Impact of Pre-transplant Individual Comorbidities on Risk of ICU Admission and Survival Outcomes Following Allogeneic Hematopoietic Stem Cell Transplantation

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Article

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Abstract

Patients undergoing allogeneic hematopoietic stem cell transplantation (allo-hsct) can require intensive care unit (ICU) admission in the post-transplant period. Whereas outcomes of ICU admission are known to be poor, little is known about the pre-transplant risk factors leading to them. We conducted a retrospective analysis of 304 patients to investigate the impact of pre-transplant individual comorbidities on acute inpatient complications, focusing on ICU admission, ventilator support and multi-system organ failure, following allo-hsct. During the initial hospitalization, 33 (11%) patients required ICU admission, 29 (10%) required ventilator support and 33 (11%) developed multi-system organ failure. Risk factors for ICU admission and ventilator support included pre-transplant infection, pre-transplant diabetes, time to neutrophil engraftment, donor type and HSCT era. Risk factors for multi-system organ failure included pre-transplant diabetes, time to neutrophil engraftment and HSCT era. For ICU patients, the 60-day and 6-month mortality was 58% and 67%, respectively and the median overall survival was 1.4 months. Patients with diabetes and infection at the time of HSCT and delayed neutrophil engraftment during transplant are at an increased risk for ICU admission, ventilator support and multi-system organ failure. Patients admitted to the ICU are also at a high risk for mortality leading to poor survival.

Introduction

Our ability to offer allogeneic hematopoietic stem cell transplant (HSCT) as a treatment option, to an expanded pool of patients, has been made possible by advancements in patient selection, transplant techniques and supportive care; however, morbidity and mortality within the early post-transplant period remain high.[1, 2]

Patients undergoing allogeneic HSCT can develop complications such as life-threatening infections, multi-system organ failure, intensive care unit (ICU) admission and the need for ventilator support in the immediate post-transplant period.[3] Although the outcomes of allogeneic HSCT recipients admitted to the ICU have improved overtime, overall prognosis remains poor.[4, 5] Several studies have reported these poor outcomes and have identified certain indications for the need for ICU admission such as sepsis, respiratory failure, renal and cardiovascular complications. Transplant-related characteristics such as conditioning intensity, human leukocyte antigen (HLA) mismatch, and graft versus host disease (GVHD) also have prognostic significance in determining outcomes of critically ill allogeneic HSCT patients.[5–8]

Pre-transplant risk factors for ICU admission, on the other hand, have not been investigated extensively. Sorror et al. investigated the impact of pre-transplant comorbidities on allogeneic HSCT outcomes, leading to the now widely adapted comorbidity-index (HCT-CI).[9] However, since the introduction of HCT-CI nearly 15 years ago, significant advances in the field have led to the refinement of the patient selection process, by shifting the focus on individual comorbidities within the HCT-CI, with or without additional host and disease characteristics. Studies have now shown that individual comorbidities, and not the composite HCT-CI score, can be significant risk factors for post-transplant complications.[1, 10–12]

In this context, we investigated the impact of pre-transplant individual comorbidities, in addition to transplant-related variables, on risk of ICU admission and survival outcomes following allogeneic HSCT.

Methods

Patient population and data collection

We created a retrospective cohort of patients who had undergone allogeneic HSCT for hematological malignancies at the University of Alabama at Birmingham (UAB) between 2008 and 2016. Patients were 18 year of age or older at the time of transplant.

The abstracted variables included age, sex, race/ethnicity, primary diagnosis, remission status at HSCT (complete or partial remission or primary induction failure/no response), disease risk index (DRI), transplant regimens and intensity (myeloablative or reduced intensity), donor source (matched related, matched unrelated, or haploidentical), and GVHD prophylaxis. We defined myeloablative-conditioning regimens as use of the following in any combination: Busulfan AUC ≥ 16,000 (Per PK, 'mg'), TBI (single fraction ≥ 5 Gray, fractionated ≥ 8 Gray), Thiotepa (≥ 10 mg/kg) and Melphalan ≥ 150 mg/m2; we considered all else as reduced intensity.

We abstracted individual comorbidities using the definitions provided by Sorror's HCT-CI. In addition, the HCT-CI composite score was also captured. We also captured health risk behaviors, including smoking (ever/never) and alcohol use (ever/never). Due to inability to distinguish between moderate and excessive alcohol use (unavailable data), the variable was included for descriptive purposes and not included in the statistical model. The Karnofsky Performance Status (KPS) score was also noted for each patient.

Data were abstracted on complications in the immediate post-transplant period during initial hospitalization. Outcomes of interest included the need for ICU admission, ventilator support, multi-system organ failure and infectious complications (bacterial, viral and fungal).

Medical records, National Death Index (NDI) Plus[13] and Accurint databases[14] were used to obtain a comprehensive assessment of vital status and cause of death. We assigned all deceased patients a primary and, if present, a secondary cause of death. We defined NRM as death in the absence of relapse after HSCT and classified all deaths that occurred in the setting of post-HSCT relapse as RRM. For NRM, the infectious deaths were categorized by GVHD status. The cause of death for any infectious death, occurring in the setting of active GVHD, was listed as GvHD. The UAB Institutional Review Board approved this study, and all research was performed in accordance with the Declaration of Helsinki.

Statistical analysis

We used Kaplan–Meier techniques to describe overall survival at 1 year from allogeneic HSCT, and Cox regression analysis to identify predictors of acute inpatient complications. We calculated cumulative incidence of cause-specific mortality using competing risk methods. We used proportional sub-

distribution hazards model (Fine-Gray) for competing risks for identifying potential risk factors for RRM and NRM. Two-sided tests with $p < 0.05$ were considered statistically significant. We performed all analyses with SAS software version 9.4 (SAS Institute Inc., Cary, North Carolina, USA

Results

We included 304 patients in this analysis (Table 1) with a median age of 52.1 year (range 18.1–72.3); 48.7% of the recipients were female, and 81.9% were non-Hispanic white. The leading indication for HSCT was acute myeloid leukemia (AML) (45.4%). At the time of HSCT, 58.6% patients were in complete remission (CR) and 54.9% patients had high/very high DRI. Donor source mainly included matched unrelated donor (53.3%) followed by haploidentical donor type (34.9%). Majority of the patients (73.7%) received myeloablative conditioning.

Table 1
Demographic & Clinical Characteristics

	Entire cohort (n = 304)
Age at HSCT (years)	
Median (range)	52.1 (18.1–72.3)
≥ 50 years (n, %)	175 (57.6%)
Gender (n, %)	
Male	156 (51.3%)
Race/ethnicity (n, %)	
Non-Hispanic White	249 (81.9%)
Non-Hispanic Black	45 (14.8%)
Other	10 (3.3%)
Primary Diagnosis (n, %)	
Acute myeloid leukemia	138 (45.4%)
Myelodysplasia	47 (15.5%)
Acute lymphoblastic leukemia	39 (12.8%)
Non-Hodgkin lymphoma	26 (8.6%)
Myeloproliferative neoplasms	11 (3.6%)
Other	43 (14.1%)
Disease Status at Transplantation (n, %)	
Complete remission	178 (58.6%)
Partial remission	82 (27%)
Primary induction failure/No response	38 (12.5%)
Disease Risk Index at Transplantation (n, %)	
High/Very high	167 (54.9%)
Intermediate	103 (33.9%)
Low	26 (8.6%)
Stem Cell Source (n, %)	
Peripheral blood	300 (98.7%)

	Entire cohort (n = 304)
Other	4 (1.3%)
Donor Type (n, %)	
Matched unrelated	162 (53.3%)
Haploidentical	106 (34.9%)
Matched related	36 (11.8%)
Conditioning Regimen Intensity (n, %)	
Myeloablative	224 (73.7%)
Reduced Intensity	76 (25%)

The prevalence of health behaviors and comorbidities at the time of HSCT are shown in Table 2. Using HCT-CI, 38.8% had a score of ≥ 3. At the time of HSCT, 33.6% of the patients were obese, 35.6% had moderate-severe pulmonary compromise, 35.5% were hypertensive, 22% had a psychiatric disorder, 12.5% had diabetes mellitus (DM), 10.2% had cardiac abnormalities, 9.2% had a history of a prior solid tumor, and 5.6% had a history of concurrent infection. A KPS < 80 was noted in 15.1% of the patients.

Table 2
Health Behavior and Comorbidities at Transplantation

	Entire cohort (n = 304)
Health Behaviors	
Smoking History (n, %)	
Ever	136 (44.7%)
Never	160 (52.6%)
Alcohol History (n, %)	
Ever	116 (38.2%)
Never	180 (59.2%)
Comorbidities	
Body Mass Index (BMI)	
Median (range)	27.4 (15.9–55.2)
BMI category (n, %)	
<25	105 (34.5%)
25–29	97 (31.9%)
≥30	102 (33.6%)
Pulmonary compromise (n, %)	
None/Mild	193 (63.5%)
Moderate	69 (22.7%)
Severe	39 (12.8%)
Psychiatric disorder (n, %)	
Yes	67 (22%)
Prior history of a solid tumor (n, %)	
Yes	28 (9.2%)
Infection (n, %)	
Yes	17(5.6%)
Hypertension (on medication) (n, %)	

	Entire cohort (n = 304)
Yes	108(35.5%)
Diabetes Mellitus (n, %)	
Yes	38(12.5%)
Cardiac abnormalities (n, %)	
Yes	31(10.2%)
Hepatic compromise (n, %)	
Moderate/Severe	8(2.6%)
Mild	24(7.9%)
Prior history of stroke (n, %)	
Yes	4(1.3%)
Rheumatologic disorder (n, %)	
Yes	6(2%)
Peptic Ulcer Disease (n, %)	
Yes	5(1.6%)
Inflammatory Bowel Disease (n, %)	
Yes	1(0.3%)
KPS Score (n, %)	
<80	46(15.1%)
HCT Comorbidity Index (n, %)	
0	82(27%)
1	56(18.4%)
2	44(14.5%)
3+	118(38.8%)

During the initial hospitalization, 33 (10.9%) patients required ICU admission, 29 (9.5%) required ventilator support, 32 (10.5%) developed multi-system organ failure, 69 (22.7%) developed bacterial infections, 12 (4.0%) developed viral infections and 7 (2.3%) developed fungal infections. The median time to neutrophil and platelet engraftment was 13 days (7–48 days) and 13 days (7-195 days), respectively. (Table 3)

Table 3
Complications during Initial Hospitalization (n = 304)

ICU admission (n, %)	
Yes	33 (10.9%)
Ventilator Support (n, %)	
Yes	29 (9.5%)
Infection	
Bacterial (n, %)	
Yes	69 (22.7%)
Fungal (n, %)	
Yes	7 (2.3%)
Viral (n, %)	
Yes	12 (4.0%)
Sepsis (n, %)	
Yes	55 (18.1%)
Multi-system Organ Failure (n, %)	
Yes	32 (10.5%)
ANC Engraftment (Days)	
Median (Range)	13 (7–48)
Platelet Engraftment (Days)	
Median (Range)	13 (7-195)

In multivariable Cox regression analysis (Table 4), risk factors for ICU admission included pre-transplant infection (HR 6.50, 95% CI 1.82–23.26, p = 0.004), pre-transplant DM (HR 4.14, 95% CI 1.56–10.97, p = 0.004), time to neutrophil engraftment (HR 1.13, 95% CI 1.05–1.21, p = 0.0007), donor type (ref: matched related donor; haplo: HR 0.24 95% CI 0.07–0.82, p = 0.02) and SCT era (ref: 2008–2010; 2010–2013: HR 0.18 95% CI 0.04–0.88, p = 0.03; 2014–2016: HR 0.12 95% CI 0.03–0.4, p = 0.0006). Risk factors for ventilator support included pre-transplant infection (HR 10.09, 95% CI 2.44–41.64, p = 0.001), pre-transplant DM (HR 3.61, 95% CI 1.31–9.91, p = 0.01), time to neutrophil engraftment (HR 1.17, 95% CI 1.11–1.23, p < 0.0001) and SCT era (ref: 2008–2010; 2010–2013: HR 0.21 95% CI 0.06–0.81, p = 0.02; 2014–2016: HR 0.07 95% CI 0.02–0.31, p = 0.0005). Risk factors for multi-system organ failure included pre-transplant DM (HR 4.38, 95% CI 1.64–11.74, p = 0.003), time to neutrophil engraftment (HR 1.13, 95% CI 1.08–1.19, p < 0.0001) and SCT era (ref: 2008–2010; 2010–2013: HR 0.21 95% CI 0.05–0.80, p =

0.003; 2014–2016: HR 0.16 95% CI 0.05–0.48, p = 0.001).Risk factor for bacterial infection included SCT era (ref: 2008–2010; 2010–2013: HR 0.30 95% CI 0.14–0.65, p = 0.002; 2014–2016: HR 0.24 95% CI 0.12–0.49, p < 0.0001) and for fungal infection included pre-transplant pulmonary compromise (ref: no compromise; severe pulmonary compromise HR 5.16, 95% CI 1.05–25.4, p = 0.04).

Table 4
Risk Factors for Complications during Hospitalization

Parameter	HR (95% CI)	p-value
ICU Admission		
Pre-transplant infection (ref: no infection)		
Yes infection	**6.50 (1.82–23.26)**	**0.004**
Pre-transplant diabetes mellitus (ref: no diabetes)		
Yes diabetes	**4.14 (1.56–10.97)**	**0.004**
HSCT era (2008–2010)		
2010–2013	**0.18 (0.04–0.88)**	**0.03**
2014–2016	**0.12 (0.03–0.4)**	**0.0006**
Donor Type (ref: matched related donor)		
Haploidentical	**0.24 (0.07–0.82)**	**0.02**
Time to neutrophil engraftment	**1.13 (1.05–1.21)**	**0.0007**
Ventilator Support		
Pre-transplant infection (ref: no infection)		
Yes infection	**10.09 (2.44–41.64)**	**0.001**
Pre-transplant diabetes mellitus (ref: no diabetes)		
Yes diabetes	**3.61 (1.31–9.91)**	**0.01**
HSCT era (2008–2010)		
2010–2013	**0.21 (0.06–0.81)**	**0.02**
2014–2016	**0.07 (0.02–0.31)**	**0.0005**
Time to neutrophil engraftment	**1.17 (1.11–1.23)**	**< 0.0001**
Bacterial Infection		
HSCT era (2008–2010)		
2010–2013	**0.30 (0.14–0.65)**	**0.002**
2014–2016	**0.24 (0.12–0.49)**	**< 0.0001**
Fungal Infection		
Pre-transplant pulmonary compromise (ref: no pulmonary compromise)		
Severe pulmonary compromise	**5.16 (1.05–25.4)**	**0.04**

Parameter	HR (95% CI)	p-value
Viral Infection		
Donor Type (ref: matched related donor)		
Matched Unrelated	**0.20 (0.05–0.73)**	**0.01**
Time to neutrophil engraftment	**1.08 (1.03–1.13)**	**0.003**
Multi-System Organ Failure		
Pre-transplant diabetes mellitus (ref: no diabetes)		
Yes diabetes	**4.38 (1.64–11.74)**	**0.003**
HSCT era (2008–2010)		
2010–2013	**0.21 (0.05–0.80)**	**0.02**
2014–2016	**0.16 (0.05–0.48)**	**0.001**
Time to neutrophil engraftment	**1.13 (1.083–1.19)**	**< 0.0001**

The 1-year overall survival, NRM and relapse rate for the entire cohort was 60.5%, 22.7% and 13.5%, respectively. The 1-year and median overall survival for patients admitted to the ICU was 32.8% and 1.4 months, respectively **(Fig. 1)**. For patients admitted to the ICU, the 60-day and 6-month mortality was 58% and 67%, respectively. No deaths, in patients admitted to the ICU, were attributed to relapse disease.

There were 35 patients who experienced NRM within the first 100 days after HSCT. Among these, there were 10 deaths prior to day 30 post-transplant and 25 between days 31 and 100. All deaths during the first 30 days were attributed to infectious complications. Infection (56%) was the leading cause of death between days 31 and 100, followed by GvHD (36%). In **Supplementary Table 1**, we provide the underlying causes of death for patients with pre-HSCT infection and diabetes.

Discussion

In our study, we investigated the impact of pre-transplant individual comorbidities on the risk of ICU admission and other acute inpatient complications following allogeneic HSCT. We also examined the outcomes of those patients admitted to the ICU following HSCT. We found that pre-transplant DM and infection, along with delayed neutrophil engraftment, were independent risk factors for ICU admission, ventilator support and multi-system organ failure following allogeneic HSCT. Patients admitted to the ICU had high mortality and low survival rates, although outcomes were not entirely futile.

In our cohort, 11% of allogeneic HSCT recipients required ICU admission and nearly 10% required ventilator support. With a median age of 52 and with majority of the patients receiving myeloablative conditioning, these rates are consistent with recent studies reporting an ICU admission rate of 11%-15%.[4,

[8, 15, 16] However, the rate of ICU admission varies from center to center and depending on the patient population as well as the time-period, can be as high as 30%-57%.[5, 17]

Our mortality and survival rates for patients admitted to the ICU are similar to previous reports. We find that these patients remain at a high risk of death, with only a minority surviving 1y post-transplant. The 1y mortality rate of allogeneic HSCT recipients in the ICU can be as high as 80–85%[7, 17] and survival as low as 10–15%.[5, 8, 18] However, outcomes of allogeneic HSCT patients admitted to the ICU have gradually improved with time due to advancements in supportive care, patient selection and transplant techniques.[15, 16] Although the 1y survival for our patients was only 32.8%, it is consistent with the recently reported gradual improvement in outcomes in this high-risk population.[5, 15, 16] We found HSCT era to be significantly associated with risk of ICU admission, ventilator support, bacterial infections, and multi-system organ failure; Patients undergoing HSCT in recent years (2014–2016 and 2010–2013 compared to 2008–2010) had a lower risk of experiencing these life-threatening complications. Other studies have also reported improved outcomes in more recent years for patients admitted to the ICU with a 1y survival rate of approximately 30%.[5, 15] These findings highlight that select patients admitted to the ICU following allogeneic HSCT can still have relatively favorable outcomes and that collaborative research efforts with intensivists are needed.

Our analysis of the impact of individual pre-transplant comorbidities on the risk of ICU admission, ventilator support and multi-system organ failure identified pre-transplant DM and infection as significant risk factors for these complications. An HCT-CI score of ≥ 3 was not associated with risk of ICU admission in our analysis. Studies investigating pre-transplant risk factors for ICU admission in allogeneic HSCT recipients are lacking. Bayraktar et al. identified an HCT-CI score of ≥ 2 to be associated with a higher risk of inpatient mortality and a score of ≥ 4 to be associated with inferior survival in allogeneic HSCT patients admitted to the ICU with the first 100 days post-transplant.[19] Pre-transplant DM has previously been shown to be a risk factor for NRM, particularly infection-related mortality, in allogeneic HSCT recipients.[12] Hyperglycemia has been correlated with increased NRM rate and acute GVHD incidence as well.[20, 21] Infection, followed by GVHD, were the leading causes of non-relapse mortality in patients with pre-transplant DM in our study. Furthermore, the pro-inflammatory state induced by DM may have a negative impact on the volume of circulating CD34 + cells, stem cell nice and hematopoietic progenitor cell function, potentially leading to issues with engraftment.[20–22] Interestingly, both delayed neutrophil engraftment and pre-transplant DM were significant risk factors, in our multivariable model, for ICU admission, ventilator support and multi-system organ failure. Given these significant findings, optimizing glycemic control prior to transplant should be prioritized in patients with DM.

Pre-transplant infection was another risk factor for ICU admission and ventilator support. Infection was defined as culture-positive infection requiring treatment or fever of unknown origin requiring antimicrobial therapy on admission (Recipients were on antimicrobial therapy at the start of preparative regimen and/or day of admission). Reports on impact of pre-transplant infection on allogeneic HSCT outcomes

have shown conflicting results with one study finding a lower incidence of pneumonia if transplant was delayed in patients with pre-transplant respiratory syncytial pneumonia[23] and another reporting no influence on survival in recipients with multidrug-resistant gram-negative colonization pre-transplant.[24] Given the significant risk of morbidity and mortality as shown in our analysis, delaying transplant until the infection is resolved is recommended, provided that the underlying malignancy would allow so.

The risk of bacterial infection improved overtime, perhaps a reflection of improved supportive care. Although there are conflicting data on the impact of pulmonary function abnormality on mortality, we found severe pre-transplant pulmonary compromise to be associated with risk of fungal infection.[25]

Our limitations include the retrospective nature of the study along with a relatively small sample size from a single center. However, the ability to abstract data in detail provided us with an opportunity to examine the associations with greater precision. The impact of pre-transplant individual comorbidities on the risk of ICU admission, ventilator support and multi-system organ failure was previously unclear. Our report answers this knowledge gap by identifying certain comorbidities which may help identify patients at a high risk for life-threatening complications in the immediate post-transplant period and provide an opportunity to improve both morbidity and mortality in transplant recipients.

Declarations

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Author contributions:

OJ, RB, and SB contributed towards the conception of the presented study. OJ and AC contributed towards data collection. OJ, AC and SB contributed towards data analysis.

OJ, JD, AC, DS, RB and SB contributed towards drafting, revising and approving the manuscript.

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Figures

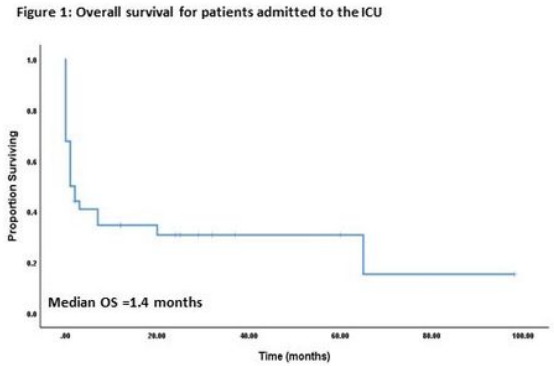

Figure 1

Overall survival for patients admitted to the ICU

Supplementary Files

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- SupplementalTable1.docx