compared to patients with no comorbidities whose five-year OS was ~70% (Figure 2).

Alternatively, Model 3 for NRM only added a history of pulmonary disease and prior malignancy, and its performance (C-statistic = 0.708) was unchanged from Model 1. Subsequently, the final models that also included psychological factors (Model 4) showed that the PACT score trended towards significance in the NRM model. Yet, the model fit was not significantly different when compared to Model 1 (LR, p = 0.138). The addition of the PACT score did not modify the performance of the model for OS (C-statistic = 0.712). The psychosocial variable was not included in any of the final models following variable selection.

	Model 1 (D+T) C-statistic=0.672	Model 2 (D+T+S) C-statistic=0.683	Model 3 (D+T+C) C-statistic=0.703	Model 4 (D+T+C+P) C-statistic=0.712
Variable	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Race/Ethnicity				
Hispanic	1.37 (0.89-2.10)	1.42 (0.92-2.17)	1.61 (1.03-2.52)*	1.61 (1.03-2.52)*
African American	2.39 (1.12-5.11)*	2.20 (1.03-4.73)*	2.47 (1.12-5.43)*	2.46 (1.12-5.40)*
Asian	0.57 (0.27-1.19)	0.57 (0.27-1.18)	0.72 (0.35-1.47)	0.72 (0.35-1.48)
Caucasian	1.00	1.00	1.00	1.00
DRI				
High	3.55 (1.72-7.36)*	3.49 (1.67-7.31)*	3.76 (1.79-7.90)*	3.70 (1.76-7.78)*
Intermediate	2.19 (1.07-4.47)*	2.14 (1.05-4.38)*	2.51 (1.22-5.16)*	2.44 (1.18-5.02)*
Low	1.00	1.00	1.00	1.00
HLA mismatch				
2+	1.31 (0.67-2.57)	1.17 (0.60-2.30)	1.17 (0.60-2.30)	1.16 (0.59-2.28)
1	1.96 (1.23-3.10)*	1.88 (1.19-2.98)*	1.88 (1.17-3.00)*	1.95 (1.21-3.13)*
0	1.00	1.00	1.00	1.00
Engraftment				
No	3.78 (1.61-8.88)*	4.02 (1.71-9.44)*	3.60 (1.52-8.49)*	3.61 (1.53-8.53)*
>14 days	0.52 (0.34-0.79)*	0.54 (0.35-0.82)*	0.50 (0.33-0.77)*	0.49 (0.32-0.76)*
</= 14 days	1.00	1.00	1.00	1.00
HCT-CI Score				
3+ points		1.81 (1.03-3.16)*		
1-2 points		1.38 (0.75-2.53)		
0 points		1.00		
Infection				
Yes			2.05 (1.14-3.70)*	1.93 (1.06-3.50)*
No			1.00	1.00
Prior tumor				
Yes			2.25 (1.00-5.06)*	2.37 (1.05-5.33)*
No			1.00	1.00
Lung disease				
Severe			1.76 (1.07-2.91)*	1.78 (1.08-2.95)*
Moderate			1.63 (1.05-2.54)*	1.61 (1.03-2.51)*
No			1.00	1.00
PACT				
>Poor				1.62 (0.72-3.62)
Poor				1.00

Table 3. Multivariable models and corresponding hazard ratios for OS. *= p <0.05.

C = comorbidities; D = demographics; P = psychological factors; S = HCT-CI score; T = transplant-related factors.

	Model 1 (D+T) C-statistic=0.707	Model 2 (D+T+S) C-statistic=0.706	Model 3 (D+T+C) C-statistic=0.708	Model 4 (D+T+C+P) C-statistic=0.714
Variable	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Race/Ethnicity				
Hispanic	0.87 (0.50-1.50)	0.89 (0.51-1.55)	0.91 (0.51-1.60)	0.91 (0.51-1.62)
African American	2.37 (1.03-5.44)*	2.33 (1.02-5.31)*	2.12 (0.92-4.87)	2.14 (0.95-4.82)
Asian	0.56 (0.21-1.48)	0.57 (0.22-1.49)	0.59 (0.23-1.52)	0.60 (0.23-1.55)
Caucasian	1.00	1.00	1.00	1.00
CMV-recipient				
Negative	0.61 (0.34-1.07)	0.63 (0.36-1.13)	0.67 (0.37-1.19)	0.66 (0.37-1.18)
Positive	1.00	1.00	1.00	1.00
HLA mismatch				
2+	2.21 (0.99-4.96)	2.11 (0.96-4.66)	2.20 (0.97-4.97)	2.21 (0.99-4.93)
1	2.72 (1.53-4.83)*	2.64 (1.48-4.69)*	2.53 (1.38-4.65)*	2.66 (1.43-4.96)*
0	1.00	1.00	1.00	1.00
Engraftment				
No	5.78 (2.10-15.9)*	5.91 (2.17-16.1)*	5.86 (2.13-16.1)*	5.83 (2.12-16.1)*
>14 days	0.44 (0.26-0.77)*	0.46 (0.27-0.80)*	0.42 (0.24-0.75)*	0.41 (0.23-0.73)*
</= 14 days	1.00	1.00	1.00	1.00
HCT-CI Score				
3+ points		1.62 (0.73-3.57)		
1-2 points		1.49 (0.65-3.40)		
0 points		1.00		
Prior tumor				
Yes			2.34 (0.96-5.71)	2.41 (0.99-5.90)
No			1.00	1.00
Lung disease				
Severe			1.63 (0.84-3.17)	1.64 (0.84-3.19)
Moderate			1.31 (0.73-2.38)	1.28 (0.70-2.32)
No			1.00	1.00
PACT				
>Poor				2.03 (0.80-5.19)
Poor				1.00

Table 4. Multivariable models and corresponding hazard ratios for NRM. *p-values <0.05. C = comorbidities; D = demographics; P = psychological factors; S = HCT-CI score; T = transplant-related factors.

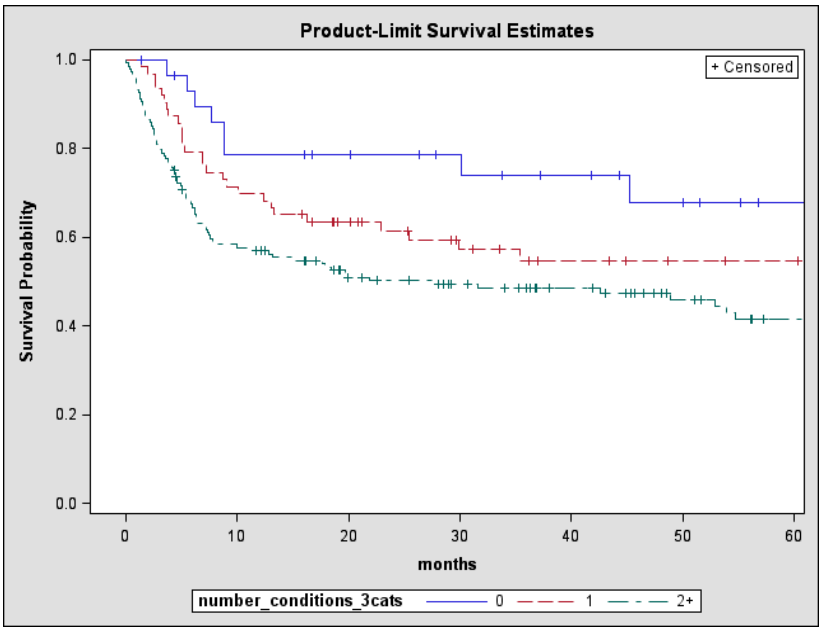


Figure 2. Kaplan-Meier survival curves stratified by number of comorbidities.

4. DISCUSSION

4.1 Purpose of study

Although the HCT-CI is a useful model to predict outcomes in adults, it is less practical for AYA patients since many of the comorbidities included in the HCT-CI are age-related, and the model does not adequately address other unique risk factors seen in this population. The current study determined the prevalence of multiple comorbidities in AYA patients undergoing allogeneic HSCT including a psychosocial factor, and then used multivariable models to show which variables were most valuable in predicting outcomes.

4.2 Outcomes for AYAs were poor

Both OS and NRM for AYAs undergoing allogeneic HSCT was poor in our study, consistent with past reports demonstrating inferior outcomes for this population, primarily due to

higher rates of NRM.[8,9] However, the prior studies only included patients with a diagnosis of hematologic malignancy, and therefore, the one-year cumulative incidence of NRM of 26% in our study is especially concerning, as we also included patients with nonmalignant disease. Surprisingly, this rate is not only higher than what has been seen in pediatric patients, but is similar to the rates observed in older adults, reportedly as high as 30%.[19,20]

These poor outcomes may reflect the nearly one-third of patients identified as high-risk disease by the DRI, and represents a similar proportion as compared to other studies conducted at large transplant centers.[16,21] This included many patients, particularly in the early years of this study, who were transplanted with either active disease or evidence of morphologic minimal residual disease. Similar to prior studies, we found that high-risk patients based upon the DRI were more likely to die from disease recurrence or treatment-related causes.[16] Better patient selection criteria including the use of more sensitive minimal residual disease testing and risk scores such as the HCT-CI and DRI has begun to improve outcomes for these patients in recent years.[22]

4.3 The HCT-CI does not strengthen model prediction

Our initial models corroborated the importance of both patient and graft selection, as we demonstrated that high-risk DRI, CMV positive status, HLA-mismatched grafts, and non-engraftment were predictors of poor outcomes.[23,24] We also revealed similar racial disparities previously shown in prior studies, that may be explained by differences in socioeconomic status that could not be explored in this study, and biological differences resulting in variable frequencies and severities of comorbidities, many of which may be treatment-related.[25,26] However, these findings should be taken with caution given the small number of African American patients in this study.

Surprisingly, patients with two or more HLA mismatches did not have worse outcomes than patients with only one HLA mismatch, but this difference was likely not observed because

most of the patients with two HLA mismatches received cord blood transplants, and these patients have been shown to have good outcomes as long as they receive an adequate cell dose.[27] More unexpected was the finding that later engraftment was significantly associated with better outcomes when compared to engraftment less than fourteen days. However, given our younger patient population and institutional practices, the majority of patients received stem cells from cord blood or bone marrow, that are known to result in later engraftment but similar outcomes to patients who receive peripheral blood stem cells.[28] We speculate that these patients may also have had lower rates of GVHD than patients with earlier engraftment, represented primarily by peripheral blood stem cell recipients, and this may have contributed to their improved survival outcomes.

Interestingly, the addition of the HCT-CI score to the baseline model did not improve the accuracy of the model in predicting both OS and NRM. This suggests that the HCT-CI score is less useful for this younger population. This finding is not surprising given that we have demonstrated that only several of the comorbidities included in the HCT-CI were prevalent in the AYA population. Further, fewer of these comorbidities were associated with worse OS and higher NRM.

4.4 Unique comorbidities among AYAs are predictors of worse outcomes

The risk factors associated with inferior outcomes for AYAs undergoing allogeneic HSCT included a history of pulmonary disease, infection, and prior malignancy. When these important comorbidities were included in the models instead of the HCT-CI, the model performance was greatly improved, particularly for OS. This suggests that a simpler model may actually be more beneficial and practical for evaluating AYA patients. In addition, the presence of at least two pre-transplant risk factors appeared to significantly impact OS, which is quite useful as this high-risk group included more than 50% of the patients from our study. Still, the accuracy of Model 3 was modest and not significantly better than Model 1. A larger sample size

likely would have allowed us to demonstrate a statistical difference in this analysis, and may have led to more compelling results in regards to our NRM models.

Of the comorbidities included, a history of pulmonary disease was most prevalent and appeared to have the greatest effect on mortality. This association was previously demonstrated in a smaller, retrospective study of AYA patients with similarly high rates of pulmonary disease.[3] The reason why AYAs undergoing allogeneic HSCT have such a substantial rate of reduced pulmonary function is not clear, but is likely related to adverse effects from previous chemotherapeutic agents, irradiation, or infections during prior therapy, as a systematic review of studies of childhood cancer survivors demonstrated that these factors all contributed to pulmonary late effects.[29] It is also possible that some of these patients had germline mutations that predisposed to worsening pulmonary function regardless of the therapies they received. Our findings are not surprising given that infectious and noninfectious pulmonary complications are very common following allogeneic HSCT,[30] and prior studies have shown that abnormalities in pulmonary function before transplant increase a patient' risk more than 2-fold of developing respiratory failure post-transplant.[31]

The other comorbidities that were associated with worse outcomes in our multivariable models were a history of infection and prior malignancy. Patients with active infections preceding allogeneic HSCT were fairly common in our study, and these patients are known to be high-risk as they approach a period of immunosuppression that is likely to worsen any underlying infection and impact survival.[32,33] Similarly, patients with prior malignancies frequently have very aggressive therapy-related leukemias, as well as additional cumulative toxicity from past therapies; therefore, poor outcomes are not unexpected.[34] However, there were few patients in our study with a prior malignancy so it is more difficult to interpret this data.

Another important comorbidity to discuss even though it was not included in the final models was a history of psychiatric disease, as this was a relatively frequent comorbidity in AYA patients undergoing allogeneic HSCT. Such findings have not specifically been described in

prior studies in the transplant setting, yet a substantial rate of anxiety and depression has been reported in AYAs with cancer.[35] Our study showed that a history of psychiatric disease was associated with a higher incidence of NRM in univariate analysis, but not in the multivariable analysis. Yet our analysis may have been limited by our small sample size and this factor likely contributes to poor outcomes as prior studies revealed higher rates of acute GVHD and lower OS in patients with a history of psychiatric disease.[36,37] It is not clear how mental illness impacts survival outcomes, but it likely is associated with the high rates of noncompliance seen in patients with psychiatric disorders.[38] Other studies have demonstrated that depression leads to immune activation that could favor the development of inflammatory processes such as acute GVHD.[39]

Besides psychiatric disease, we found that other psychosocial issues were also common in AYA patients, yet they did not correlate with increased mortality. However, it was challenging to obtain accurate data on this factor retrospectively, and this may have impacted our findings. Recent studies have demonstrated that the PACT scale may be useful in predicting outcomes for patients undergoing allogeneic HSCT.[14,15] Therefore, assessing psychosocial issues throughout the transplant process remains an important practice, and barriers should be addressed through a multidisciplinary approach.[40]

4.5 Targeting high-risk patients may be a way to improve outcomes

Most importantly, by carefully assessing these specific risk factors, physicians could implement targeted interventions particularly for the high-risk patients to attempt to improve overall outcomes. One strategy is to utilize reduced-intensity conditioning regimens for high-risk patients to reduce the risk of NRM, though this practice is likely to impact OS as well given that several studies have demonstrated that the incidence of relapse mortality is not significantly higher with less intensive conditioning.[41,42] However, these studies primarily examined older adults and it is not clear whether such an approach would yield similar outcomes for AYAs.

Overall, larger studies are needed to corroborate our findings, including the development of a specific risk score for the AYA population. Some of these risk factors may be modifiable through additional therapy or supportive care measures that may reduce the rate of mortality. Preemptive strategies would be preferable, given that complications following transplant including GVHD and organ dysfunction are often difficult to treat. Prospective studies would be particularly useful to better assess and understand the psychosocial issues observed during transplant, as these issues are complex and data is not collected uniformly.

4.6 Limitations

The main limitations of this study are related to its retrospective design. Comorbidity data was obtained primarily from the electronic medical record, but all comorbidities may not have been assessed on every patient or the data may not have been documented properly. Limited sample size made it difficult to determine accurate hazard ratios for each comorbidity given the many covariates that had to be considered in these complex patients. Evaluation of the data by year of transplant may also have impacted these factors as we included patients over a ten-year period and patient and donor selection, as well as overall management likely changed throughout this time.

4.7 Conclusion

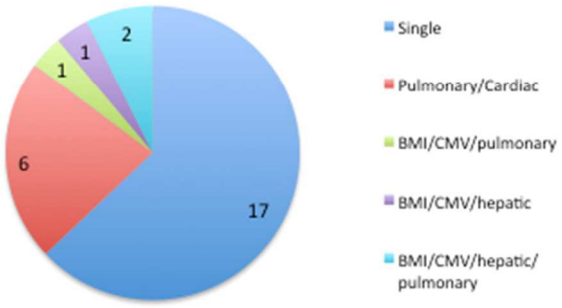
In summary, it appears that the use of the HCT-CI does not provide additional support in helping to predict OS and NRM in AYA patients undergoing allogeneic HSCT. Instead, the inclusion of just three comorbidities comprised of a history of pulmonary disease, infection, and prior malignancy significantly improved the ability to predict OS prior to transplant. Use of a validated risk score for AYAs should become the standard-of-care in evaluating these patients prior to allogeneic HSCT, as it will lead to changes in patient management that will ultimately improve outcomes.

5. APPENDIX

A

Clinical factors/comorbidities	No. (%)
Pulmonary	14 (5.8)
Cardiac	9 (3.7)
Hepatic	7 (2.9)
CMV status	6 (2.5)
BMI	5 (2.1)
Psychosocial	2 (0.8)

B



Appendix 1. Missing data. (A) Table demonstrates the distribution of missing data among various comorbidities. (B) Chart illustrates the number and type of comorbidity combinations observed among patients with missing data.

A

AST 1	Count Total % Col % Row %	AST 2: 0	AST 2: 1	AST 2: Total
0		152 74.88 94.41 91.02	15 7.39 35.71 8.98	167 82.27
1		9 4.43 5.59 25.00	27 13.30 64.29 75.00	36 17.73
Total		161 79.31	42 20.69	203

B

ALT 1	Count Total % Col % Row %	ALT 2: 0	ALT 2: 1	ALT 2: Total
0		131 64.22 92.25 87.33	19 9.31 30.65 12.67	150 73.53
1		11 5.39 7.75 20.37	43 21.08 69.35 79.63	54 26.47
Total		142 69.61	62 30.39	204

C

Bili 1	Count Total % Col % Row %	Bili 2: 0	Bili 2: 1	Bili 2: Total
0		186 89.42 94.90 96.88	6 2.88 50.00 3.13	192 92.31
1		10 4.81 5.10 62.50	6 2.88 50.00 37.50	16 7.69
Total		196 94.23	12 5.77	208

Appendix 2. Two-by-two plots for liver function tests. (A) Two-by-two plot for AST. 24/203 (12%) of values showed disagreement and this equates to a 14% chance of misclassification. Therefore, using the available data will be incorrect in about three cases. (B) Two-by-two plot for ALT. 30/204 (15%) of values showed disagreement and this equates to a 19% chance of misclassification. Therefore, using the available data will be incorrect in about four cases. (C) Two-by-two plot for total bilirubin. 16/208 (8%) of values showed disagreement and this equates to an 8% chance of misclassification. Therefore, using the available data will be incorrect in about two cases.

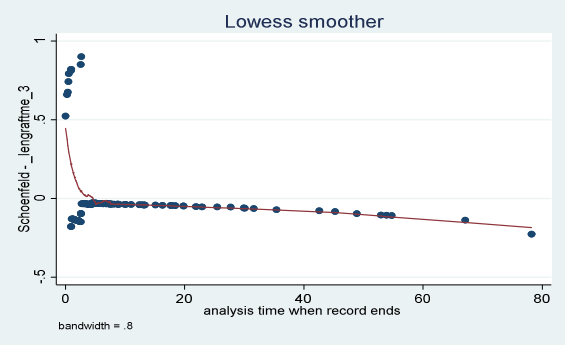
A

Test of proportional-hazards assumption

Time: Time

	rho	chi2	df	Prob>chi2
_Irace_2	0.07415	0.68	1	0.4089
_Irace_3	0.14458	3.03	1	0.0816
_Irace_4	0.06682	0.81	1	0.3694
_Idri_2	0.01464	0.03	1	0.8711
_Idri_3	0.07104	0.63	1	0.4286
_Iconditio~2	0.24197	9.52	1	0.0020
_Iconditio~3	-0.00872	0.01	1	0.9184
_Iblood_ma~2	0.02086	0.06	1	0.8118
_Iblood_ma~3	0.00614	0.00	1	0.9443
_Iengraftm~2	0.07166	0.69	1	0.4049
_Iengraftm~3	-0.19282	5.31	1	0.0212
_Iinfectio~1	-0.07499	0.67	1	0.4132
_Imalignan~1	-0.12795	2.21	1	0.1367
_Ilung_2	-0.02524	0.08	1	0.7713
_Ilung_3	-0.16050	3.30	1	0.0692
global test		21.67	15	0.1169

B



Appendix 3. Evaluation of model assumptions. (A) Test of proportional hazards assumption. Conditioning and engraftment variables violated the proportional hazards assumption. (B) Analysis of residuals of non-engraftment over time. The effect of non-engraftment on mortality was most pronounced in the first few months of follow-up. The variable was included in the final models after it was not shown to significantly impact the estimates of the other variables in a sensitivity analysis. “rho” = correlation; “conditio~2” = nonmyeloablative; “conditio~3” = reduced-intensity conditioning; “engraftm~2” = >14 days; “engraftm~3” = non-engraftment.

	Early engraftment (N=61)	Late engraftment (N=168)
Age, median (years)	29	25.5
Gender, no. (%) Male Female	 36 (59) 25 (41)	 101 (60) 67 (40)
Race/Ethnicity, no. (%) White Hispanic African American Asian	 23 (38) 27 (44) 2 (3.3) 9 (15)	 62 (37) 75 (45) 11 (6.6) 20 (12)
CMV status-recipient Positive Negative	 38 (62) 22 (36)	 109 (65) 55 (33)
Disease Risk Index, no. (%) Low Intermediate High	 6 (10) 39 (64) 16 (26)	 36 (21) 88 (52) 44 (26)
Sibling-match, no. (%) Yes No	 23 (38) 38 (62)	 96 (57) 72 (43)
HLA mismatch, no. (%) 0 1 2 3	 55 (90) 3 (4.9) 2 (3.2) 1 (1.6)	 118 (70) 35 (21) 15 (8.9) 0 (0)
Cell source, no. (%) Bone marrow Peripheral blood Cord blood	 8 (13) 50 (82) 3 (4.9)	 68 (40) 49 (29) 51 (30)

Appendix 4. Stratifying patient characteristics by engraftment period. Early engraftment </= 14 days; late engraftment > 14 days.

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