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Incidence Of Supraventricular Arrhythmias During Autologous Peripheral Blood Stem Cell Transplantation

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Abstract

Arrhythmias, especially supraventricular arrhythmias, often complicate the clinical course during autologous hematopoietic cell transplantation (AHCT). We undertook this study to determine the incidence and risk factors for cardiac arrhythmias during AHCT. The study included 983 patients who underwent AHCT between August 2006 and December 2010 at a single institution, and in whom all the relevant medical records were available for review. The median age was 58 years (range; 19–77); 61% were male. AHCT was done for plasma cell disorders in 58% patients and for lymphoma or leukemia in the remaining. Overall, 92 (9.4%) patients developed a supraventricular tachyarrhythmia at a median of 9 days post transplant (range; 0, 18) and with a median duration of <1 day (range; <1 to 17 days). Atrial fibrillation (AF) was the most common and seen in 71 (7%) patients, followed by atrial flutter and supraventricular tachycardia in 12 (1%) and 8 (1%) patients respectively. In multivariate analysis, age > 63 years, presence of premature supraventricular complexes or Atrio-ventricular conduction delay on pre-transplant ECG, and history of any prior arrhythmia increased the risk of arrhythmia. Development of arrhythmia resulted in longer outpatient follow up after AHCT, with the median follow-up for those developing an arrhythmia of 22 days compared with 19 days for the rest; $P < 0.001$. In conclusion, 9% of patients undergoing ASCT develop supraventricular arrhythmias post transplant and this risk is elevated among the older patients, those with a prior history of arrhythmias, and those with pre-transplant ECG abnormalities.

Keywords

Arrhythmia; autologous stem cell transplantation; atrial fibrillation; anti-arrhythmics Autologous hematopoietic cell transplant (AHCT); electrocardiographic (EKG)

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INTRODUCTION

Autologous hematopoietic cell transplantation (AHCT) has become the standard of care for a variety of malignancies and is also increasingly being used for congenital as well as acquired disorders. Among more than 50,000 first HSCTs reported for 2006 worldwide; the leading indications were lymphoproliferative disorders (54.5%), leukemia (33.8%), solid tumors (5.8%) followed by nonmalignant disorders (5.1%) [1]. The majority of these transplants were done in either Europe (48%) or North America (36%), with AHCT constituting the majority. In the United States, AHCT is performed most commonly for multiple myeloma followed by the lymphomas. Although the process has become considerably safer over the past two decades, high dose chemotherapy and AHCT can be associated with significant morbidity related to a variety of side effects [2–4].

One of the more serious complications of AHCT remains cardiac toxicity. With the use of conventional pre-AHCT clinical cardiac evaluation, major cardiotoxic events such as heart failure, cardiac tamponade, and life-threatening cardiac arrhythmias have been reported to be uncommon, occurring in <1% of patients [5]. Arrhythmias, especially supraventricular arrhythmias, however more commonly complicate the clinical course of these patients [6–9]. This has been clear since the initial report in 1998 by Olivieri et al, who reported five cases of atrial fibrillation in stem cell transplantation recipients following high dose melphalan [10]. Subsequent studies reported the occurrence of supraventricular arrhythmias in 4–10% of bone marrow transplant recipients [6–9]. However factors predisposing to such arrhythmias have not been well studied to date.

While these arrhythmias are easily treatable in the majority of patients, they can still result in prolongation of hospital stay as well as an increased rate of intensive care admissions. We undertook this study to determine the incidence and risk factors for cardiac arrhythmias during AHCT.

PATIENTS AND METHODS

Following the approval from the Mayo Clinic Institutional Review Board, we retrospectively analyzed the medical records of 1000 consecutive patients who underwent AHCT for various malignancies between August 2006 and December 2010. All patients had given informed consent for the use of their records for research purposes. Seventeen patients who had AHCT for non-hematological malignancies and those who had incomplete information regarding various parameters described below were excluded leaving 983 patients who met the criteria. Twenty-two of the 983 patients received a combination of marrow and Peripheral Blood Stem Cell (PBSC) graft and all other patients received PBSC only. These patients were managed by multidisciplinary team on an outpatient basis and were admitted to hospital as and when indicated [11]. Patients were seen on a daily basis or more often if needed, with daily monitoring of CBC and chemistry with replacement of electrolytes and transfusions as clinically indicated. Patients were not routinely placed on cardiac monitoring of any nature irrespective of prior cardiac history.

For all patients, the medical records were reviewed for age, sex, height, weight, and clinical risk factors for atrial arrhythmia including presence of systemic hypertension, diabetes mellitus, coronary artery disease, valvular heart disease and thyroid diseases. Information regarding history of arrhythmia was obtained from the medical records. Additionally, we also reviewed the electrocardiographic (EKG) records in our Mayo EKG Database for any reports of arrhythmias or conduction abnormalities. All patients also underwent transthoracic echocardiography before transplant. The echocardiographic data were electronically retrieved and reviewed for parameters that could predispose to arrhythmias

such as LV diastolic dysfunction, LV ejection fraction, indexed LA volume index and valvular lesions.

Logistic regression was used to identify the best cut-point for continuous variables, associated with the maximum risk of developing an arrhythmia. The Kaplan Meier method was used to estimate the median time to onset of any arrhythmia, with patients not developing any arrhythmia censored at the time of dismissal home post AHCT. The Cox proportional hazards model was used to estimate the risk associated with various baseline factors. Patient related variables included age, gender, diagnosis, history of coexisting illnesses such as coronary artery disease (CAD), hypertension, diabetes, prior history of arrhythmias, antiarrhythmic medications, or beta-blocker use. Cardiac parameters examined included LV ejection fraction, left atrial size, or presence of valvular abnormalities on echocardiogram, PR interval, QTc interval, presence of supraventricular complexes or Atrio-ventricular (AV) conduction delays/blocks which included 1st and 2nd degree AV blocks on pre-transplant ECG. Transplant related factors examined include position of central line tip (right atrium vs. superior vena cava), conditioning regimen, neutropenic fever, hypokalemia in the post transplant period, development of mucositis, and diarrhea. All the baseline variables were evaluated, and those which were found to be significantly associated with arrhythmia at a P level of <0.05 on univariate analysis were then considered for multivariate analyses. All analyses were performed using JMP[®] 9.03 software (SAS Institute Inc., North Carolina).

RESULTS

The median age of 983 patients who underwent AHCT between August 2006 and December 2010 was 58 years (range; 19–77), of which 61% were male. Among these patients, 41% had myeloma and together with amyloidosis and POEMS, plasma cell disorders were the indication for transplant in 58% of patients, followed by lymphomas (40%) and acute leukemia (2%) (Table 1). Eighty-two (8.3%) patients had a prior history of arrhythmia and 38 (3.9%) had a history of arrhythmia during the month prior to transplant. Eighteen (0.2%) of the patients had atrial fibrillation or flutter at the start of transplant. Two hundred seven (21.1%) patients were on a beta-blocker and 24 (2.4%) were on verapamil or diltiazem at the time of AHCT. The median estimated duration to dismissal from outpatient area to home hematologist (home-dismissal) post transplant was 19 days (95% CI; 19, 20). Overall, 29 (3%) patients died during the 100 days post transplant due to various reasons, including infectious causes, multi-organ failure, pulmonary complications, and progressive disease in 15 patients and infection, multi-organ failure syndrome, ARDS and or thromboembolic complications in the remaining 14 patients.

Overall, 92 (9.4%) patients developed a symptomatic supraventricular arrhythmia during the stem cell transplant course, at a median of 9 days post-transplant (range; 0, 18). The cumulative incidence of symptomatic arrhythmia in the post transplant period is as shown in Figure 1 (Kaplan Meier estimate). Atrial fibrillation was the most common and was seen in 71 (7%) patients, followed by atrial flutter in 12 (1%) and supraventricular tachycardia in 8 (1%) (Table 2). One patient developed multifocal atrial tachycardia. The rhythm had normalized in 81 (88%) patients at the time of dismissal post-transplant, with a median duration of arrhythmia of <1 day (range; <1 to 17 days). 82 (89%) of patients developing arrhythmia required treatment with most of them receiving a beta-blocker and/or calcium channel blocker. 36% of the patients with an arrhythmia developed hypotension, but only 14% required vasopressor support and 8% were electrically cardioverted during the peri-transplant period. 23 patients (25%) had recurrence of their arrhythmia before dismissal at a median time of 12.5 days (range, 5–21). The median time to dismissal after transplant for

patients developing an arrhythmia was 22 days as compared to 19 days in those who did not; $P < 0.001$ (Figure 2).

We then examined various pre and peri-transplant clinical and laboratory parameters to identify risk factors for onset of supraventricular arrhythmias. In a univariate analysis, older age, presence of supraventricular complexes or AV conduction delays such as 1st or 2nd degree AV block on pre-transplant ECG, presence of any valvular abnormality, presence of premature atrial complexes on ECG pre-transplant, increased atrial size, history of hypertension, history of CAD, any prior history of arrhythmia, or being on a beta blocker or an antiarrhythmic agent all increased the risk of developing a supraventricular arrhythmia following transplant (Table 3). We specifically examined the relation between amyloid heart disease and risk of developing arrhythmia. While there was a trend towards increased risk in the presence of amyloid heart disease, this was not significant ($p=0.08$). Using logistic regression, the best cutoff for age and for atrial size in terms of risk of developing arrhythmia was 63 years and 33 cc/m². However, in a multivariate analysis, only age > 63 years, presence of supraventricular complexes or AV conduction delays on pre-transplant ECG, and history of any prior arrhythmia, increased the risk of arrhythmia during transplant. Among the patients with age > 63 years, presence of supraventricular complexes or AV conduction delays on pre-transplant ECG, and history of any prior arrhythmia, 20%, 26% and 23% respectively developed an arrhythmia compared to 4%, 8% and 8% among those without the risk factors, respectively ($P < 0.0001$ for each of the three comparisons). Patients with two or more risk factors, and those with one risk factor present were at 12.7 (95% CI; 6.7, 24) and 6.4 (95% CI; 3.8, 11.3) fold higher risk of developing arrhythmia compared to those with no risk factors (Figure 3). None of the underlying hematological malignancy or medical co-morbidities impacted the risk of developing arrhythmia.

DISCUSSION

Supraventricular arrhythmias are a well-recognized complication after hematopoietic stem cell transplantation [6–9]. The incidence of these complications was 9% in this study, which is consistent with the previously reported incidence of 4–10% [6–9]. However, none of the studies so far including ours had patients on continuous cardiac monitors, so the true incidence may be even higher.

Atrial fibrillation was the most common arrhythmia and was present in about three-quarters (77%) of patients developing an arrhythmia. The median time of onset of arrhythmias was 9 days after AHCT and this is slightly later than the onset of between 3–7 days as reported by earlier studies [6, 8, 9]. Most arrhythmias were however short lasting with median duration of less than a day. Interestingly, one fourth of these patients had a recurrence of the arrhythmia at a median of 12.5 days but still most patients (88%) were discharged in sinus rhythm. Though a difference in mortality was not seen, these arrhythmias were associated with an increase in the median time to dismissal home from outpatient follow up by 3 days.

Though well known, studies evaluating risk factors for these arrhythmias are scarce. Most studies done so far have implicated older age and the presence of cardiac dysfunction in predisposition to this risk [6, 7, 9]. Even in the general population, the risk of developing AF increases with age, with approximately 70% of patients with AF being between age 65 and 85 years [12]. Statistical analysis of our results showed age >63 as a major risk factor with a risk ratio of 4.7.

Another predisposing factor emphasized in the multiple studies is the use of chemotherapeutic agents. Amongst the agents which are currently in use in transplant patients, the association of melphalan with AF is most well established and has been

implicated in a significant proportion of patients including those without any structural or functional cardiac defects as well as those who are young [10]. Studies have shown melphalan use to be associated with AF in 6.6–11% of bone marrow transplant patients, which is significantly higher than any other chemotherapeutic agent [9, 13–15]. Our study cohort was mainly composed of patients with plasma cell disorders or lymphoma as the indication for transplant in most and thus melphalan free regimens were given in only a few patients. Hence the role of melphalan could not be ascertained from our study.

History of arrhythmias in the past was another predisposing factor we observed in this study. Surprisingly, being on an antiarrhythmic agent was shown as a risk factor but only on univariate analysis. This may reflect identification of those with prior history of arrhythmias. A predominance of older patients in our study with multiple co-morbidities requiring the use of these agents may explain this finding. Similarly, factors such as increased atrial size, history of hypertension or CAD were found significant on univariate model but not on the multivariate model. It is possible that all of these risk factors are inter related and may be predisposing to atrial arrhythmias even before the transplant.

More than half of our study group patients had a plasma cell disorder. Whether the presence of cardiac amyloidosis in these patients predisposes to arrhythmias, has always been a question. We found that even though a higher percentage of patients developing a supraventricular arrhythmia had evidence of cardiac amyloidosis by echo than the controls, the results were not statistically significant. However at the same time it must be kept in mind that sensitivity of echocardiograms to detect early cardiac involvement in amyloidosis tends to be low even with recent advances [16–18].

EKG changes such as AV conduction delays (1st or 2nd degree blocks) and PACs were present in about 7% patients during pre-transplant period and their presence independently predicted atrial arrhythmias post-transplant. Both frequent PACs and AV conduction abnormalities have been previously shown to predict new AF in general population [19, 20]. Several studies have demonstrated the association between delayed intra-atrial or inter-atrial conduction and increased risk of AF [21–23]. Although first-degree AV block usually involves conduction delay in the atrioventricular node, it is frequently accompanied by abnormalities in other parts of the conduction system. In addition, a prolonged PR interval can lead to delayed and ineffective mitral valve closure and diastolic mitral regurgitation, especially when the PR interval exceeds 230 milliseconds. Early asymptomatic cardiac amyloidosis predisposing to AV conduction problems as well as post-transplant AF could be a possibility that will need further investigation [24–26]. Meanwhile, the presence of asymptomatic conduction blocks or SVC on EKG even prior to stem cell transplants should not be disregarded.

In conclusion, among patients undergoing autologous peripheral blood stem cell transplantation, the risk of developing a supraventricular arrhythmia in the peri-transplant period is approximately 9%. The risk is higher among older patients, those with a prior history of arrhythmias and those with ECG abnormalities suggesting AV conduction delay and premature supraventricular complexes. Though no association with increase in mortality has been shown, these arrhythmias may warrant additional management and can increase the time to discharge, thereby increasing the cost of care. Identification of these high-risk patients may allow development of specific interventions in future.

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Abbreviations

AF	Atrial fibrillation
AFI	Atrial flutter
AHCT	Autologous hematopoietic cell transplantation
AV	Atrio-ventricular
CAD	Coronary artery disease
EKG	Electrocardiogram/electrocardiographic
HSCT	Hematopoietic stem cell transplantation
LA	Left atrium
LV	left ventricle
PBSC/PBSCT	Peripheral Blood Stem Cell/Peripheral blood stem cell transplantation
SVC/PACs	Supraventricular complexes/Premature atrial contractions.

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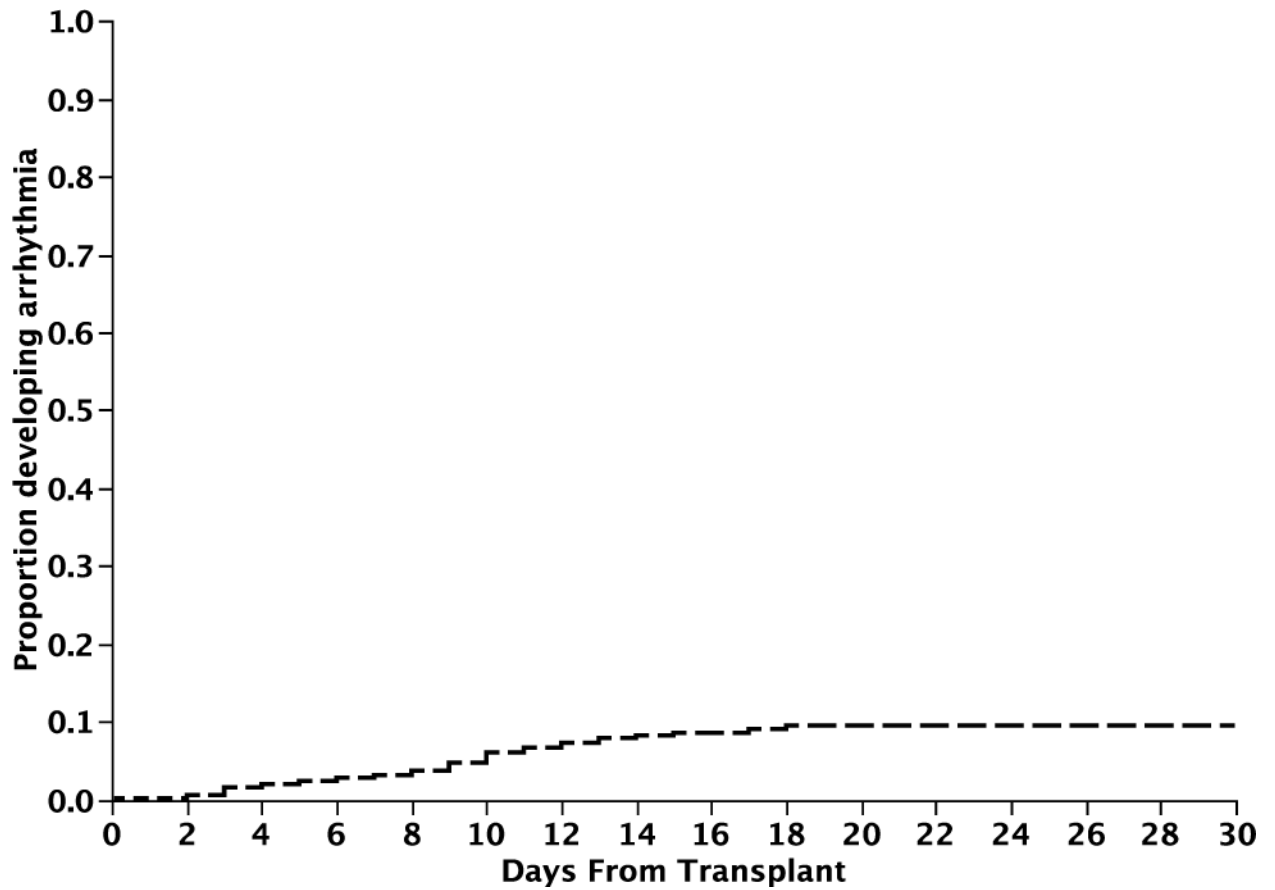


Figure 1. Time to onset of arrhythmia post-transplant

Figure 1 depicts the median time to onset of arrhythmia post transplant (Kaplan Meier estimate). The median estimated time was 9 days (95% CI; 8, 10).

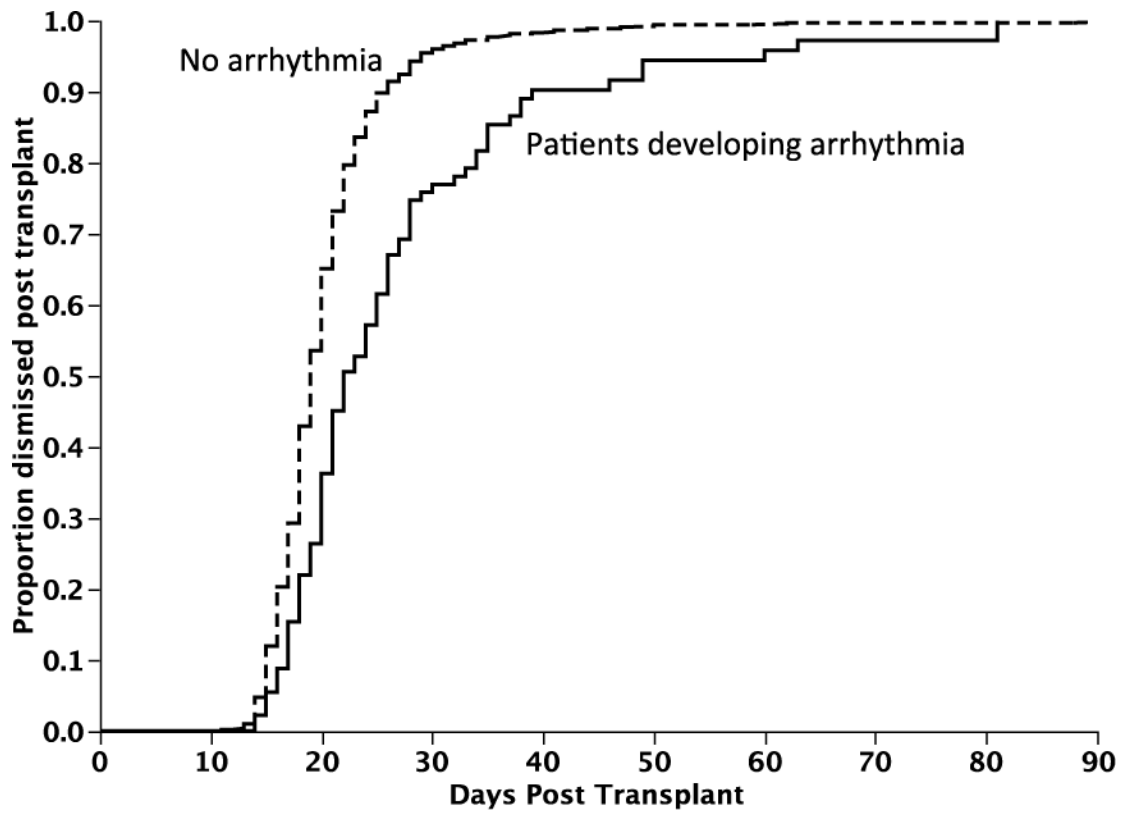


Figure 2. Time to dismissal home after transplant

Figure 2 depicts the median time to dismissal home following transplant (Kaplan Meier estimate). The median time to dismissal after transplant for patients developing an arrhythmia was 22 days as compared to 19 days in those who did not; $P < 0.001$.

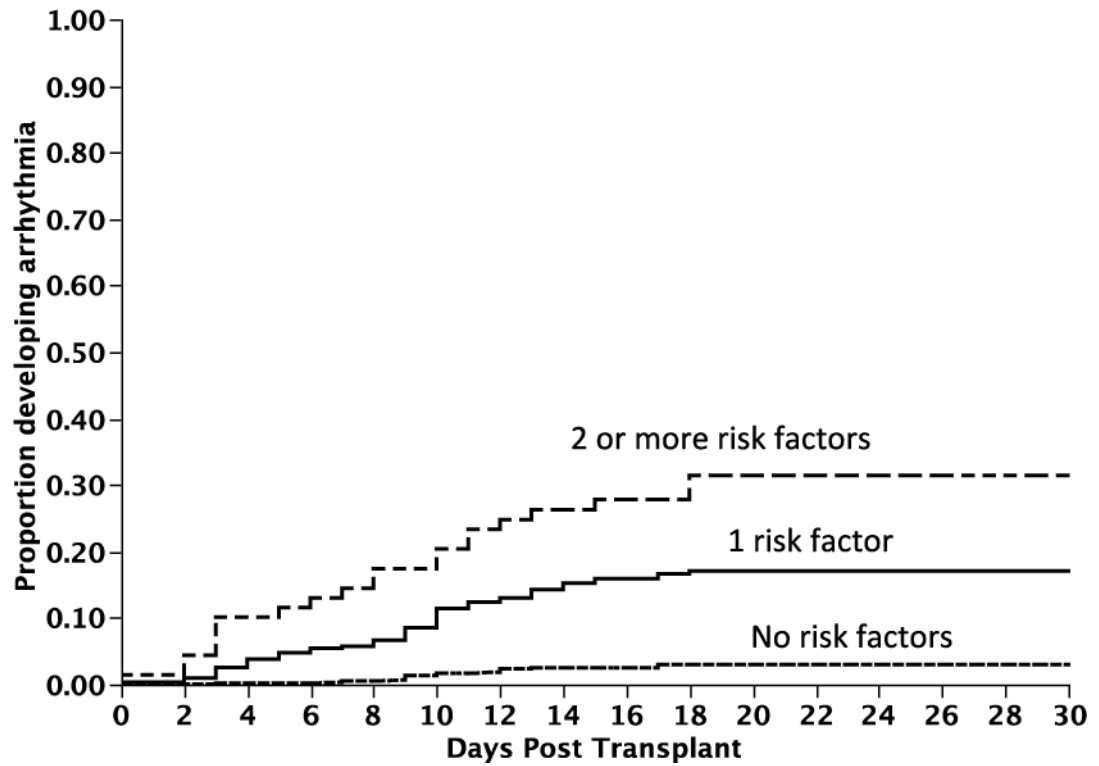


Figure 3. Risk factors predicting development of arrhythmia post transplant

Figure 3 provides the cumulative incidence curves for onset of arrhythmia following transplant. Patients with two or more risk factors, and those with one risk factor present were at 12.7 (95% CI; 6.7, 24) and 6.4 (95% CI; 3.8, 11.3) fold higher risk of developing arrhythmia compared to those with no risk factors.

Table 1

Baseline characteristics

	N	%
No. of patients	983	–
Age (range)	58 years	(19–77)
<i>Gender: Male</i>	603	61%
<i>Disease</i>		
Acute Leukemia (%)	10	2%
Amyloidosis (%)	140	14%
Hodgkin Disease (%)	63	6%
Myeloma (%)	404	41%
NHL (%)	337	34%
POEMS (%)	29	3%
<i>Conditioning</i>		
BEAM	395	40%
Busulfan + Cytosan	3	0.3%
Cytosan + TBI	10	1%
Melphalan	565	58%
ThioTEPA/BCNU	1	0.1%
Zevalin/Melphalan	8	0.8%
<i>Medical comorbidities</i>		
Hypertension	372	37.8%
CAD	75	7.6%
DM	105	10.6%
Hypothyroidism	114	11.6%
Hyperthyroidism	2	0.2%
Renal insufficiency	152	15.5%
COPD	27	2.7%
Obstructive Sleep Apnea	70	7.1%

Table 2

Arrhythmia characteristics (n=92)

Arrhythmia onset, BMT day (range)	9	0-18
Duration, mean (range)	<1 day	(<1 to 17 days)
<i>Type of arrhythmia</i>		
Atrial Fibrillation	71	78%
Atrial Flutter	12	13%
SVT	8	1%
MAT	1	<1%
<i>Management</i>		
Treatment required	82	89%
Beta blockers	68	74%
Calcium channel Blockers	40	43%
DC Cardioversion	7	8%
<i>Outcome</i>		
Hypotension	33	36%
Vasopressors	13	14%
Relapse	23	25%

Table 3

Univariate Comparisons of patients with or without arrhythmia

Characteristics	Arrhythmia (n=92)		Controls (n=891)		Risk Ratio (95% CI)	P-value
	N	%	N	%		
Age > 63 years	62	67%	246	28%	4.8 (3.2, 7.6)	<0.0001
Prior history of arrhythmia	19	20%	63	7%	3.2 (1.9, 5.2)	<0.0001
History of Hypertension	47	51%	325	36%	1.7 (1.1, 2.6)	0.01
History of CAD	15	16%	60	7%	2.5 (1.4, 4.2)	0.003
Beta blockers/antiarrhythmic at transplant	31	34%	183	21%	1.9 (1.2, 3.0)	0.005
<i>ECG features</i>						
AV conduction delay or Premature supraventricular complexes	17	18.5%	49	5.5%	3.2 (1.8, 5.4)	0.0002
<i>ECHO characteristics</i>						
Atrium >33 cc/m2	49	54%	304	35%	2 (1.3, 3.1)	0.0008
Presence of valvular abnormalities	12	13%	55	6%	2.2 (1.1, 3.9)	0.02

• Cox proportional hazards models

• Bolded rows indicate variables significant in multivariate analysis