Published in final edited form as:
Bone Marrow Transplant. 2011 December ; 46(12): 1532–1539. doi:10.1038/bmt.2010.345.

Changes in echocardiographic measures of systolic and diastolic function in children 1 year after hematopoietic SCT

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Abstract

Hematopoietic SCT (HSCT) is a life-saving therapy in children, but has been associated with heart failure. Little is known about subclinical changes in cardiac function. We examined changes in systolic and diastolic function from pre- to 1-year post HSCT by echocardiography. All patients (*n* = 74, 61% men, median age 9.1 years, mean left-ventricular (LV) ejection fraction 61.3 ± 4.9%) who underwent HSCT at Children's Hospital Boston between 2005 and 2008, were <21 years at time of HSCT, and had routine pre- and 1-year post echocardiograms were included. Systolic function parameters, including LV ejection fraction, rate-corrected velocity of fiber shortening (Vcfc) and stress-velocity index and diastolic parameters, including tissue Doppler imaging (TDI)-derived velocities, and left-ventricular flow propagation, were compared before and after transplant. At 1-year post HSCT, systolic function, as measured by Vcfc (1.10 ± 0.15 vs 1.04 ± 0.12 circ/s; $P = 0.03$) and stress-velocity index (*z*-score 0.40 ± 1.4 vs –0.20± 1.1; $P = 0.02$), had worsened; diastolic function parameters, including mitral E′ velocity (16.6 ± 3.9 vs 15.0 ± 3.4 cm/s; $P = 0.01$) and tricuspid E′ velocity (14.3 ± 3.6 vs 12.4 ± 2.8 cm/s; $P = 0.002$) had also decreased. At 1-year post HSCT, children have subclinical declines in systolic and diastolic function. These small changes might become clinically important over time. Serial non-invasive assessment of cardiac function should be considered in all children following HSCT.

Keywords

pediatrics; SCT; cardiac function; diastolic function

Introduction

Hematopoietic stem cell transplant (HSCT) is a life-saving therapy for a variety of pediatric conditions, including cancer, BM failure syndromes and immunodeficiency syndromes.[1,2] The indications for HSCT are expanding and the number of transplants performed each year is increasing.[1] Thus, it becomes imperative to fully understand the long-term complications

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Conflict of interest The authors declare no conflict of interest.

associated with HSCT, particularly in children who receive this intensive treatment during periods of rapid physical growth and emotional development.[3–5]

Previously defined risk factors for heart failure following HSCT include pre-HSCT mediastinal radiation and the development of universal cardiovascular risk factors, such as obesity, dyslipidemia, hypertension and diabetes, following HSCT.[6] Allogeneic HSCT is associated with an increased incidence of combined cardiovascular, cerebrovascular and peripheral vascular arterial disease.[7,8] It is also well understood that there are long-term effects on cardiac function associated with pre-HSCT chemo- and radiation therapies. These effects are particularly well documented with anthracycline exposure.[9,10] In addition, cardiac function can be adversely affected by treatment with high-dose CY and TBI, the two most common conditioning therapies used in HSCT.[11–15]

Previous studies have examined parameters of systolic function in patients following HSCT and showed detrimental effects.[16–23] Diastolic dysfunction is an earlier manifestation of cardiac injury but has not been evaluated systematically after HSCT. Tissue Doppler imaging (TDI) has been suggested as an important area for study in patients after HSCT, particularly because it may show changes earlier than traditional cardiovascular outcome measures.[24] In particular, changes in early diastolic TDI-derived velocities have been shown to correlate with elevated left-ventricular (LV)-filling pressures, and are thought to be useful in early detection of cardiomyopathy.[25–27] In this study, we examined changes in measures of diastolic and systolic cardiac function by comparing pre-HSCT with 1-year post-HSCT echocardiographic findings. Our *a priori* hypothesis was that there would be a decrease in LV diastolic function, as measured by TDI at the lateral mitral annulus.

Patients and methods

Study design

We performed a single center, retrospective chart review of all pediatric patients (age <21 years old) who had undergone their first HSCT at Children's Hospital Boston/Dana-Farber Cancer Institute between 1 January 2005 and 15 December 2008. According to standard protocol, all patients undergo comprehensive echocardiographic assessment of systolic and diastolic function before HSCT and annually thereafter using Philips iE33 (Andover, MA, USA) or HP Sonos 7500 (Hewlett Packard Company; Palo Alto, CA, USA) echocardiographic equipment. Measurements were performed on the ultrasound machines and/or after the study using HeartSuite Vericis (Emageon; Birmingham, AL, USA) digital image management software. We included patients with a pre-HSCT echocardiogram performed at our institution 0–4 months before HSCT and a post-HSCT echocardiogram performed at our institution between 8 and 18 months following HSCT. If multiple studies were performed, the echocardiogram that included the required measurements performed closest to HSCT, and the 1-year post-HSCT follow-up date was selected. Patients with a history of complex congenital heart disease (defined as anything other than an isolated atrial septal defect, ventricular septal defect, and patent ductus arteriosus) were excluded from the study ($n = 1$). Patients who did not have either peak E′ wave velocity at the lateral mitral annulus or LV ejection fraction measured at two time points (pre-HSCT and 1-year post-HSCT) were excluded from the primary analysis. Baseline patient characteristics, information about known cardiac risk factors (including lifetime anthracycline dose and history of mediastinal radiation), HSCT characteristics and echocardiographic function data were collected from all eligible patients.

Patients undergoing tandem HSCT were included in the study as long as their first HSCT fell within the study period, and the pre- and 1-year post-HSCT echocardiographic data were available relative to their first transplant. Conditioning therapy, given either for the first or

second (tandem) transplant, was recorded as being given during the first transplant for the purpose of analysis.

Total lifetime anthracycline dose was corrected for the cardiotoxic potential of each drug by multiplying individual doses by a correction factor and summing the results as described in previous studies.[19] The following correction factors were used: 1 for doxorubicin, 0.75 for daunorubicin, 3 for idarubicin and 3 for mitoxantrone.[19]

End points—The primary end point was changed in tissue Doppler velocity (E′ and A′ waves) at the lateral mitral annulus from the pre-HSCT to the 1-year post-HSCT echocardiogram. We hypothesized that there would be a decrease in this measure of diastolic function during the first year after HSCT, despite the fact that TDI-derived velocities normally increase throughout childhood.[28]

The following secondary end points were also collected and analyzed: LV ejection fraction (a preload- and after-load-dependent measure of global systolic function), corrected velocity of circumferential fiber shortening (Vcfc) (an afterload-dependent measure of contractility corrected for heart rate), LV end diastolic dimension (a measure of LV dilation), LV end diastolic posterior wall thickness, LV mass, LV end diastolic volume, LV end systolic volume, LV wall stress (a measure of myocardial fiber stress), stress-velocity index (a load independent contractility index that adjusts for preload, afterload and heart rate; hereafter, referred to as LV contractility), stress-shortening index (a preload-dependent contractility index), mitral inflow velocities, LV flow propagation (an independent measure of early ventricular relaxation) and tissue Doppler velocities (E′, A′, and S′ waves) at the lateral mitral annulus, interventricular septum and lateral tricuspid annulus. Tissue Doppler velocities were measured from an apical four-chamber view with the pulse wave Doppler region of interest placed at the base of the heart in the specified locations.

Patients who died before 1 year follow-up—Echocardiographic, clinical and demographic data were collected for patients who died before 1-year follow-up. The primary cause of death was determined by chart review and the potential contribution of cardiac disease to mortality was assessed in this group of patients. The decision to compare pre-HSCT echocardiographic data between this group of patients and the study cohort was made *post hoc*.

The Children's Hospital Boston Committee on Clinical Investigation and the Department of Cardiology Scientific Review Committee approved the study protocol.

Statistical methods

Baseline characteristics, including age, sex, indication for HSCT, type of HSCT and stem cell source, of the study cohort were tabulated. Comparisons of normally distributed continuous variables were made using the two-group Student's *t*-test. When possible, echocardiographic variables were standardized for age or body-surface area by calculating *z*-scores (the number of s.d's above or below the predicted value) based on previously derived normative data.[10,29] Changes in measured and derived data from the pre-HSCT to the post-HSCT echocardiogram were compared using paired Student's *t*-test. Relationships between changes in E′ tissue Doppler velocity at the lateral mitral and lateral tricuspid annuli, and known or suspected cardiac risk factors, including total lifetime anthracycline dose and dose of HSCT-conditioning therapy were explored using linear regression analysis. Statistical analysis was performed using STATA 10.0 (StataCorp, College Station, TX, USA). All reported *P*-values represent two-sided tests. *P*-values were considered to be statistically significant at an alpha level of <0.05. As this was an exploratory analysis, we did not adjust for multiple testing.

Results

Study cohort

A total of 74 patients underwent their first HSCT at Children's Hospital Boston between 1 January 2005 and 15 December 2008, and met study criteria. Altogether, 166 patients underwent HSCT during the study period but did not meet study criteria; a total of 23 of these 166 patients were not included in the primary analysis because they died before 1-year follow-up.

Patient characteristics

The median age of the study cohort was 9.1 years (IQR 3.0–13.5; minimum 0.1, maximum 20.3), and 61% of the patients were male. Approximately 65% of the transplants performed were allogeneic. Of the 26 autologous transplants, 11 were tandem transplants. Leukemia was the most common indication for transplant in the study cohort (38%), followed by solid tumors (28%), benign hematological disorders (16%), lymphoma (11%) and immunodeficiency (7%). The study cohort was not significantly different, with respect to age, sex and indication, for HSCT from the 166 patients who received HSCT at our institution during the study period and did not have qualifying echocardiograms.

Pre-HSCT cardiac risk factors

Approximately 61% of the study cohort ($n = 45$) was exposed to anthracyclines before HSCT (Table 1), with a median equivalent dose of 120 mg/m^2 (minimum–maximum: 60–375 mg/m^2). Four patients (5.4%) in the cohort had been exposed to mediastinal radiation before HSCT, one patient was taking enalapril for a cardiovascular indication and six (8.1%) patients carried a cardiovascular diagnosis; These were anomalous origin of the right coronary artery from the ascending aorta above the sinotubular junction ($n = 1$), syncope ($n = 1$), tricuspid regurgitation ($n = 1$) and mild LV dysfunction ($n = 3$).

HSCT conditioning therapy

The most common conditioning regimen used in this cohort was CY (74%; $n = 55$) and TBI (53%; $n = 39$) at average doses of 3849 ± 1112 mg/m^2 and 1310 ± 230 cGy, respectively (Table 1). Conditioning regimens varied on the basis of indication for HSCT and type of transplant. Anti-thymocyte globulin (24.3%) was more commonly used in aplastic anemia and immunodeficiency disorders. Carboplatin (27.0%) and etoposide (35.1%) were more commonly used for treatment of solid tumors, particularly medulloblastoma and neuroblastoma. Full frequency information and mean dose received can be found in Table 1.

Changes in echocardiographic function measurements

Diastolic function—There was a statistically significant decrease in lateral mitral annulus E′ velocity from the pre-HSCT to the 1-year post-HSCT echocardiogram (16.7 ± 3.7 to 15.0 ± 3.5 cm/s; $P = 0.003$) but no difference in A′ velocity (Table 2). The tissue Doppler E′ velocity at the lateral tricuspid annulus also showed a statistically significant decrease from 14.3 ± 3.5 to 12.5 ± 2.7 cm/s ($P = 0.002$), whereas the A′ and S′ velocities at the lateral tricuspid annulus were not significantly different. None of the tissue Doppler velocities, measured at the base of the interventricular septum, were significantly different between the pre-HSCT and 1-year post-HSCT echocardiogram. Although our data show trends for decreases in the S′ velocities, none of these differences reach statistical significance.

LV flow propagation (Vp), a preload independent measure of early diastolic relaxation, decreased from 70.9 ± 23.6 to 61.2 ± 20.8 cm/s ($P = 0.04$) after HSCT (Table 2). Mitral E

and A wave peak= velocities in a small subset of patients did not show any differences between the pre-HSCT and 1-year post-HSCT echocardiogram.

Systolic function—There was no difference in LVEF from the pre-HSCT echocardiogram to the 1-year post-HSCT echocardiogram (61.2 ± 5.0 to 60.6 ± 5.4%; P = 0.45) (Table 2). LV fractional shortening z-score was also not significantly different. Age- and heart rate-corrected LV fiber shortening (Vcfc), a preload independent measure of myocardial performance, was significantly decreased by the 1-year post-HSCT echocardiogram (z-score –0.02 ± 1.8 to –0.62 ± 1.54; P = 0.03). LV contractility was significantly decreased between the two time points (LV contractility z-score: 0.39 ± 1.4 to –0.22 ± 1.09; P = 0.01). There was no difference in age-corrected LV end-systolic wall stress, systolic blood pressure, or diastolic blood pressure. Two-dimensional measurements of LV size were not significantly different between echocardiograms. Calculated three-dimensional volumes were also similar (data not shown).

Risk factors for changes in measures of systolic and diastolic function—Changes in E′ tissue Doppler velocity at the lateral mitral and lateral tricuspid annuli were modeled using linear regression analysis with known and suspected cardiac risk factors, including total lifetime anthracycline dose, dose of CY, and dose of TBI. No statistically significant associations could be found between these cardiovascular risk factors and differences in tissue Doppler velocities. Change in LV contractility was also modeled using the same group of known or suspected cardiac risk factors. No significant associations were found with LV contractility.

To explore the possible relationship between cumulative lifetime anthracycline dose and our outcome variables, a subgroup analysis of patients who had never received anthracycline chemotherapy was performed. This group of patients showed a statistically significant decrement in LV flow propagation (79 ± 21 to 54 ± 19.2 cm/s; P = 0.002), Vcfc z-score (–0.09 ± 2 to –1.08 ± 1.7; P = 0.04), and LV contractility z-score (0.47 ± 1.6 to –0.43 ± = 1.3; P = 0.05). Decreases in TDI-derived E′ velocity at the lateral mitral annulus and tricuspid annulus showed trends but did not reach statistical significance (Mitral E′: 17.2 ± 3.5 to 16.1 ± 4.0 cm/s; P = 0.26; tricuspid E′: 14.7 ± 4.5 to 12.8 ± 2.7 cm/s; P = 0.08).

Patients who died before 1-year follow-up

Cause of death—A total of 23 of the 240 patients, who received their first HSCT during the study period, died before 1-year follow-up. Of these deaths, one was due to unstable ventricular tachycardia, which occurred in the context of relapsed acute lymphoblastic leukemia. The most common cause of death was relapsed disease (n = 9), and the respiratory system was the most common primary organ system involved in the death (n = 9).

Baseline echocardiographic function in patients who died before 1-year follow-up—Pre-HSCT echocardiographic function measurements from the group of patients who died before 1-year follow-up were compared with the pre-HSCT function measurements of our primary study cohort (Table 3). As a group, the patients who died had a slightly lower pre-HSCT LVEF measurement compared with the patients in our primary study cohort (57.3 ± 5.7 vs 61.2 ± 5.0 P = 0.003). In addition, the tissue Doppler E′ peak velocity at the lateral mitral annulus was significantly lower in the group of patients who died before 1-year follow-up compared with the primary study cohort (14.0 ± 3.3 vs 16.5 ± 3.8 cm/s; P = 0.02). The remainder of the echocardiographic function measurements were not significantly different between patient groups.

Discussion

Our study showed that indices of systolic and diastolic ventricular function in children worsened during the first year after HSCT as compared with pre-transplant assessments. There were small but statistically significant changes in LV diastolic function, as measured by peak E′ tissue Doppler velocities and by LV flow propagation. In addition, there is also a modest decrease in systolic performance, as evidenced by change in LV contractility during the first year after HSCT. Of note, cumulative lifetime anthracycline dose did not correlate with the observed changes in function. We did not observe severe or life-threatening cardiotoxicity in our patient cohort.

Our finding of worsened measures of ventricular systolic function after HSCT is supported by previous studies. A prospective cohort study of 162 pediatric patients identified a 26% cumulative incidence of cardiac dysfunction (shortening fraction < 30%) over the first 5 years after allogeneic HSCT.[30] Furthermore, 5.5 years after transplant, children treated with HSCT and high-dose anthracycline (> 300 mg/m^2) had a cumulative incidence of symptomatic heart failure of 5.3%.[31] Although the percentage of patients with anthracycline exposure is similar between our study cohort and the two study populations above, the median lifetime anthracycline dose in our cohort is significantly lower (120 vs 300 mg/m^2).

In all of these studies, anthracycline exposure represents an important potential confounder of the results. Previous studies have clearly shown that 1 year following ALL diagnosis, LV contractility falls 0.5 *z*-scores below the population mean in patients treated with anthracyclines.[9] The population of anthracycline exposed patients shows an improvement in LV contractility and LVEF over the next 5 years. Beginning 6 years after ALL diagnosis, LV contractility undergoes a slow, progressive and irreversible decline because of the effects of chronically elevated wall stress.[9] Cancer patients typically undergo HSCT between one and three years after their original cancer diagnosis. Independent of new risk factors, this would place our patient cohort in the recovery portion of the curve for LV contractility. In this study, we showed that the observed changes in measures of systolic performance remained statistically significant in the subgroup of patients without exposure to anthracycline chemotherapy. As a result, the decrease in LV contractility that we observed is likely to be secondary to other risk factors, such as HSCT conditioning therapy.

Anthracycline exposure affects indices of diastolic function as well. Anthracycline chemotherapy is associated with acute decreases in E′ and S′ tissue Doppler velocities at the time of administration.[32] However, when anthracycline-exposed patients were studied at a median follow-up of 5 years, there was no difference in E′ velocity, measured at the interventricular septum and at the lateral mitral annulus.[33] In this study, measures of diastolic performance continued to show a trend towards decreased function in the subgroup of patients without exposure to anthracycline chemotherapy. Given these findings, we suspect that anthracycline exposure is not the sole factor associated with the changes in diastolic function observed in this report.

The current study has demonstrated that as a population, there are small but definite decreases in E′ tissue Doppler velocity, measured at the lateral mitral and tricuspid annuli, LV flow propagation and LV contractility. The decreases in E′ tissue Doppler velocity shown in this study likely underrepresent the true change given that tissue Doppler velocities normally increase as pediatric patients age.[28] Despite these measurable changes, it is important to note that we did not observe severe or life-threatening cardiotoxicity in our patient cohort. One patient who died before 1-year follow-up experienced an acute ventricular arrhythmia in the context of relapsed ALL.

Post hoc secondary analysis comparing pre-HSCT echocardiographic characteristics between patients who died before 1-year follow-up and our primary study cohort suggest that lower ejection fraction (57 vs 61%) and lower lateral mitral annulus E′ velocity (14.0 vs 16.5 cm/s) may be pre-HSCT risk factors for death. These data confirm that ejection fraction is an important predictor of post-HSCT cardiovascular complications, as other studies have previously reported.[13,14] In addition, it suggests that ventricular function and cardiovascular reserve should be carefully assessed before transplant. These data may be useful in selecting conditioning therapy and managing patients in the peri-transplant period. These data do not imply that low-ejection fraction or low lateral mitral annulus E′ velocity should be used as a contraindication to HSCT. In fact, there are multiple reports showing that it is safe for patients with low-ejection fraction to undergo HSCT.[22,34]

This survivor study is limited by its retrospective design and incomplete, non-random patient sampling. It is vulnerable to survivor bias and may underrepresent the true degree of cardiac dysfunction that occurs after HSCT. A number of HSCT patients could not be included in the analysis because of incomplete or absent echocardiographic data, leaving this study vulnerable to selection bias. In particular, the inclusion of patients who had multiple echocardiograms at Children's Hospital Boston may bias the study towards a group of sick patients who received closer follow-up at Children's Hospital Boston. The lack of appropriately modeled, age-corrected tissue Doppler normative data limits the ability to quantify age-related changes in our analysis. However, general trends in tissue Doppler velocities during childhood run opposite to the direction observed in this study, suggesting that age correction would only increase the magnitude of the observed differences.[28] The *a priori* definition of E′ and A′ tissue Doppler velocity at the lateral mitral annulus as the primary end point is a major strength of the study. This eliminates concern of increased alpha error because of multiple comparisons.

Taken together, the observed changes in echocardiographic measures of systolic and diastolic function seen in the first year after HSCT suggest that this group of patients warrants longitudinal screening for the development of a secondary cardiomyopathy. Careful clinical assessment and serial quantitative echocardiography, examining measures of both systolic and diastolic function, should be considered in all children following HSCT. Future, well-powered, prospective studies using clinical and echocardiographic end points are necessary to further delineate the long-term effects of HSCT on cardiac function in children.

Acknowledgments

Acknowledgment of research support: Dr Daly received salary support from a NIH training grant (T32 HL07572) while working on this study. Dr Chen is supported by the Children's Hospital Boston Department of Cardiology Translational Fund for Research in Cardiac Oncology. Dr Blume is supported by the Children's Hospital Boston Department of Cardiology Heart Failure/Transplant Research Fund. *Previously presented*: Young Investigator Oral Abstract Presentation, 2nd International Conference on Cardiomyopathy in Children, 13 May, 2010 in Bethesda, MD, USA.

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Table 1

Patient characteristics and conditioning regimen of the study cohort (*n* = 74) before HSCT and 1-year post HSCT

Patient characteristic	***Before HSCT***		***1-year post HSCT***		**P-*value***
	n	**%**	**n**	**%**	
Wt (kg), mean (*n* = 72)	34.9 ± 24.6		37.7 ± 25.1		0.03
Wt (z-score), mean (*n* = 73)	–0.11 ± 1.49		–0.21 ± 1.20		0.31
Height (cm), mean (*n* = 72)	125.3 ± 35.4		128.6 ± 34.8		0.008
Height (z-score), mean (*n* = 74)	–0.42 ± 1.16		–0.77 ± 1.17		<0.001
Hemoglobin (g/dl), mean (*n* = 71)	10.4 ± 1.4		12.3 ± 1.3		<0.001
Anthracycline exposure	45	60.8			
Median total lifetime dose (mg/m^2)	150 (120, 195)				
Min–max total lifetime dose (mg/m^2)	60–375				
Conditioning regimen					
CY	55	74.3			
Mean dose in pts receiving drug (mg/m^2)	3849 ± 1112				
TBI	39	52.7			
Mean dose in pts receiving therapy (cGy)	1310 ± 230				
Etoposide	26	35.1			
Mean dose in pts receiving drug (mg/m^2)	1806 ± 790				
Carboplatin	20	27.0			
Mean dose in pts receiving drug (mg/m^2)	1871 ± 329				
Anti-thymocyte globulin	18	24.3			
Mean dose in pts receiving drug (mg/kg)	77.7 ± 28.7				
Melphalan	18	24.3			
Mean dose in pts receiving drug (mg/m^2)	165 ± 21				
BU	11	14.9			
Mean dose in pts receiving drug (mg/kg)	17.5 ± 3.9				
Thiotepa	9	12.2			
Mean dose in pts receiving drug (mg/m^2)	4517 ± 4256				
Carmustine	5	6.8			
Mean dose in pts receiving drug (mg/m^2)	300 ± 0				

Patient characteristic	*Before HSCT*		*1-year post HSCT*		*P-value*
	n	**%**	**n**	**%**	
Cytarabine	5	6.8			
Mean dose in pts receiving drug (mg/m^2)	800 ± 0				
Prior mediastinal radiation	4	5.4			
Inotropic support after HSCT			5	6.8	
GVHD by 1 year			13	17.6	

Abbreviations: HSCT = hematopoietic stem cell transplant; Max = maximum; Min = minimum; pts = patients.

Mean ± s.d.; interquartile range displayed in brackets [25,75]; comparisons made by the paired Student's *t*-test.

Table 2

Echocardiographic characteristics of the study cohort (*n* = 74) before HSCT and 1-year post HSCT

Echocardiographic characteristic	*Before HSCT Mean ± s.d.*	*1-year post HSCT Mean ± s.d.*	P-*value*
Timing of echocardiogram relative to HSCT (months)	–0.7 ± 0.5	12.8 ± 1.6	
Heart rate, mean (*n* = 67)	94.6 ± 20.4	89.7 ± 20.0	0.05
Systolic BP (mm Hg), mean (*n* = 64)	104.7 ± 12.7	104.8 ± 15.4	0.98
Diastolic BP (mm Hg), mean (*n* = 64)	56.3 ± 10.2	59.4 ± 10.3	0.08
Parameters of systolic function			
LVEF (%), mean (*n* = 70)	61.2 ± 5.0	60.6 ± 5.4	0.45
LV fractional shortening (*z*-score), (*n* = 68)	–0.72 ± 1.20	–1.08 ± 1.31	0.06
Vcfc (*z*-score), (*n* = 64)	**–0.02 ± 1.80**	**–0.62 ± 1.54**	**0.03**
LV end systolic stress (*z*-score), (*n* = 60)	0.64 ± 1.84	0.72 ± 1.77	0.78
LV contractility (*z*-score), (*n* = 60)	**0.39 ± 1.40**	**–0.22 ± 1.09**	**0.01**
Stress-shortening index (*z*-score), (*n* = 60)	–0.08 ± 1.11	–0.41 ± 1.07	0.09
LV mass (g), (*n* = 66)	69.7 ± 43.8	66.6 ± 39.1	0.22
LV mass/volume ratio, (*n* = 67)	0.89 ± 0.16	0.86 ± 0.16	0.20
LV EDD (cm), (*n* = 68)	4.1 ± 0.9	4.1 ± 0.8	0.73
LV PWED (cm), (*n* = 66)	0.63 ± 0.16	0.65 ± 0.16	0.45
IVS ED (cm), (*n* = 56)	0.67 ± 0.17	0.66 ± 0.18	0.94
Parameters of diastolic function			
TDI Derived Velocities			
Lateral mitral annulus E′ (cm/s), (*n* = 60)	**16.7 ± 3.7**	**15.0 ± 3.5**	**0.003**
Lateral mitral annulus A′ (cm/s), (*n* = 56)	6.4 ± 2.1	6.3 ± 2.0	0.87
Lateral mitral annulus S′ (cm/s), (*n* = 60)	9.3 ± 2.5	8.7 ± 2.2	0.09
Septal E′ (cm/s), (*n* = 60)	11.4 ± 2.0	10.9 ± 2.1	0.10
Septal A′ (cm/s), (*n* = 57)	6.7 ± 1.8	6.2 ± 1.9	0.18
Septal S′ (cm/s), (*n* = 60)	7.5 ± 1.5	7.2 ± 1.2	0.10
Lateral tricuspid annulus E′ (cm/s), (*n* = 57)	**14.3 ± 3.5**	**12.5 ± 2.7**	**0.002**
Lateral tricuspid annulus A′ (cm/s), (*n* = 47)	10.4 ± 3.8	10.1 ± 3.2	0.59
Lateral tricuspid annulus S′ (cm/s), (*n* = 58)	12.4 ± 2.5	11.9 ± 2.2	0.25
LV flow propagation (cm/s), (*n* = 51)	**70.9 ± 23.6**	**61.2 ± 20.8**	**0.04**
Mitral A wave time (ms), (*n* = 27)	110.4 ± 24.4	108.2 ± 20.4	0.73
Mitral E wave peak vel (m/s), (*n* = 42)	0.87 ± 0.23	0.83 ± 0.21	0.34
Mitral A wave peak vel (m/s), (*n* = 37)	0.50 ± 0.12	0.49 ± 0.13	0.56
Mitral E decel time (ms), (*n* = 38)	135.8 ± 42.2	126.3 ± 40.8	0.37

Abbreviations: BP = blood pressure; Decel = deceleration; EDD = end-diastolic dimension; HSCT = hematopoietic stem cell transplant; IVSED = end-diastolic interventricular septal thickness; LVEF = left-ventricular ejection fraction; LV = left-ventricular; PWED = end-diastolic posterior wall thickness; TDI = tissue Doppler imaging; Vcfc = rate-corrected velocity of fiber shortening; Vel = velocity.

All comparisons made by paired Student's *t*-test. Comparisons with *P*-values <0.05 are highlighted in bold text.

Table 3

Comparison of pre-HSCT echocardiographic characteristics of HSCT recipients who died before 1 year compared with the study cohort, all of whom survived to 1 year

Echocardiographic characteristic	*Study cohort*		*Died before 1 year*		P-*value*
	n	*Mean ± s.d.*	n	*Mean ± s.d.*	
Heart rate, mean	69	96.1 ± 22.1	21	101.2 ± 28.1	0.38
Systolic BP (mm Hg), mean	68	104.1 ± 13.5	21	103.0 ± 10.3	0.73
Diastolic BP (mm Hg), mean	68	56.2 ± 11.3	21	60.7 ± 10.2	0.11
Parameters of systolic function					
LVEF (%), mean	**70**	**61.2 ± 5.0**	**21**	**57.3 ± 5.7**	**0.003**
LV fractional shortening (z-score)	71	–0.72 ± 1.18	21	–1.27 ± 1.10	0.06
Vcfc (z-score)	68	–0.01 ± 1.77	19	–0.92 ± 2.11	0.05
LV end systolic stress (z-score)	67	0.66 ± 1.90	19	1.17 ± 2.01	0.32
LV contractility (z-score)	67	0.48 ± 1.41	18	–0.06 ± 1.52	0.16
Stress-shortening Index (z-score)	67	0.02 ± 1.12	18	–0.37 ± 1.29	0.21
LV mass (g)	68	69.5 ± 44.1	21	65.6 ± 39.9	0.72
LV mass/volume ratio	69	0.89 ± 0.17	21	0.92 ± 0.25	0.54
LV EDD (cm)	71	4.1 ± 0.9	21	3.9 ± 1.0	0.40
LV PWED (cm)	71	0.63 ± 0.16	20	0.60 ± 0.20	0.98
IVS ED (cm)	63	0.62 ± 0.12	15	0.60 ± 0.10	0.44
Parameters of diastolic function					
TDI-derived velocities					
Lateral mitral annulus E′ (cm/s)	**63**	**16.5 ± 3.8**	**16**	**14.0 ± 3.3**	**0.02**
Lateral mitral annulus A′ (cm/s)	61	6.4 ± 2.0	14	6.7 ± 2.4	0.62
Lateral mitral annulus S′ (cm/s)	63	9.2 ± 2.6	16	8.9 ± 2.7	0.71
Septal E′ (cm/s)	63	11.3 ± 2.1	15	10.5 ± 3.0	0.22
Septal A′ (cm/s)	61	6.7 ± 1.9	12	6.1 ± 2.8	0.35
Septal S′ (cm/s)	63	7.4 ± 1.5	15	7.6 ± 2.6	0.76
Lateral tricuspid annulus E′ (cm/s)	60	14.2 ± 3.6	13	14.3 ± 4.7	0.98
Lateral tricuspid annulus A′ (cm/s)	52	10.4 ± 3.7	9	11.3 ± 7.1	0.55
Lateral tricuspid annulus S′ (cm/s)	61	12.3 ± 2.6	13	12.2 ± 2.8	0.89
LV flow propagation (cm/s)	56	70.5 ± 23.1	14	59.8 ± 18.2	0.11

Echocardiographic characteristic	*Study cohort*		*Died before 1 year*		P-*value*
	n	***Mean ± s.d.***	**n**	***Mean ± s.d.***	
Mitral A wave time (ms)	39	108.9 ± 22.6	10	110.9 ± 28.3	0.82
Mitral E wave peak vel (m/s)	55	0.88 ± 0.24	16	0.81 ± 0.14	0.29
Mitral A wave peak vel (m/s)	46	0.50 ± 0.12	14	0.49 ± 0.25	0.81
Mitral E decel time (ms)	49	132.7 ± 41.0	10	140.1 ± 32.5	0.59

Abbreviations: BP = blood pressure; Decel = deceleration; EDD = end-diastolic dimension; HSCT = hematopoietic stem cell transplant; IVS ED = end-diastolic interventricular septal thickness; LVEF = left-ventricular ejection fraction; LV = left-ventricular; PWED = end-diastolic posterior wall thickness; TDI = tissue Doppler imaging; Vcfc = rate-corrected velocity of fiber shortening; Vel = velocity.

All comparisons made by paired Student's *t*-test. Comparisons with *P*-values <0.05 are highlighted in bold text.