original reports abstract

Atrial Fibrillation in Patients Undergoing Allogeneic Hematopoietic Cell Transplantation

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PURPOSE To examine the incidence and risk factors for de novo atrial fibrillation (AF) after allogeneic hematopoietic cell transplantation (HCT) and to describe the impact of AF on HCT-related outcomes.

METHODS A retrospective cohort study design was used to examine AF and associated outcomes in 487 patients who underwent allogeneic HCT from 2014 to 2016 and to characterize patient- and HCT-related risk factors. A nested case-control study design was used to describe the association between pre-HCT echocardiographic measures and future AF events.

RESULTS The median age at HCT was 52.4 years (18.1-78.6); the median time to AF was 117.5 days (4.0-1,405.0). The 5-year cumulative incidence of AF was 10.6%. Older (≥ 50 years) age (hazard ratio [HR], 2.76; 95% CI, 1.37 to 5.58), HLA-unrelated donor (HR, 2.20; 95% CI, 1.18 to 4.12), dyslipidemia (HR, 2.40; 95% CI, 1.23 to 4.68), and pre-HCT prolonged QTc interval (HR, 2.55; 95% CI, 1.38 to 4.72) were independent risk factors for AF. Despite having comparable left ventricular systolic function, patients who developed AF were significantly more likely to have lower left atrial ejection fraction, left atrial reservoir function, and elevated tricuspid regurgitant jet velocity prior to HCT, compared with patients who did not. The incidence rate of stroke after AF was 143 per 1,000 person-years. In adjusted analyses, AF was associated with a 12.8-fold (HR, 12.76; 95% CI, 8.76 to 18.57) risk of all-cause mortality and 15.8-fold (HR, 15.78; 95% CI, 8.70 to 28.62) risk of nonrelapse mortality.

CONCLUSION The burden of AF after allogeneic HCT population is substantial, and the development of AF is associated with poor survival. We identified important associations between patient demographics, pre-HCT cardiac parameters, HCT-related exposures, and risk of AF, setting the stage for targeted prevention strategies during and after HCT.

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INTRODUCTION

Hematopoietic cell transplantation (HCT) is an established and effective treatment for hematological disorders and malignancies.[1] Improvement in HCT strategies during the past five decades has led to an increasing number of long-term survivors.[2,3] There are currently an estimated 250,000 HCT survivors in the United States, a number that will double within the next 10 years.[4] Despite improvements in long-term outcomes, HCT survivors continue to have substantially higher mortality rates compared with the general population.[5-7] In particular, the risk of cardiovascular-related mortality is more than twice that of the general population,[6-8] and the magnitude of risk increases with time from HCT.[8] In HCT survivors, cardiovascular complications such as myocardial infarction, stroke, and heart failure are a leading cause of long-term morbidity,[9] and there are well-described pre-HCT (eg, anthracycline chemotherapy and chest radiation), conditioning-related (eg, high-dose cyclophosphamide), and post-HCT (eg, de novo comorbidities [hypertension, diabetes, and dyslipidemia]) risk factors for these health conditions.[10-11]

Atrial fibrillation (AF) is the most common cardiac arrhythmia in the general population.[12] AF is associated with a five-fold increased risk of stroke, three-fold increased risk of heart failure, and two-fold increased risk of dementia and death in the general population,[13,14] and there are established clinical (eg, older age and hypertension) and ECG (eg, prolonged QTc interval and abnormal P axis) risk factors for AF.[15-18] Studies in nononcology patients have further shown that echocardiographic measures of left atrial (LA) dysfunction (eg, low LA ejection fraction [EF] and abnormal reservoir strain) may provide incremental value in determining future AF risk.[19,20] There is a paucity of information on the incidence and risk factors of de novo AF in HCT patients, especially in those

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CONTEXT

Key Objective

To examine the incidence and risk factors for atrial fibrillation (AF) after allogeneic hematopoietic cell transplantation (HCT) and describe the impact of AF on HCT-related outcomes.

Knowledge Generated

The 5-year cumulative incidence of AF was 10.6%. Older (≥ 50 years) age at HCT, having an HLA-unrelated donor, dyslipidemia, and pre-HCT prolonged QTc interval were independent risk factors for AF. Despite having comparable left ventricular systolic function, patients who developed AF were more likely to have lower left atrial ejection fraction, left atrial reservoir function, and elevated tricuspid regurgitant jet velocity prior to HCT, compared with patients who did not. AF was associated with a > 15-fold risk of nonrelapse mortality.

Relevance

This information may help set the stage for informed decision making between healthcare providers and high-risk patients prior to HCT and consideration of innovative monitoring approaches for these patients during HCT or in the community after HCT.

undergoing allogeneic HCT, and there have been no studies to examine the association between pre-HCT echocardiographic parameters and future AF risk. In these patients, it is especially important to understand outcomes following the onset of AF, given the increasing indications for HCT and greater numbers of older (> 65 years) individuals referred for higher-risk allogeneic HCT.

For the current study, we used both a retrospective cohort study design and a nested case-control approach to describe the incidence of de novo AF and its associated health outcomes after HCT and to evaluate the role of patient demographics, chronic comorbidities, pre-HCT treatment–related exposures, transplant conditioning, and cardiac (electrocardiographic and echocardiographic) risk factors associated with the development of AF after allogeneic HCT.

METHODS

Cohort Analysis

A total of 599 consecutive patients underwent allogeneic HCT at City of Hope (COH) between January 1, 2014, and December 31, 2016. Patients included in the current study were identified from the COH long-term follow-up research protocol, which ensures the active and comprehensive follow-up of all patients who undergo HCT at COH. The human subjects committee at COH approved the protocol, and informed consent was obtained according to the Declaration of Helsinki. Children (< 18 years at HCT; n = 65), individuals with a prior history of AF (n = 34), or those undergoing a second HCT (n = 13) were excluded from the current study; 487 patients were included in the retrospective cohort analysis. The median follow-up for the cohort was 3.1 years (range, 0-6.0), representing 1,400 person-years of follow-up, and 81% of the cohort was followed through December 31, 2019 (if alive), or death.

Medical records maintained at COH were the primary source of data and were used to abstract demographics (age, sex, and race or ethnicity), medical history (hypertension, diabetes, dyslipidemia, thyroid disorder, and cardiovascular disease [eg, heart failure and coronary artery disease]), pre-HCT treatment (chemotherapy and radiation), indication for and relapse risk at HCT,[21] HCT-related exposures (conditioning agents and intensity,[22] HLA match [related and unrelated], stem-cell source, and graft *v* host disease [GVHD] prophylaxis), and post-HCT outcomes (acute GVHD severity[23] and cause-specific mortality). Pre-HCT ECGs obtained per standard of care were also evaluated for heart rate, PR interval, and QTc interval; 468 patients (96.1% of the cohort) had available ECGs. Information on vital status and cause of death was obtained from the National Death Index and COH medical records.

Case definition of AF, including categorization of lone versus paroxysmal or persistent AF, was according to established guidelines for the management of patients with AF,[14] which required ECG documentation of an irregular R-R interval, the absence of distinct repeating P waves, and irregular atrial activity, or was based on physician documentation of AF followed by initiation of medical management. Individuals were considered to have pre-HCT diabetes, hypertension, dyslipidemia, or hypothyroidism if they were on medications for management of these conditions in the 4 weeks prior to HCT.

The cumulative incidence of AF after HCT was calculated taking into consideration the competing risk of death for right-censored data.[24] The time to AF was computed from the start of conditioning therapy to onset of AF; for those who did not develop AF, the follow-up ended on the date of death or the date of last contact (censored: December 31, 2019), whichever came first. We calculated the incidence rate of stroke after AF onset, reported as the number of events per person-years of follow-up.

Fine-Gray proportional subdistributional hazard models (hazard ratios [HRs], 95% CI) were used to estimate the

relationship between clinically relevant variables and risk of AF, accounting for death as competing risk.[24] Univariate analyses were performed initially with patient demographics, comorbidities, pre-HCT ECG parameters, and HCT-related exposures. Multivariable regression analysis was conducted by including all variables in univariate analyses with $P < .1$ and then using backward stepwise elimination to obtain the final model with only the significant ($P < .05$) independent variables; the multivariable analysis was limited to the 468 patients with available ECGs.

In addition, we examined the effect of AF onset on nonrelapse mortality (NRM) and relapse-related mortality treating AF as a time-varying covariate, with each outcome serving as competing risk in the Fine-Gray model.[24] Cox proportional hazards regression was used to examine the relationship between AF and overall survival, treating AF as a time-varying covariate. Multivariable Fine-Gray regression analysis was used to examine the association between AF onset and cause-specific mortality, adjusting for pre-HCT prognostic CHARGE-AF score (derived from age at HCT, race, height, weight, blood pressure, current smoking, use of antihypertensive medication, diabetes, and history of cardiovascular disease),[16] severity of acute GVHD after HCT, conditioning intensity, and stem-cell donor type. Data were analyzed using SAS Version 9.4 software (SAS Institute, Cary, NC). All statistical analyses were two-sided, and a P value $< .05$ was considered statistically significant.

Case-Control Analysis

To examine the association between pre-HCT echocardiographic measures and risk of AF, we first determined the number of patients with AF who had available pre-HCT echocardiograms. Of the 50 patients who developed AF, 39 (78%) had an echocardiogram that was available and interpretable; the median time from echocardiogram to the start of conditioning was 17 days (range, 0-82). Of the 437 individuals who did not develop AF, 389 (89%) had available echocardiograms. Of note, there were no statistically significant differences in clinical and treatment characteristics between individuals with and without pre-HCT echocardiograms. Cases (all patients who developed AF with echocardiograms, n = 39) were matched to up to three controls (did not develop AF and had an echocardiogram, n = 97). Cases and controls were matched on age at HCT (± 5 years), sex, and length of follow-up (control follow-up was equivalent to or exceeded that of the case). We elected to use a nested case control design because of the time commitment (approximately 2 hours) required for central review of each echocardiogram, the need to match for length of follow-up, and variables (eg, age and sex) that may affect echocardiographic measures of interest. All echocardiograms were reviewed by a single observer (L.C.) who was blinded to the case or control status. Measurements included left ventricular (LV) dimensions, wall thickness, volumes, mitral velocity, and tricuspid regurgitant (TR) jet velocity; and LA dimensions, volumes, and strain; LV and LA EF% was calculated as $(Vol_{max} - Vol_{min})/Vol_{max} \times 100$. Twenty echocardiograms were randomly selected for quality control evaluation, confirming previously reported high intraobserver reliability.[25-27] We used multivariable conditional logistic regression to compare echocardiographic indices between cases and controls and to estimate the odds ratio (OR) of AF occurrence. Variables in the models included echocardiographic variables (LA EF [< 45%], TR [> 2.8 m/s], and reservoir function [<39%]) and relevant treatment-related differences between the two groups. Data were analyzed using SPSS Version 26.0 (IBM Corp, Armonk, NY).

RESULTS

Patient and Clinical Characteristics

The characteristics of the cohort are summarized in Table 1. The median age at HCT was 52.4 years (range, 18.1-78.6); the majority of patients were male (57.7%) and non-Hispanic White (48.7%). Primary diagnoses included acute myeloid leukemia (42.3%), acute lymphoblastic leukemia (25.7%), myelodysplastic syndrome or myeloproliferative neoplasm (21.6%), and others (10.5%); 53.2% were at low risk of relapse at HCT, 50.7% received nonmyeloablative conditioning, and 53.0% had an HLA-unrelated donor; the most common GVHD prophylaxis medications were tacrolimus (95.1%) and sirolimus (73.1%).

The cumulative incidence of AF at 1 and 5 years was 6.8% and 10.6%, respectively (Fig. 1); the median time to AF was 117.5 days (range, 4.0-1,405.0). Of the 50 patients who developed AF, three (6%) had lone AF and 47 (94%) had paroxysmal or persistent AF. Univariate analysis using Fine-Gray regression showed that older (≥ 50 years) age at HCT (HR, 3.52; 95% CI, 1.77 to 7.01), male (HR, 2.17; 95% CI, 1.15 to 4.08), diabetes (HR, 2.21; 95% CI, 1.07 to 4.56), dyslipidemia (HR, 3.19; 95% CI, 1.71 to 5.96), pre-HCT prolonged QTc interval (HR, 2.64; 95% CI, 1.48 to 4.69), HLA-unrelated donor (HR, 2.14; 95% CI, 1.17 to 3.92), and nonmyeloablative conditioning (HR, 2.39; 95% CI, 1.32 to 4.37) are significantly associated with AF risk (Table 1). In the multivariable regression model, older (≥ 50 years) age (HR, 2.76; 95% CI, 1.37 to 5.58), having an HLA-unrelated donor (HR, 2.20; 95% CI, 1.18 to 4.12), dyslipidemia (HR, 2.40; 95% CI, 1.23 to 4.68), and prolonged QTc interval (HR, 2.55; 95% CI, 1.38 to 4.72) were significant independent predictors of AF risk (Table 2).

An examination of echocardiograms obtained before HCT revealed that despite having comparable LV EF (Table 3), patients who developed AF had significantly lower median LA EF (39.7% *v* 53.4%, $P < .001$) and LA reservoir function (31.1% *v* 39.1%, $P = .001$) and had a higher prevalence of abnormal TR jet velocity (30.8% *v* 8.2%, $P = .006$), compared with those who did not develop AF. In the multivariable regression model, having an abnormal (< 45%) LA EF,

TABLE 1. Characteristics of the Cohort and Univariate Fine-Gray Regression for Risk of AF

Variable	Entire Cohort (N = 487)	HR	95% CI	P[a]
Age at HCT (years), no. (%)				
≥ 50	266 (54.6)	3.52	1.77 to 7.01	<.001
Sex, no. (%)				
Male	281 (57.7)	2.17	1.15 to 4.08	.016
Race and ethnicity, no. (%)				
Non-Hispanic White	237 (48.7)	1.00	—	.149
Hispanic	151 (31.0)	0.46	0.22 to 0.97	
Asian	67 (13.8)	1.09	0.52 to 2.28	
Other	32 (6.6)	0.49	0.12 to 2.10	
Comorbidities at HCT, no. (%)				
Hypertension	120 (24.6)	1.47	0.81 to 2.65	.205
Diabetes mellitus	47 (9.7)	2.21	1.07 to 4.56	.033
Dyslipidemia	59 (12.1)	3.19	1.71 to 5.96	<.001
BMI ≥ 25 kg/m^2	317 (65.1)	1.38	0.74 to 2.57	.308
Thyroid disease	37 (7.6)	1.38	0.55 to 3.45	.494
Cardiomyopathy	17 (3.5)	1.19	0.28 to 5.03	.810
Coronary artery disease	19 (3.9)	1.65	0.51 to 5.39	.697
Smoking (ever)	198 (40.7)	1.60	0.92 to 2.79	.094
Electrocardiographic risk factors, no. (%)[b]				
Ventricular rate, median (range)	75.0 (37-148)	1.01	0.99 to 1.02	.204
Prolonged QTc interval, no. (%)	95 (20.8)	2.64	1.48 to 4.69	.001
Diagnosis, no. (%)				
ALL	125 (25.7)	1.00	—	.385
AML	206 (42.3)	1.29	0.61 to 2.72	
MDS or MPN	105 (21.6)	1.91	0.86 to 4.23	
Other	51 (10.5)	1.02	0.31 to 3.29	
Pre-HCT cardiotoxic therapy				
Anthracycline dose, median (range)	150.0 (0.0-700.0)	0.99	0.99 to 1.02	.687
Chest radiation, no. (%)	15 (3.1)	N/A	N/A	N/A
Risk of relapse at HCT, no. (%)				
High	228 (46.8)	1.37	0.79 to 2.39	.264
Conditioning regimen, no. (%)				
Nonmyeloablative	247 (50.7)	2.39	1.32 to 4.37	.004
HLA matching, no. (%)				
HLA-related	229 (47.0)	1.00	—	.001
HLA-unrelated	258 (53.0)	2.14	1.17 to 3.92	
Stem-cell source, no. (%)				
Bone marrow	34 (7.0)	1.00	—	.499
Peripheral stem cells	433 (88.9)	1.86	0.45 to 7.69	
Cord blood	20 (4.1)	0.81	0.08 to 8.78	
Stem-cell donor age (years)				
Median (range)	32.0 (0.0-72.2)	1.00	0.99 to 1.02	.847

(continued on following page)

TABLE 1. Characteristics of the Cohort and Univariate Fine-Gray Regression for Risk of AF (continued)

Variable	Entire Cohort (N = 487)	HR	95% CI	P[a]
GVHD prophylaxis, no. (%)[c]				
Tacrolimus, no. (%)	463 (95.1)	1.26	0.31 to 5.15	.101
Sirolimus, no. (%)	356 (73.1)	1.47	0.74 to 2.95	.272
Methotrexate, no. (%)	60 (12.3)	1.38	0.65 to 2.90	.700
Mycophenolate mofetil, no. (%)	87 (17.9)	N/A	N/A	N/A
Cyclophosphamide, no. (%)	68 (14.0)	1.09	0.27 to 4.45	.910

Abbreviations: AF, atrial fibrillation; ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; BMI, body mass index; GVHD, graft versus host disease; HCT, hematopoietic cell transplantation; MDS, myelodysplastic syndrome; MPN, myeloproliferative neoplasm; N/A, not applicable because of low prevalence of exposure or events.

[a]Test of heterogeneity.

[b]Limited to 468 patients with available pre-HCT ECGs.

[c]Patients could have received more than one agent for GVHD prophylaxis; statistical comparison is with patients not on these agents.

low (< 39%) LA reservoir function, or elevated (> 2.8 m/s) TR jet velocity was significantly associated with the odds of developing AF (LA EF: OR, 12.7, $P < .001$; LA reservoir function: OR, 3.8, $P = .010$; TR jet velocity: OR, 4.2, $P = .023$); having two or more abnormal indices was associated with an 18.0-fold (OR, 18.0, $P < .001$) odds of developing AF after HCT.

Five patients developed stroke during 34.8 person-years of follow-up after AF onset. The incidence rate of stroke after AF was 143 per 1,000 person-years. The overall 1- and 5-year survival probabilities for the entire cohort were 75.4% and 55.8%, respectively. The most common cause of death was relapse or progression; the prevalence of nonrelapse cause-specific mortality differed between patients with and without AF (Table 4). In adjusted analyses, AF was associated with a 12.8-fold (HR, 12.76; 95% CI, 8.76 to 18.57) risk of all-cause mortality and 15.8-fold (HR, 15.78; 95% CI, 8.70 to 28.62) risk of NRM. There were no differences in the risk of relapse-related mortality between the two groups (HR, 1.08; 95% CI: 0.43 to 2.68).

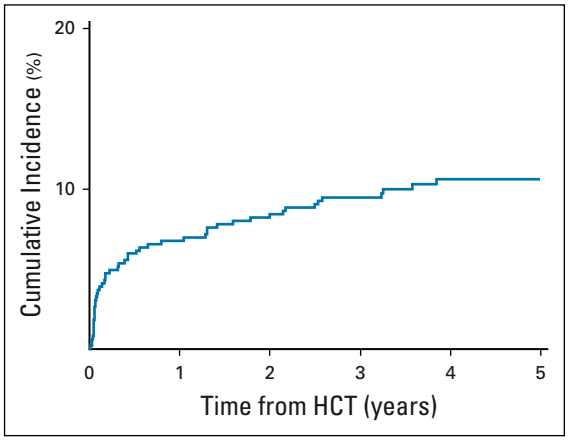

FIG 1. Cumulative incidence of AF after allogeneic HCT. AF, atrial fibrillation; HCT, hematopoietic cell transplantation.

DISCUSSION

In this contemporary cohort of patients undergoing allogeneic HCT, there was a high burden of AF soon after the start of conditioning that persisted into long-term survivorship. One in ten patients developed AF at a median of 117 days after HCT, and the steepest increase in the incidence of AF was in the first year after HCT. Outcomes in patients who developed AF were poor, largely because of the high risk of nonrelapse-related mortality. Similar to what has been reported in nononcology populations,[28-31] we found older age, pre-HCT dyslipidemia, and prolonged QTc interval to be significant independent risk factors for AF. Specific to the HCT population, patients who had an HLA-unrelated donor had an especially high risk of AF. We also identified pre-HCT echocardiographic predictors of future AF risk. Overall, our findings speak to the importance of comprehensive risk assessment for AF prior to HCT, focusing on patient-related, clinical, and HCT-related risk factors, as well as key cardiac parameters, allowing for implementation of prevention and treatment strategies to mitigate adverse cardiovascular outcomes after HCT.

To date, studies examining AF after HCT have been limited to patients undergoing autologous HCT,[32-38] representing an older population with greater comorbidities and a higher proportion of pre-HCT cardiotoxic (eg, chest radiation and anthracyclines) exposures, compared with patients undergoing allogeneic HCT. To our knowledge, our study is the first to describe the incidence and risk factors for AF in a contemporary cohort of allogeneic patients, allowing us to capture evolving HCT practices (eg, expanding donor stem-cell source, use of nonmyeloablative conditioning, increasingly older age at HCT, and expanded indications for HCT). Finally, we excluded patients with a history of AF prior to conditioning, allowing us to characterize the incidence and predictors of de novo AF after HCT.

We identified significant and independent HCT-related risk factors that warrant an additional study. Specifically, we found that patients who had an unrelated donor had a > 2-fold risk

TABLE 2. Multivariate Regression of Risk Factors for Developing AF After HCT

Risk Factor	HR	95% CI	*P*
Age at HCT (years)			
< 50	1.00		
≥ 50	2.76	1.37 to 5.58	.005
Pre-HCT dyslipidemia			
None	1.00		
Any	2.40	1.23 to 4.68	.011
HLA matching			
HLA-related	1.00		
HLA-unrelated	2.20	1.18 to 4.12	.014
Pre-HCT ECG QT interval prolongation			
No	1.00		
Yes	2.55	1.38 to 4.72	.003

Abbreviations: AF, atrial fibrillation; HCT, hematopoietic cell transplantation; HR, hazard ratio.

of AF, compared with individuals who had related donors. This risk may be driven by the higher incidence of GVHD in these patients,[39-41] and the resultant complex multi-organ (eg, renal and vascular) dysfunction that may persist after HCT. Pre-HCT cardiotoxic exposures such as chest radiation or anthracyclines were not associated with AF risk, which may be due to the low dose and low prevalence of these exposures in our cohort. Although there has been increased recognition of the arrhythmogenic potential of newer anticancer therapies (eg, protein kinase and checkpoint inhibitors) in patients with hematologic malignancies,[42] < 5% of our cohort were treated with these agents prior to or shortly after HCT. It remains to be seen whether increased utilization of these therapies in the future will add to the already high burden of AF after allogeneic HCT.

Studies in nononcology populations have highlighted the association between echocardiographic LA dimensions or volumes and a range of cardiovascular outcomes, including AF and cardiovascular mortality.[43-46] Speckle tracking echocardiography, initially developed for the left ventricle, has been applied to assess LA deformation (LA strain) and can provide important clinical information on LA performance and tissue health.[47-49] To our knowledge, the current study is the first to examine the association between these novel echocardiographic parameters and the risk of AF in the oncology setting. We used a standardized protocol to perform a blinded review of echocardiograms and were careful to consider parameters that would be obtained as part of standard of care. We found that pre-HCT low (< 45%) LA EF, low (< 39%) LA reservoir function, and elevated (> 2.8 m/s) TR jet velocity were significantly associated with AF risk. Although there are currently no established recommendations for the use of echocardiography to screen for AF risk in the general population,

TABLE 3. Pre-HCT Echocardiographic Parameters Among Cases and Controls

Echocardiographic Parameter	Case (n = 39) AF	Control (n = 97) No AF	*P*
LV EF, median, % (range)	61.0 (50.0 to 65.3)	60.0 (50.0 to 65.0)	.582
LV septal wall thickness, median, mm (range)	10.2 (7.3 to 13.3)	10.1 (8.0 to 13.2)	.762
LV posterior wall thickness, median, mm (range)	10.4 (8.0 to 12.5)	10.1 (8.0 to 12.5)	.369
Mitral E/A, median, (range)	0.9 (0.4 to 2.3)	1.0 (0.5 to 2.4)	.265
LA diameter (min), median, mm (range)	40.0 (29.0 to 63.0)	37.8 (21.7 to 59.4)	.218
LA diameter (max), median, mm (range)	47.8 (37.1 to 72.0)	48.1 (30.2 to 63.9)	.957
LA volume (min), median, mL (range)	29.6 (9.5 to 77.0)	20.1 (8.6 to 53.9)	.008
LA volume (max), median, mL (range)	46.7 (14.8 to 100.8)	44.6 (15.2 to 102.0)	.710
LA EF, median, % (range)	39.7 (17.7 to 65.9)	53.4 (6.6 to 67.7)	<.001
Abnormal (> 2.8 m/s) TR velocity, no. (%)	12 (30.0)	8 (8.2)	.006
LA reservoir function, median, % (range)	31.1 (20.4 to 55.7)	39.1 (20.4 to 68.1)	.001

Abbreviations: AF, atrial fibrillation; EF, ejection fraction; HCT, hematopoietic cell transplantation; LA, left atrial; LV, left ventricular; TR, tricuspid regurgitant.

TABLE 4. Vital Status and Cause-Specific Mortality

	Entire Cohort (N = 487)	Patients With AF (n = 50)	Patients Without AF (n = 437)
Alive, no. (%)[a]	281 (57.7)	10 (20.0)	271 (62.0)
Cause of death, No. (%)			
Relapse or disease progression	77 (15.8)	6 (12.0)	71 (16.2)
Multi-organ failure	28 (5.7)	10 (20.0)	16 (3.7)
GVHD	28 (6.4)	6 (12.0)	22 (5.0)
Cardiovascular	15 (3.4)	7 (15.0)	8 (1.8)
Sepsis	21 (4.8)	7 (14.0)	14 (3.2)
Pneumonia or respiratory failure	19 (3.9)	4 (8.0)	16 (3.7)
Other	5 (1.0)	—	5 (1.1)
Unknown	13 (2.7)	—	14 (3.2)

Abbreviations: AF, atrial fibrillation; GVHD, graft versus host disease.
[a]As of censor date December 31, 2019.

there may be a role for its use in certain high-risk populations, such as those undergoing allogeneic HCT.

Patients who developed AF had especially poor outcomes after HCT. The risk of all-cause mortality was nearly thirteen-fold higher, whereas the risk of NRM was more than fifteen-fold higher in patients who developed AF compared with those who did not. More than one third of NRM in patients with AF was attributable to cardiovascular causes or multi-organ failure. It is important to note that our multivariable models included the calculated CHARGE-AF score[16,50] for each patient, accounting for well-established risk factors for all-cause and cardiovascular mortality in the general population. Our study highlights the need for HCT-specific comprehensive (demographic, cardiac, and HCT-related risk factors) prognostic scores that may guide screening and prevention of AF prior to HCT. These strategies would have to balance the relative benefits and harms of pre-emptive management, including anticoagulation in the setting of prolonged thrombocytopenia or hepatotoxicity from medications (eg, amiodarone) used to manage AF in patients at risk for sinusoidal obstruction syndrome or liver GVHD during HCT.

The findings from this study have to be considered in the context of its limitations. Our study relied on retrospectively collected patient and treatment information, which limited the number of variables that could be reliably included in our analyses, including the chronic use of beta-blockers or other preventive pharmacotherapies in the months to years after HCT. We were careful to include objective variables that could be accurately extracted from medical records, using a strategy that has been successfully implemented to describe cardiovascular outcomes in HCT.[9,51,52] We used a standardized definition for AF, which would allow future studies to compare rates and outcomes reported in our population with theirs. That said, we acknowledge that the incidence of AF reported in our study may be an underestimate of the true incidence of disease in this population, given that some patients may be asymptomatic. All patients who developed AF in our cohort required medical intervention (eg, pharmacologic rate and/or rhythm control or cardiac resynchronization) and thus represent clinically relevant events. Of note, anticoagulation was rarely in used because of contraindications such as profound thrombocytopenia or organ (eg, hepatorenal) dysfunction or because of a low CHA_2DS_2-VASc score[14] in a minority (< 5%) of individuals.

In summary, to our knowledge, our study describes for the first time the incidence of AF in allogeneic HCT patients and identifies novel associations between pretreatment echocardiographic abnormalities and HCT-related risk factors for AF in these patients. We also highlight the poor survival outcomes in patients who develop AF, emphasizing the need for increasing awareness regarding AF after allogeneic HCT. The information from the current study may help set the stage for informed decision making between healthcare providers and high-risk patients prior to HCT and consideration of innovative monitoring (eg, wireless wearable ECG) for these patients during HCT or in the community after HCT. The growing number of patients undergoing allogeneic HCT (more than 25,000 per year in the United States and Europe alone)[53,54] makes the development of personalized transplant strategies imperative, to ensure that these patients live long and healthy lives well beyond the immediate HCT period.

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PRIOR PRESENTATION

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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