Weight Loss Post Allogeneic Stem Cell Transplant is Associated with Increased Transplant Related Mortality

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Abstract

Purpose: Allogeneic Stem Cell Transplant (allo-HSCT) patients are at risk of malnutrition and weight loss from impaired oral intake resulting from gastrointestinal toxicities, dysgeusia, and psychological effects.
Methods: A retrospective review of 264 adult patients transplanted at Princess Margaret Cancer Centre who achieved relapse-free survival up to 3 months after allo-HSCT was performed.

Results: Overall incidence of patients who experienced WL (WL) ≥10% from HSCT to 3 months post-transplant was 45.9% and from HSCT to 6 months was 56.6%. Patients with ≥10% WL from allo-HSCT at 3-months and 6 months had similar 2-year overall survival (OS) compared to those with <10% WL, 55.7% vs. 62.8% (HR=1.38, p=0.11) and 71.1% vs. 77.2% (HR=1.37, P=0.27), respectively. Patients with ≥10% WL 3- and 6-months from allo-HSCT also had similar 2-year relapse-free survival (RFS) compared to those with <10% WL, 48.1% vs. 55.8% (HR=1.26, p=0.22), and 62.7% vs 69.8% (HR=1.29, p=0.31), respectively.

The 2-year transplant-related mortality (TRM) was higher for those with ≥10% WL from allo-HSCT to 3-months, 35.4% vs. 16.9% (HR=2.39, p=0.0007) and 6 months, 22% vs. 8% (HR=3.1, p=0.0034). Although statistical significance was not observed for OS or RFS, patients who experienced ≥10% WL 3- and 6-months post allo-HSCT experienced higher 2-year TRM. These results highlight the importance of early intervention and close monitoring of weight post allo-HSCT.
Conclusion: Approaches to WL post allo-HSCT should be multifaceted and include members of the interdisciplinary team in order to decrease TRM.

Introduction

Allogeneic hematopoietic stem cell transplantation (HSCT) offers the potential for prolonged remission and a cure for many malignant and non-malignant hematological diseases. In recent years, the number of transplants has increased, mainly due to expanded donor availability and the modification of conditioning regimens. Nevertheless, the curative intent of this treatment can often come with a multitude of clinically significant transplant-related morbidity and mortality.

HSCT typically involves high dose chemotherapy with or without radiation, as well as several medications used to prevent graft-versus-host disease (GVHD) and infections. These necessary components of treatment often cause gastrointestinal (GI) toxicity. This toxicity can result in nausea, vomiting, mucositis, taste alterations and intestinal GVHD, often leading to diarrhea and malabsorption [1–3], and subsequent malnutrition and impaired oral intake [4].

Despite efforts to limit transplant-related toxicity, many patients suffer acute and chronic sequelae. Pre-transplant risk factors have been identified to prognosticate post-transplant outcomes[5–7]. One such prognostic score, the Hematopoietic Cell Transplantation-specific Comorbidity Index (HCT-CI)[8], incorporates obesity as determined by a body mass index (BMI) greater than 35 kg/m^2 pre-transplant as an unfavourable prognostic indicator at pre-transplant assessment. Although obesity has historically

been part of pre-transplantation comorbidity scoring, studies have shown that overweight and obese patients actually have improved overall survival (OS) compared to underweight or normal weight patients [9]. Instead, being underweight is associated with inferior outcomes such as decreased OS and treatment related mortality (TRM)[10, 11]. Further, the presence of severe malnutrition defined by weight loss after allogeneic HSCT was associated with a poor subsequent clinical outcome due to an increased risk of non related mortality (NRM), mainly relating to graft versus host disease (GVHD)[12]. Though study results are conflicting, overall the published data collectively does not support obesity as a risk factor at transplant, and this suggests that the HCT-CI scoring system may not account for an important and potentially modifiable risk factor such as low BMI at the time of transplant. Complicating the interpretation of the published literature, the majority of studies examining the effects of pre-transplant BMI and weight loss on patient outcome either had a small sample size and/or were based in the United States (US), where the average BMI tends to be significantly higher than other developed country medians[13]. In comparison, one of the largest studies to date was conducted in Japan where the average BMI was lower and consisted of a much smaller sample of overweight and obese patients [14]. Furthermore, the homozygous populations previously studied may be difficult to translate to Canada's diverse population. Therefore, we undertook a retrospective study examining the clinical impact of pre-transplant BMI and weight loss post HSCT on patient outcomes.

Materials And Methods

This retrospective single-centre study included 264 adult patients who underwent allogeneic HSCT for any indication using either myeloablative (MAC) or reduced intensity conditioning (RIC) regimens at Princess Margaret Cancer Centre between January 2016 and January 2018. Second allogeneic HSCTs recipients and patients who relapsed or died within 90 days after receiving an allogeneic HSCT were excluded. This study was approved by the Cancer Registry Data Access Committee (CRDAC) and the Research Ethics Board of the University Health Network/Princess Margaret Cancer Centre.

Variables

The most common indications for transplant were acute leukemias (51.6%) and myelodysplastic syndromes (MDS; 15.5%). Overall, 54.5% of patients were male with a median age of 57.5 years (18.0–74.0). Karnofsky Performance Scale (KPS) was 100 percent in 14.1%, 90 percent in 66.5%, 80 percent in 16.5%, and 70 percent in 2.9% of patients. Median pre-transplant BMI was 25.4 (range: 16.6–51.7). Most patients had a matched unrelated donor (MUD; 52.9%) or matched related donor (MRD; 30.1%) with the remainder having a haploidentical donor (HID; 17.0%). Of all patients, 46 (18.9%) developed acute GVHD of the gut (all grades), while 15 (6.2%) had chronic GVHD involving the gastrointestinal tract. Patient variables are shown in Table 1.

Table 1
Patient characteristics of study participants.

	N (%) or median (range)
No. of patients	246
Diagnosis	
Acute leukemia	127 (51.6%)
Myelodysplastic syndrome	38 (15.5%)
Chronic leukemia	23 (9.3%)
Myelofibrosis	19 (7.7%)
Lymphoma	15 (6.1%)
Other	24 (9.8%)
Recipient Sex	
Male	134 (54.5%)
Female	112 (45.5%)
Recipient Age	57.5 (18.0–74.0)
KPS	90.0 (70.0–100.0)
70	7 (2.9%)
80	40 (16.5%)
90	161 (66.5%)
100	34 (14.1%)
Missing	4
Donor Type	
Matched unrelated donor	130 (52.9%)
Matched related donor	74 (30.1%)
Haploidentical donor	42 (17.0%)
Stem Cell Source	
PBSC	242 (98.4%)
BM	4 (1.6%)
Conditioning	

	N (%) or median (range)
Reduced Intensity	228 (92.6%)
Myeloablative	18 (7.3%)
Conditioning	
Flu(4) + Bu(2) + TBI (200)	219 (89.0%)
Other	27 (11.0%)
GVHD Prophylaxis	
ATG-PTCy-CsA	200 (81.3%)
CsA-MTX	32 (13.0%)
ATG-CsA-MTX	13 (5.3%)
PTCy-CsA	1 (0.4%)
GVHD Diagnosis	
acute GVHD (gut)	46 (18.9%)
chronic GVHD (gut)	15 (6.2%)

Conditioning/GVHD Prophylaxis

Most patients received RIC, 92.6% (n = 228), with the most common regimen being fludarabine 30 mg/m^2 × 4 days, busulfan 3.2 mg/kg × 2 days ± TBI 200 cGy (n = 219, 89%). Myeloablative conditioning was given in 7.3% (n = 18), with the most common conditioning regimen being fludarabine 50 mg/m^2 × 4 days, busulfan 3.2 mg/kg × 4 days ± TBI 4 Gy. For GVHD prophylaxis, most patients received antithymocyte globulin (ATG), cyclophosphamide 50 mg/kg IV on days + 3 and + 4, and cyclosporine (CsA) 2.5 mg/kg IV q12h starting on day + 5 (813 %, n = 200). Conditioning and GVHD prophylaxis are shown in Table 1.

All patients received granulocyte colony-stimulating factor (G-CSF) 5 µg/kg subcutaneously starting on day + 7 until three consecutive days of an absolute neutrophil count (ANC) of ≥ 1.5x10^9/L. Antimicrobial prophylaxis included ciprofloxacin 500 mg twice daily from day − 6 to engraftment, acyclovir 400 mg twice daily from day + 1 to 1-year following transplant, micafungin 50 mg IV daily from day + 1 until engraftment followed by posaconazole 300 mg daily until day + 90. For pneumocystis jirovecii pneumonia (PJP) prophylaxis, trimethoprim/sulfamethoxazole or pentamidine from day + 21 or upon engraftment until 1-year post transplantation.

BMI and Weight Loss Definitions

BMI was calculated using the World Health Organization (WHO) equation of weight (in kg)/(height squared in m^2) and were categorized as follows: underweight (BMI < 18.5 kg/m^2), normal (18.5 ≤ BMI < 25 kg/m^2), overweight (25 kg/m^2 ≤ BMI < 30 kg/m^2), and obese (BMI ≥ 30 kg/m^2)[15]. Weight and BMI were recorded at baseline, which was within one month of HSCT and at 3 and 6 months post HSCT. Weight loss was categorized into 2 groups based on weight loss at 3 months and 6 months after allogeneic HSCT: normal/mild malnutrition (weight loss less than 10%) and severe malnutrition (weight loss of 10% or more).

Clinical Endpoints

The study endpoints included the incidence of patients with ≥ 10% weight loss from HSCT to 3 months and HSCT to 6 months post-transplant. Clinical outcomes included 2-yr rate of OS, TRM, and RFS; 100-day incidence of acute GVHD and moderate-severe chronic GVHD were also collected. Overall survival was measured as the time of allogeneic HSCT to death from any cause. Transplant-related mortality was defined as the time of transplant to death from any other cause than relapse. Relapse-free survival was defined as the time of transplant to first occurrence of disease or death from any cause. To summarize patients' characteristics, a descriptive statistical analysis was performed.

Statistical Analysis

Descriptive analyses were performed. Counts (proportions) were calculated for categorical variables whereas mean (SD) and median (range) were provided for continuous variables. Variables analyzed included: demographics, diagnosis and treatment related factors, and clinical measures. Kaplan-Meier curve of OS were plotted. Overall survival curves were stratified by two weight loss categories and the differences between groups were assessed using log-rank test. Weight loss over two time frames were assessed: HSCT to 3 months and 6 months post-transplant respectively. In addition, cumulative incidence curve of TRM was plotted and stratified by weight loss. The differences between weight loss categories were analyzed using Gray's tests. Univariate analyses were conducted to examine the variables associated with outcomes of interest including OS, RFS, Relapse and TRM. Cox proportional hazard models were performed for OS and RFS, whereas Fine-Gray models [16] were built for Relapse and TRM, accounting for the effects competing risk events. Moreover, two-year estimates for the outcomes were provided. Multivariable analyses were performed, and clinically important variables such as baseline BMI and weight loss were included regardless of their statistical significance. Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated for the clinical variables, and stepwise selection procedure was performed for model selection using p = 0.05 as criteria for variable entry. All statistical analyses were carried out using SAS 9.4 software (Cary, NC, USA).

Results

Incidence

At 3 months, 54% (n = 133) of patients had < 10% weight loss, with 45.9% (n = 113) having ≥ 10% weight loss. At 6 months, 43.3% (n = 88) had < 10% weight loss, with 56.6 (n = 115) having ≥ 10% weight loss. Compared to pre-HSCT, at 3 months the median reduction in BMI was 1.7 (9.85.7) and at 6 months, 1.6 (-10.5-7.9). Comparing pre-transplant BMI and weight loss of ≥ 10% at 3 months, we found that the obese patients had significantly higher weight loss compared to those with normal weight (44.4% vs 27.0%, p = 0.03), or the underweight group (44.0% vs 0.0%, p = 0.03). Weight loss patterns comparing other groups were not significantly different. At 6 months, patients obese at pre-transplant assessment had significantly higher weight loss compared to the normal weight group (64.3% vs 21.0%, p < 0.0001), the underweight group (64.29% vs 0%, p = 0.004), as well as the overweight group (64.29% vs 31.75%, p = 0.001). Weight loss patterns comparing other groups were similar.

Overall Survival

For all patients, the median 2-year OS was 52.1% (95% CI: (46.6–58.2). Patients who developed weight loss of ≥ 10% from 0–3 months post-transplant had similar 2-year OS compared to those who did not: 55.7% vs. 62.8% (HR = 1.38 [95% CI: 0.92–2.06], p = 0.11). Patients who developed weight loss of ≥ 10% from 0–6 months post-transplant also had similar 2year OS compared to those who did not (71.1% vs. 77.2%, HR = 1.37 [95% CI: 0.78–2.41], p = 0.27, Table 2 and Fig. 1A). In multivariate analysis, OS was not significantly different for those who had weight loss of more than 10% from 0–3 months post-transplant (HR = 1.33 [95% CI: 0.87–2.03], p = 0.184). Overall survival trended towards lower for those who experienced weight loss of 10% or more from 0–6 months post-transplant (HR = 1.70 [95% CI: 0.94–3.08], p = 0.079, Table 3).

Table 2
Overall survival (OS), relapse free survival (RFS), transplant related mortality (TRM), CI: confidence interval, HR: hazards ratio, N.A.: not applicable.

Overall Survival			
Group	Event/Total	2 year OS (%, 95% CI)	HR (95% CI), P value
All patients	141/288	52.1 (46.6–58.2)	N.A.
0–3 months weight loss			
≥10% weight loss	38/79	55.7 (45.7–67.8)	1.38 (0.92–2.06), p = 0.11
<10% weight loss	63/167	62.8 (55.9–70.7)	Reference
0–6 months weight loss			
≥10% weight loss	19/59	71.1 (60.5–83.7)	1.37 (0.78–2.41), p = 0.27
<10% weight loss	33/133	77.2 (70.3–84.7)	Reference
Relapse Free Survival			
Group		2 year RFS (%, 95% CI)	HR (95% CI), P value
All patients	166/288	45.9 (40.4–52.0)	N.A.
0–3 months weight loss			
≥10% weight loss	43/79	48.1 (38.3–60.5)	1.26 (0.87–1.83), p = 0.22
<10% weight loss	77/167	55.8 (48.7–63.9)	Reference
0–6 months weight loss			
≥10% weight loss	24/59	62.7 (51.5–76.3)	1.29 (0.78–2.11), p = 0.31
<10% weight loss	45/133	69.8 (62.3–78)	Reference
TRM			
Group		2 year TRM (%, 95% CI)	HR (95% CI), P value
All patients	80/288	27.7 (23.0–33.4)	N.A.
0–3 months weight loss			
≥10% weight loss	29/79	35.4 (26.3–47.8)	2.39 (1.43–3.98), p = 0.0007
<10% weight loss	28/167	16.9 (12.1–23.7)	Reference
0–6 months weight loss			
≥10% weight loss	14/59	22 (13.6–35.8)	3.1 (1.42–6.76), p = 0.0034
<10% weight loss	11/133	8.3 (4.7–14.7)	Reference

Table 3
Multivariate analysis of the association between weight loss and outcomes. OS: overall survival, RFS: relapse-free survival, TRM: transplant related mortality, BMI: body mass index, GVHD: graft-vs-host-disease, KPS: karnofsky performance scale, aGVHD: acute graft-vs-host disease, MRD: matched related donor, URD: unrelated donor, HID: haploidentical donor, cGVHD: chronic graft vs-host disease

	OS	*RFS*	*TRM*
Weight loss: 3 months (P-value)	0.89	0.37	0.015
BMI at SCT (Overweight/Obesity vs underweight/normal)	0.02	0.93	0.11
GVHD prophylaxis (ATG-PTCy-CSA vs others)	0.03	-	-
KPS (90/100 vs 70/80)	< 0.001	< 0.001	0.007
aGVHD (gut)	0.18	0.06	< 0.001
Age (≥ 60 vs < 60)	-	-	0.002
Donor type			0.004
- MRD vs Haplo	-	-	0.54
- URD vs Haplo	-	-	0.004
Weight loss: 6 months (P value)	0.079	0.50	0.004
BMI at SCT	0.99	0.90	0.21
KPS (90/100 vs 70/80)	0.02	0.027	0.25
cGVHD (gut)	0.13		0.10
Diagnosis (AML vs others)		0.013	
Age			0.007

Relapse Free Survival

We next examined the relationship between weight loss and RFS. For all patients, the median 2year RFS rate was 45.9% (95% CI: 40.4–52.0). Patients who developed weight loss of ≥ 10% from 0–3 months had similar 2-year RFS compared to those who did not (48.1% vs. 55.8%, HR = 1.26 [95% CI: 0.87–1.83], p = 0.22). Similarly, there was no statistical significance in 2-year RFS in those who developed weight loss of ≥ 10% from 0–6 months post-transplant compared to those who did not, 62.7% vs 69.8% (HR = 1.29 [95% CI: 0.78–2.11], p = 0.31, Table 2). In multivariate analysis, weight loss ≥ 10% vs < 10% was not statistically significant for RFS at both 0–3 months (HR = 1.19 [95% CI: 0.81–1.76], p = 0.374) and 0–6 months post-transplant (HR = 1.2 [95% CI: 0.70–2.05], p = 0.506, Table 3).

Transplant Related Mortality

We then examined the relationship between weight loss and TRM. For all patients, the 2year TRM rate was 27.7% (95% CI: 23.0-33.4). Patients who developed weight loss from 0–3 months post-transplant of ≥ 10% had significantly higher TRM, 35.4% vs. 16.9% (HR = 2.39 [95% CI: 1.43–3.98], p = 0.0007). Those who developed weight loss of ≥ 10% from 0–6 months post-transplant also had higher TRM compared to those who did not, 22% vs. 8.3% (HR = 3.1 [95% CI: 1.42–6.76], p = 0.0034, Table 2). In multivariate analysis, patients with weight loss of ≥ 10% had significantly higher TRM at both 0–3 months (HR = 1.91 [95% CI: 1.13–3.22], p = 0.015) and 0–6 months post-transplant (HR = 3.29 [1.47–7.35], p = 0.004, Table 3, Fig. 1a/b).

Discussion

The present study has found that patients with weight loss at 3- and 6-months post transplant were associated with increased TRM which remained significant in multivariable analysis when other competing factors such as gut GVHD were included. First, the increased TRM in the subgroup of patients with weight loss ≥ 10% could be attributed to malnourishment. While nutritional status is a known risk factor for metabolic and endocrine disorders [17], there is also emerging data supporting poor immune reconstitution secondary to nutritional status and alternations of the gut microbiome [18, 19], placing patients at higher risk for infections. Furthermore, prolonged periods with no oral intake have been associated with acute GVHD, potentially related to changes in gut permeability, cytokine production, and disturbance of the gut microbiome [20].

There may be a correlation between certain underlying diseases and weight loss related outcomes. Although not explored in this study, research has shown that patients with AML and MDS who lose weight prior to allogeneic HSCT have inferior outcomes [7, 21]. These findings highlight the importance of early intervention and collaboration with referring physicians to limit as much weight loss as possible during induction treatment, as well as to optimize patients' nutritional status prior to transplantation.

Our study also found that obese patients were more likely to experience weight loss post-transplant. This is not surprising given the greater impact of reduced calorie intake in this cohort; however, obesity is typically associated with comorbidities that may have impacted the increased TRM in the weight loss group. Higher weight-based chemotherapy may also increase TRM due to correspondingly higher toxicity. Nevertheless, the number of obese patients in the current study was relatively low, so it is difficult to translate its clinical significance. Further studies should be performed to examine outcomes on obese patients post-transplant with a larger sample size.

Reduced oral intake post-transplantation leading to weight loss is a common occurrence. Causative factors in this setting are typically related to xerostomia, oral pain, dysgeusia and nausea [22]. Previously studied risk factors for GI toxicity include prolonged oral mucositis, and myeloablative conditioning regimens [2]. Further, it is remarkable that only 7.3% of patients received MAC, but despite this, more than 45% experienced ≥ 10% weight loss. Clinical implementations to address weight loss and inadequate nutrition should centre around increasing supportive care strategies to help mitigate these risk factors. Symptom management and supportive care is an important aspect of post allogeneic HSCT, as these

patients tend to experience high symptom burden which can impact overall recovery [23]. Strategies should include the involvement of specialist palliative care input to help alleviate symptoms related to weight loss as well as coping strategies, which is imperative given that weight loss, oral complaints and reduced appetite have a negative impact on quality of life [24, 25]. With this specialized approach to addressing symptom management, along with the use of coping strategies, other long-term outcomes related to overall physical function and psychological wellbeing may be improved [26].

Though there is a general consensus that nutritional support during allo-HSCT is required, studies have shown that standard clinical practice varies greatly amongst institutions [4], and particularly in those patients who have gastrointestinal GVHD [27]. The use of enteral and parental nutritional support proves to be significantly different depending on the age of patient, country of practice and knowledge and availability of nutritional experts [28]. It has been shown that early enteral nutrition has had a positive impact on transplant related outcomes including GVHD, perhaps due to the maintained intestinal microbiome which has been shown to be a protectant [29]. Nevertheless, there is no question that early nutritional interventions can improve outcomes post allo-HSCT, particularly those associated with weight loss demonstrated in this study. Further trials are needed comparing enteral and parental nutrition in the post allo-HSCT setting.

The limitations to our study are its single centre, retrospective design. Our study lacked other markers of nutrition such as serum proteins which may be important factors given that studies have shown serum protein and severe albumin deficiency were associated with increased non-relapse mortality [30]. Furthermore, we did not have specific nutritional strategies used to mitigate weight loss available for evaluation, such as enteral or parental nutrition, to include in our analysis. We also acknowledge that there are many confounding factors such as corticosteroid use, which can alter weight loss and gain patterns. Lastly, we were unable to assess other important factors such as degrees of nausea, mucositis and dysgeusia experienced by patients that may have affected their oral intake, and thus weight loss patterns.

Allogeneic HSCT remains the standard of care treatment for many malignant and non-malignant hematological disorders. Although many advances have been made, this potentially curative treatment comes with risks of toxicity and chronic sequelae requiring careful attention. We have shown that reducing transplant mortality requires a multifaceted approach[31] as we showed in a recent study performed at our institution which examined newly implemented strategies to reduce transplant-related complications. One of the dimensions prioritized was supportive care, with a large emphasis on oral intake and the use of calorie intake programs and highlighted the importance of close partnerships with dieticians and supportive care colleagues. This reinforces that various factors, including weight loss and nutritional status can contribute to patient overall safety and improve transplant related outcomes. Multimodal approaches including exercise therapy and nutrition have also proved to be safe and feasible for allo-HSCT patients [32] and this is an area to be focused on going forward. More prospective studies are needed to examine specific strategies to address this potentially modifiable risk factor.

Abbreviations

ATG: antithymocyte globulin, BM: bone marrow, Bu: busulfan, CsA: cyclosporine, Flu: fludarabine, GVHD: graft-vs-host disease, KPS: karnofsky performance scale; TBI: total body irradiation, MTX: methotrexate, PBSC: peripheral blood stem cells, PTCy: post-transplant cyclophosphamide

Declarations

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Ethics Approval. This study was approved by the Cancer Registry Data Access Committee (CRDAC) and the Research Ethics Board of the University Health Network/Princess Margaret Cancer Centre conducted in accordance with the principles of the Declaration of Helsinki.

Consent to Participate. As this study was a retrospective review, participants' consent was waived by previously stated Research Ethics Board of the University Health Network/Princess Margaret Cancer Centre.
Consent for Publication. N/A

Availability of Data and Materials. The data that support the findings of this study are available from the corresponding author, [J.M], upon reasonable request.

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Figures

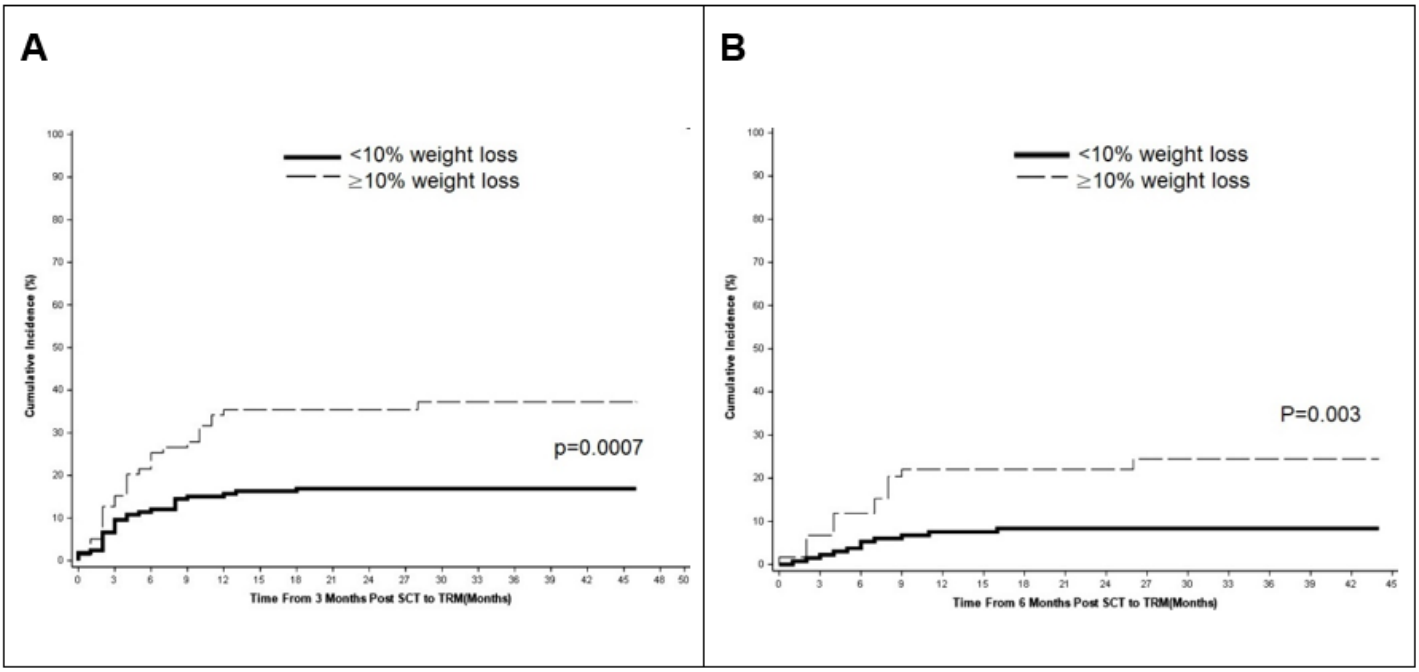

Figure 1

Cumulative Incidence of Transplant Related Mortality (TRM) stratified by weight loss: **A:** Weight Loss at 3 Months **B:**Weight Loss at 6 Months