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Moderate or Severe Valvular Heart Disease and Outcomes in Allogeneic Stem Cell Transplantation

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Abstract

Background: A Hematopoietic Cell Transplantation-Specific Comorbidity Index (HCT-CI) was previously developed showing that multiple comorbidities including moderate or greater valvular heart disease to be predictors of non-relapse mortality after allogeneic HCT. However, detailed description of the impact of valve disease on outcomes is lacking.

Methods: Among a large cohort of patients given allogeneic HCT between 2000-2017, we identified 21 patients with moderate or severe valvular disease. We also identified a cohort of 42 controls matched on age and HCT-CI score. The primary outcome was all-cause mortality, with censoring at two years of follow-up. Secondary outcomes included mortality without relapse, duration of index admission, number of readmissions, increase in creatinine and peak troponin.

Results: Non-myeloablative regimens were more common in the valve disease cohort compared to controls (86% vs 54%p=0.012). Valvular disease was associated with increased all-cause mortality with adjusted hazard ratio of 2.17 (CI 1.08-4.34, p= 0.029) and for non-relapse mortality with adjusted hazard ratio of 2.53 (CI 1.16-5.52, p = 0.020). In the valve disease cohort, creatinine increased by 1.6 vs 0.9 mg/dL (p = 0.003) and peak troponin by 1.6 vs 0.3 ng/mL (p = 0.05) compared to controls. There was no difference in readmissions or length of stay when accounting for outpatient treatment.

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Conflicts of Interest: None

Conclusions: Despite having similar pre-procedure risk factors and undergoing less aggressive chemotherapy regimens, patients with moderate valvular disease or greater, most of whom did not meet current guideline recommendations for repair, had worse non-relapse related outcomes with higher mortality, renal and myocardial injury.

Keywords

Valvular heart disease; cardio-oncology; allogeneic stem cell transplantation

Introduction

There is a considerable body of evidence on the evaluation of patients undergoing noncardiac surgery in an effort to reduce medical complications, most of which involves evaluation and reduction of cardiovascular risk factors. Many patients undergo preoperative imaging, stress testing, and potentially revascularization prior to surgery, and this is generally supported by the ACCF/AHA perioperative cardiovascular evaluation guidelines. Current guidelines also provide a Class I, Level of Evidence C recommendation that patients who meet standard indications for valvular intervention should be considered for repair or replacement before elective noncardiac surgery to reduce perioperative risk [1].

There is much less evidence and guidance for the preprocedural management of cardiovascular disease prior to stem cell transplantation. The Hematopoietic Cell Transplantation Specific Comorbidity Index (HCT-CI) is a risk model for non-relapse mortality after stem cell transplantation. It includes a broad range of comorbidities suggestive to predict adverse outcomes such as active infection, autoimmune disorders, liver and kidney dysfunction. It also includes a broad range of cardiovascular conditions such as prior coronary artery disease, atrial or ventricular arrhythmias, and valvular disease. In this model, valvular disease was defined very broadly as moderate or worse stenosis or regurgitation at any location [2]. While it was clear from the data that patients with valve disease were at risk for non-relapse mortality, the precise degree of risk was unclear. The model assigned a risk score of 3 to valvular disease and noted more than two-fold higher mortality for an HCT-CI ≥ 3 compared to an HCT-CI of 0. It also included a small number of patients with valvular disease as it was published in 2005. In the current study, we sought to determine the precise risk of mortality as well as other adverse outcomes in patients with valvular disease compared to risk-matched controls. after accrual of additional subjects.

Methods

Our institution maintains a database of all patients that have undergone allogeneic stem cell transplantation since 2000. Informed consent was obtained from each patient and the study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institution's human research committee. A retrospective chart review was performed on these patients to identify those who had an echocardiogram prior to undergoing allogeneic stem cell transplantation where moderate or severe valvular disease (stenosis or regurgitation) was identified at any valve location. Echocardiogram findings were confirmed by a level III certified echocardiographer. Additional comorbidities were

identified retrospectively by chart review and used to calculate the HCT-CI score. From this database, age and HCT-CI matched controls were identified at a 2:1 ratio. Matched controls were chosen with an HCT-CI score 3 less than the controls to account for the presence of valve disease. Control echocardiograms were reviewed if present and confirmed to have an absence of moderate or severe valvular disease. The assessment of valve severity was done using standard metrics identified in the American Society of Echocardiography guidelines [3]. Ventricular chamber dimensions, the presence of systolic dysfunction by Simpson's Biplane Ejection Fraction and estimated pulmonary artery pressure by tricuspid regurgitation velocity and inferior vena cava collapse were also noted. Right ventricular dysfunction was defined as moderate or severe as determined by the interpreting physician. The indication for stem cell transplantation was noted by chart review as well as whether or not the pre-transplant chemotherapy regimen was myeloablative vs nonmyeloablative, as it would be expected that patients undergoing a myeloablative regimen would have a higher risk of morbidity in the post-transplant period due to pancytopenia.

The primary endpoints of this study were all cause mortality and non-relapse mortality. This was adjudicated by the lead oncologist involved in the study. Additional clinical outcomes assessed included length of hospitalization after transplantation and number of readmissions in the following two years after transplantation. For length of index hospitalization, this was estimated in duplicate: (1) Patients who received outpatient myeloablation and transplantation were excluded in the first analysis, and (2) the analysis with repeated including outpatient cases, setting length of index hospitalization to zero days. Baseline creatinine and troponin were obtained prior to stem cell transplantation and compared to peak values measured in the subsequent two years after transplant. The charts were also reviewed for a diagnosis of pulmonary edema, multifocal pneumonia or pneumonitis as it was hypothesized that the presence of valvular disease may precipitate pulmonary edema. Other cardiovascular complications such as arrhythmias or suspected shock were also noted.

Student's T-test was used to assess baseline continuous variables as well as peak differences in creatinine and troponin, after assessing for normal distributions. Categorical baseline variables and percent of patients who developed multifocal pulmonary complications were analyzed using a chi-squared test. Cox Proportional Hazards Models were used for survival time analysis for all-cause mortality, non-relapse mortality. Hazard ratios were adjusted to age and HCT-CI score, myeloablative regimen and baseline creatinine. Cumulative incidence curves were created for all-cause mortality and non-relapse mortality, with log-rank comparison between curves. Zero-truncated Poisson regression was used to assess differences in length of stay and number of readmissions. P-values were considered significant for < 0.05 with a confidence interval of 95%. Means are displayed along with standard error. Analysis was performed using STATA SE 13 (StataCorp LLC, College Station, Texas)

Results

From 2000-2017, N = 21 patients were identified with valvular disease and compared to N = 42 controls from a database of 2298 patients. Baseline characteristics of each group including aggregate HCT-CI score and additional echocardiographic metrics are shown in

Table 1. Of note, HCT-CI score in the control group was lower (6.8±0.9 vs 3.9±0.4, p<0.001) as designed by the study, to take into account the score of assigned to patient's with valvular heart disease in HCT-CI and assure equalization of other comorbidities. The majority of patients in each arm underwent stem cell transplantation for acute myelogenous leukemia. A larger proportion of patients with valvular heart disease (86%) underwent non-myeloablative regimens compared to controls (54%, p = 0.012) The echocardiographic features were similar other than an increase in both left ventricle and right ventricle chamber size in the valve group. The features of the valvular disease in the case patients are noted in Table 2, as well as documented cardiovascular complications noted in available documentation.

The cumulative incidence curves for all-cause mortality and non-relapse mortality are shown in Figure 1 and results of the regression analysis shown in Table 3. Unadjusted hazard ratio for all-cause mortality was 2.29 (CI 1.2-4.1, p = 0.006). Adjusted hazard ratio for all-cause mortality was 2.16 (CI 1.1-4.3, p = 0.029). Unadjusted hazard ratio for non-relapse mortality was 2.63 (CI 1.4-5.0, p = 0.003). Adjusted hazard ratio for non-relapse mortality was 2.53 (CI 1.1-5.2, p = 0.02). 24% of the patients with valve disease were alive 1 year after transplantation, compared with 64% of control patients.

The results for the duration of index admission and number of readmissions are shown in Table 3. As shown, when the outpatient cases were censored, there was a longer length of stay in the control group compared to cases. However, when outpatient cases were included, there was no difference in length of stay. There was no significant difference in the number of readmissions.

Difference between peak and baseline troponin in the control group was 0.23±0.09 ng/dL compared with 1.62±0.61 ng/dL in the valve group (p = 0.02). Difference between peak and baseline creatinine in the control group was 0.89±0.11 mg/dL in the control group compared with 1.64±0.24 mg/dL in the valve group (p = 0.001). 38% of patients in the control group had a diagnosis of a multifocal pulmonary process outlined above as compared to 66% of the valve group. (p = 0.03).

Discussion

This relatively small case-control study highlights valve disease as a potentially under-recognized risk factor for hemodynamic deterioration and mortality in patients undergoing stem cell transplantation. The majority of patients in this study had moderate valve disease, and none of them clearly met criteria for valve replacement by the most recent valve guidelines. Yet they suffered from more than a two-fold higher mortality than patients without valve disease after stem cell transplantation. This is important because in many instances, moderate severity valvular disease is overlooked as a potential risk factor by cardiologists since it would not reach the threshold for intervention by current guidelines.

The increased mortality in the valve cohort is not surprising, but the degree of excess mortality is alarming. Patients with moderate mitral regurgitation have an annual mortality of approximately 3% [4]. Findings were similar for moderate aortic stenosis [5]. The annual

mortality of moderate tricuspid regurgitation has been reported at even higher than this at 20% [6]. Yet the current study suggests that this patient population, when undergoing stem cell transplantation, had a 76% annual mortality. While serial echocardiographic and hemodynamic data were not available, the consistently abnormal elevations in troponin and creatinine suggests these patients were much more prone to hemodynamic instability in the post-transplant period. Furthermore, the higher rates of diagnosed multifocal pneumonia or pneumonitis in the valve disease cohort raises the question of underdiagnosed pulmonary edema, which certainly fits with the pathophysiology of valve disease.

The increased risk of hemodynamic instability after stem cell transplantation is not surprising. The prolonged immunosuppressed and cytopenic state these patients frequently experience result in high risk of infection and sepsis. The inflamed and hypermetabolic state would presumably put the body in a state of very high demand, much higher than would be expected in otherwise healthy individuals or even those in the postoperative state. The valve abnormalities, which under normal circumstances would have mild or inconsequential effects on hemodynamics, could severely impair the heart's ability to meet these demands. Furthermore, standard management protocols would result in high use of intravenous fluids and a high preload state, which would be expected to further exacerbate hemodynamic abnormalities with regurgitant valvular lesions. Thus, it should be important to recognize that these patients are at high risk of cardiogenic shock and pulmonary edema as well as vasodilatory shock and inflammatory/infectious causes of respiratory compromise. Taking these into consideration as well as closer monitoring with hemodynamic monitoring or at the very least cardiology consultation could improve outcomes overall.

Based on our data, we would recommend pre-stem cell transplant cardiology consultation with discussion of risk in patients with moderate or severe valvular heart disease. In the post-stem cell transplant period, we recommend close monitoring of volume status. For cases of shock, it should not be assumed to to be a vasodilatory or infectious process and consideration for hemodynamic instability from a cardiac cause must be higher on the differential in this cohort, and cardiology shoul be consulted if the clinical picture is still uncertain. These patients would benefit from intensified observation with a higher threshold for early discharge, and close follow-up with cardiology as an outpatient.

Current valvular guidelines and their recommendations for intervention based on severity aim to strike a balance between progressive morbidity and mortality of the valve lesion itself and the complications of undergoing valve replacement [7]. All things being equal, the very high mortality of valve disease patients undergoing stem cell transplantation might suggest that they would derive benefit from earlier intervention. Traditional surgical valve replacement would make this an unattractive prospect, however. Patients with hematologic malignancies may have significant cytopenias and coagulation abnormalities that would make them unattractive surgical candidates due to propensity for bleeding, infection and poor wound healing. Also, the emergent nature of stem cell transplantation for many hematologic malignancies means that delaying transplantation to undergo valve surgery along with a recovery period of at least several weeks could further worsen malignancy-related outcomes. The advancement of catheter-based interventions for valvular heart disease over the past several years would mitigate many of these concerns, as the recovery

times are much quicker with minimal blood loss and minimal wound healing. The presence of new prosthetic material could increase risk of endocarditis, however and this would need to be taken into consideration as well if deciding to intervene.

When adjusting for the fact that many of the transplantations were done as an outpatient procedure, there was no clear difference in duration of index hospitalization, nor the number of readmissions between the two groups. This likely reflects improvements in safety of the stem cell transplantation procedure overall as well as the high mortality of subsequent readmissions. Patients with valve disease did not seem to have immediate hemodynamic deterioration after stem cell transplantation, probably because many of them underwent less aggressive chemotherapy and non-myeloablative regimens. They also could have been less likely to undergo multiple readmissions as would be expected with heart failure, and more likely to have a few readmissions with very high mortality.

The presented study has several major limitations. It is a small, heterogeneous patient population with mixed physiology. The small number of patients with any specific valvular lesion limits the ability to analyze them individually. It was a retrospective study performed on a data registry not designed for cardiovascular outcomes. Therefore, none of the studied patients had a standardized assessment of hemodynamics after transplantation, so the exact pathophysiology of the excess mortality is unknown. Troponin levels were not routinely monitored, and both groups suffer from missing data. The registry was designed to follow mainly oncologic-related outcomes and outside hospital events related to cardiovascular complications are not available. It is not possible from this data to determine if either medical or surgical intervention has any effect on this high mortality, so it should not be implied based on this data alone that patients with moderate valvular disease should undergo surgical or transcatheter valvular interventions. Many of the patients in the control group did not have pre-procedure echocardiograms reported in the chart and likely had screening with radionuclide angiography only. We are also unable to comment on the potential role of chemotherapy related cardiomyopathy or radiation induced heart disease due to the limited number of cases.

An ideal next step from this data would be to pool data from multiple registries to improve statistical power within the valvular subgroups and define which specific lesions have the highest risk of adverse outcomes. From there, either randomized or nonrandomized studies on medical or surgical management of these patients could begin. If it could be shown that transcatheter intervention on a lesser degree of valvular disease than currently recommended in the guidelines improves mortality prior to stem cell transplantation, it could represent a major paradigm change in the management of these patients.

Conclusion

Patients with moderate or severe valvular heart disease experience a significantly higher non-relapse mortality when undergoing stem cell transplantation compared to control patients with otherwise similar risk. This excessive mortality is co-associated with increased risk of renal injury, myocardial injury and pulmonary complications. This risk should be considered in the risk-benefit analysis when deciding whether or not to pursue

transplantation. Further studies are needed to determine if intervention prior to transplantation can mediate peri-transplant risk.

Acknowledgments

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Highlight

- Valve disease increases mortality in stem cell transplantation.
- It also increases troponin, creatinine, and pulmonary complications.
- Patients may benefit from valve intervention prior to transplantation.

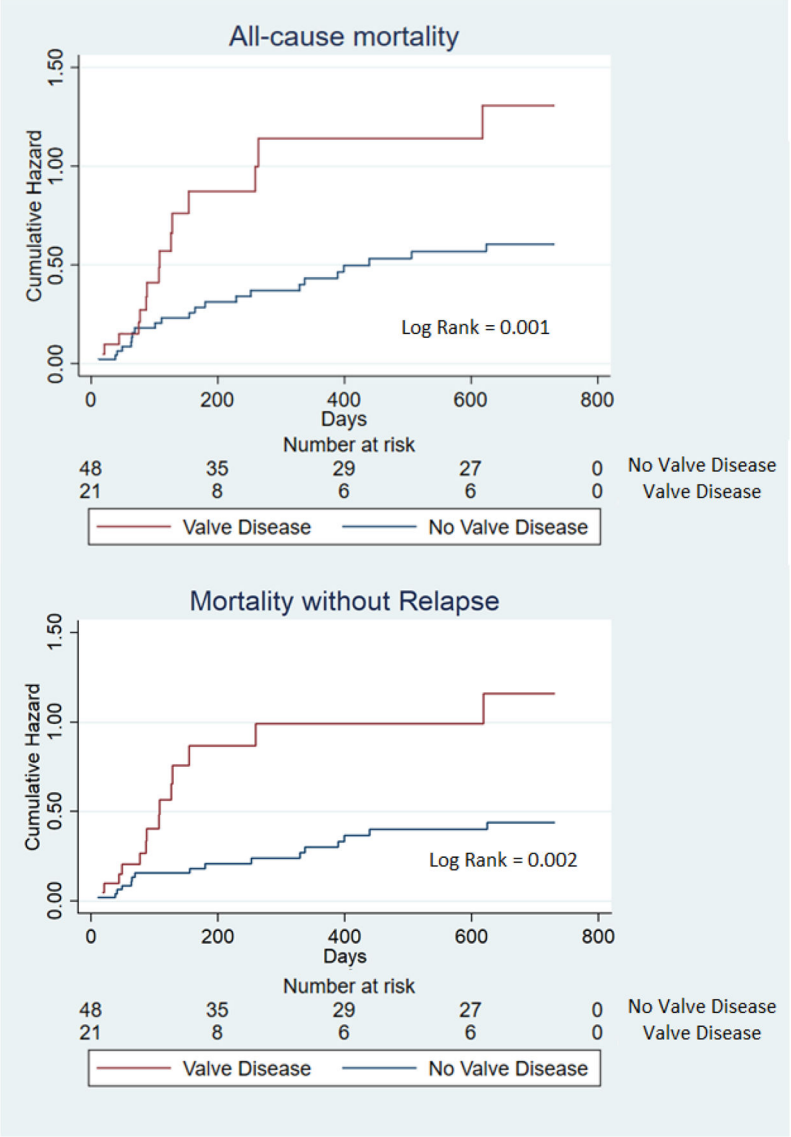

Figure 1. Cumulative hazard curves.

Curves for all-cause mortality and mortality without relapse, adjusted for age, hematopoetic stem cell comorbidity index, baseline creatinine and myeloablative regimen.

Table 1

Baseline patient characteristics

	Valve Patients *n* (%)	Controls *n* (%)	P-value
All patients	21	42	
Median age, *yrs*	59	58	0.79
HCT-CI score	6.8	3.9	<0.001
Malignancy			
AML	12 (57)	24 (57)	
NHL	2 (10)	10 (24)	
MDS	0 (0)	4 (10)	
Myelofibrosis	4 (21)	0 (0)	
ALL	0 (0)	3 (7)	
CLL	1 (5)	0 (0)	
HL	0 (0)	1 (2)	
MM	1 (5)	0 (0)	
Scleroderma	1 (5)	0 (0)	
Aplastic anemia	0 (0)	1 (2)	
Myeloablative regimen	3 (14)	22 (52)	0.002
Ejection fraction	58	60	0.16
End diastolic dimension, *mm*	52	47	0.02
Wall thickness, *mm*	10	10	0.96
Systolic pulmonary artery pressure, *mmHg*	37	32	0.27
Wall motion abnormalities	2 (10)	3(7)	0.7
Right ventricle dimension, *mm*	3.9	3.5	0.02
Right ventricular dysfunction	2 (10)	1(2)	0.22
Baseline creatinine, *mg/dL*	0.87	0.82	0.57
Baseline troponin, ng/dL	0.14	0.09	0.19

ALL: acute lymphoblastic leukemia, AML: acute myelogenous leukemia, CLL: chronic lymphoblastic leukemia, HCT-CI: Hematopoetic Cell Transplantation Comorbidity Index, HL: Hodgkins lymphoma, MDS: myelodysplastic syndrome, MM: multiple myeloma.

Table 2

Valve disease characteristics

Age	Valve Disease Severity	Valve Lesion	Valve Characteristics	CVD Comorbidities	Cardiovascular complications	History of Prior Radiation or Malignancy	Cause of Death
68	Severe	AS	AVA 2cm^2, peak velocity 2.97m/s, peak gradient 35.3, mean gradient 2.97mmHg, EF 66%				
69	Severe	AS	AVA 0.8cm^2, Peak velocity 4.5m/s, Peak Gradient 81mmHg, mean gradient 43mmHg, EF 67%		Cardiogenic shock, supraventricular tachycardia		Mixed septic and cardiogenic shock
66	Severe	MR	Bileaflet mitral valve prolapse, moderate-severe MR, normal PA pressures, EF 72%				
60	Severe	MR	Mitral Valve Prolapse, PAP 30mmHg, EF 55%				Hypoxic respiratory failure secondary to diffuse alveolar hemorrhage
60	Severe	TR	RAP 17mmHg, PAP 25mmHg, EF 71%	Pulmonary Hypertension, CAD	Heart Failure		Hypoxic respiratory failure
49	Moderate	AS	Aortic valve area 1.3 cm2, LVEF 65%, normal PA pressures		Myocardial infarction		Septic shock
63	Moderate	AS	AVA 2cm^2, peak velocity 2.81m/s, peak gradient 31.6mmHg, mean gradient 16.6mmHg, EF 50%		Atrial fibrillation		Pneumonia
48	Moderate	AS	AVA 1.3cm^2, peak velocity 3.6m/s, peak gradient 52mmHg, mean gradient 28mmHg, EF 61%			Prior radiation for lung mass	
62	Moderate	AS	Bioprosthetic valve, AVA 1.3cm^2, peak velocity 2.9m/s, peak gradient 35mmHg, mean gradient 20mmHg, EF 60%	Bioprosthetic valve		Prior localized radiation to groin, history of B-cell lymphoma	
66	Moderate	AS	Bicuspid aortic valve, AVA				

Age	Valve Disease Severity	Valve Lesion	Valve Characteristics	CVD Comorbidities	Cardiovascular complications	History of Prior Radiation or Malignancy	Cause of Death
			1.9cm^2, peak velocity 3.4m/s, peak gradient 45mmHg, mean gradient 22mmHg, EF 59%				
62	Moderate	AS			Non-ST elevation MI, Atrial fibrillation, LV dysfunction		Multiorgan dysfunction
68	Moderate	MR	PAP 30mmHg, EF 57%	Hypertrophic Cardiomyopathy	Hypotension		Septic shock
51	Moderate	MR	PAP 37mmHg, EF 55%	Mechanical valve, paravalvular leak, CAD	Atrial fibrillation, cardiogenic shock, endocarditis		Endocarditis, Cardiogenic shock
62	Moderate	MR	Mitral Valve Prolapse, PAP 35mmHg, EF 56%				
67	Moderate	MR	Bicuspid aortic valve, PAP 40mmHg, EF 40%	CABG, CAD, CHF			
61	Moderate	MR	PAP 20mmHg, EF 60%		Supraventricular tachycardia, hypotension	Germ cell seminoma treated with chemotherapy	Septic shock
60	Moderate	MS	PAP 20mmHg, EF 58%	Rheumatic heart disease, CAD	hypotension		Hypoxemic respiratory failure secondary ARDS and sepsis
58	Moderate	TR	RAP 5mmHg, PAP 35mmHg, EF 69%	Dysplastic pulmonic valve			
63	Moderate	TR	RAP 15mmHg, PAP 70mmHg, EF 59%	Pulmonary Hypertension			
50	Moderate	TR	RAP 10mmHg PAP 45mmHg, EF 55%	Pulmonary Hypertension	Atrial fibrillation, bradycardia, hypotension	Prior radiation	Hypoxic respiratory failure secondary to pneumonia
25	Moderate	TR	RAP 7mmHg, PAP 35mmHg, EF 52%			Prior radiation	Hypoxic respiratory failure secondary to diffuse alveolar hemorrhage

AS: Aortic Stenosis, AVA: Aortic Valve Area, CABG: Coronary Artery Bypass Graft, CAD: Coronary artery Disease, CVD: Cardiovascular Disease, EF: Ejection Fraction, MR: Mitral regurgitation, MS: Mitral Stenosis, PAP: Pulmonary Artery Pressure, RAP: Right Atrial Pressure, TR: Tricuspid Regurgitation

Table 3

Cox and Poisson Regression Results of Mortality and Length of Stay (LOS)

Event	Analysis Type	Ratio	95% CI	P-value
All-cause mortality	**Cox regression**	**HR**		
Unadjusted		2.287	1.26329–4.140743	0.006
Adjusted*		2.166	1.080587–4.340263	0.029
Mortality without relapse	**Cox regression**			
Unadjusted		2.632	1.377976–5.028911	0.003
Adjusted*		2.532	1.15949–5.527612	0.020
LOS, inpatient only (no mortality)	**Poisson regression**	**IRR**		
Unadjusted		0.740	0.6240688–0.8768374	0.001
Adjusted*		0.652	0.51525–0.8248377	0.000
LOS including outpatient = 0 (no mortality)	**Poisson regression**	**IRR**		
Unadjusted		0.931	0.785658–1.103876	0.412
Adjusted*		0.937	0.7499912–1.170634	0.567
Number of readmissions	**Poisson regression**	**IRR**		
Unadjusted		1.429	0.8988027–2.27272	0.131
Adjusted*		1.140	0.6475337–2.006209	0.650

Hazard Ratio (HR) and Incidence Rate Ratio (IRR) for all-cause mortality, non-relapse mortality, length of stay (LOS) and number of readmissions. Adjustments are made for age, Hematopoetic Stem Cell Comorbidity Index, myeloablative regimen and creatinine.