Brief Report

Waitlist Mortality of Patients With Amyloid Cardiomyopathy who Are Listed for Heart Transplantation and Implications for Organ Allocation

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ABSTRACT

Background: Outcomes of patients with amyloid cardiomyopathy (ACM) undergoing heart transplantation have been reported, but there are scant data concerning the waitlist mortality (WLM) of these patients.
Aim: The aim of this study was to investigate whether patients with ACM have higher waitlist mortality compared to those with other types of cardiomyopathies.
Methods: We queried the United Network for Organ Sharing registry for all patients (age $\geq$ 18 years) listed for heart transplantation between 2008 and 2015. We compared patients with ACM to those with dilated cardiomyopathy (DCM) or idiopathic restrictive cardiomyopathy (RCM) for WLM and waitlist mortality or delisting for deterioration (WLM/D). We identified 306 patients with ACM, 183 with RCM and 8416 with DCM. Patients with ACM were older (ACM 61 vs RCM 49 vs DCM 51 years, $P < .001$), were more likely to be male (82% vs 60% vs 73%, $P < .001$) but less likely to be listed as status 1A (16% vs 18% vs 23%, $P < .001$). After adjusting for baseline characteristics, ACM was associated with increased risk of mortality and mortality/delisting compared with DCM (HR 2.03 [1.36−3.04], $P = .001$ for WLM; HR 2.07 [1.55−2.78], $P < .001$ for WLM/D) but not with other RCMs (HR 1.28 [0.54−3.02], $P = .58$ for WLM; HR 0.97 [0.56−1.69], $P = .91$ for WLM/D).
Results: Patients with ACM are listed with lower acuity and have higher waitlist mortality compared with those with dilated cardiomyopathies. Further studies are needed to identify whether special prioritization should be considered for patients with ACM listed for heart transplantation. (*J Cardiac Fail 2019;25:767−771*)
Key Words: Amyloid, heart transplantation, waitlist, organ allocation.

INTRODUCTION

Amyloid cardiomyopathy (ACM) often progresses rapidly from initial diagnosis to advanced heart failure (HF).[1,2] Patients with ACM often poorly tolerate inotropes and mechanical circulatory support (MCS),[3] hence, heart transplantation (HT) may be a viable option for these patients.

Heart transplantation in ACM, however, is controversial due to historically poor post-HT outcomes, although outcomes have improved in recent years.[4] Moreover, there are scant data on the outcomes of patients with ACM on the HT waitlist. Current allocation and listing criteria assign higher priority to inotrope- and MCS-dependent patients, resulting in longer wait times for patients with ACM. Therefore, we hypothesized that patients with ACM have higher waitlist mortality than patients without ACM.

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MATERIALS AND METHODS

Data Source

We retrospectively queried the United Network for Organ Sharing (UNOS) registry for this study. UNOS records compulsory transplantation information about listed patients in all centers across the United States at listing, before transplantation and continually post-transplantation. Institutional review board approval was not required for this study because only deidentified data sets were used for analysis.

Patient Population

All patients older than 18 years of age listed for primary single-organ HT between 2008 and 2015 were included. Patients were stratified by etiology of HF: dilated cardiomyopathy (DCM), ACM or idiopathic restrictive cardiomyopathy (RCM). The RCM group excluded patients with ACM.

Study Outcomes

Patients were followed from time of listing to either mortality or delisting. Delisted patients were defined as those who deteriorated and were too sick for transplantation. Our primary outcomes in this study were adjusted waitlist mortality (WLM) or waitlist mortality/delisting (WLM/D). We compared WLM and WLM/D across our study groups (ACM vs RCM vs DCM).

Statistical Analyses

All analyses were performed using Statistical Package for Social Sciences (SPSS, v 19.0; SPSS, Chicago, IL). Categorical variables are presented as percentages and compared using the Pearson chi-squared test. Continuous variables are presented as mean and standard deviation and compared using the Student t test. When 3 groups were compared, we used the analysis of variance (ANOVA) test. Survival analyses were done using the Kaplan-Meier method with the log-rank test and adjusted survival used the Cox proportional hazard model. For adjusted models, we adjusted for characteristics that were different among groups ($P < .05$) (Table 1), namely, age, sex, race, implantable cardioverter defibrillator use, blood type, body mass index, history of cigarette use, diastolic pulmonary artery pressure, cardiac output, listed UNOS status, inotropes, and presence and type of MCS. All tests are 2-sided, and

Table 1. Baseline Characteristics

	ACM	Idiopathic RCM	DCM	*P* value
N	306	183	8416	
Age (years)	61 ± 8	49 ± 14	51 ± 12	< .001
Male gender	252 (82%)	110 (60%)	6113 (73%)	< .001
Ethnicity				< .001
White	184 (60%)	140 (77%)	4609 (55%)	
Black	98 (32%)	25 (14%)	2776 (33%)	
Other	24 (7.8%)	18 (9.8%)	1031 (12%)	
Status				< .001
1A	48 (16%)	33 (18%)	1918 (23%)	
1B	75 (25%)	64 (35%)	4023 (48%)	
2	180 (59%)	82 (45%)	2227 (27%)	
7*	3 (1%)	4 (2.2%)	248 (2.9%)	
Months on the waitlist	6.3 ± 10.1	7.3 ± 8.9	9.6 ± 12.4	< .001
ICD	101 (33%)	101 (55%)	6985 (83%)	< .001
Inotropes	77 (25%)	52 (28%)	2947 (35%)	< .001
IABP	10 (3.3%)	9 (4.9%)	395 (4.7%)	.50
ECMO	1 (0.3%)	1 (0.5%)	52 (0.6%)	.81
Ventilator	1 (0.3%)	1 (0.5%)	141 (1.5%)	.09
MCS				< .001
LVAD	5 (1.6%)	12 (6.6%)	2104 (25%)	
BiVAD	4 (1.3%)	1 (0.5%)	153 (1.8%)	
Blood type O	151 (49%)	86 (47%)	3905 (46%)	.01
BMI (kg/m^2)	26 ± 4	26±5	28 ± 5	< .001
Creatinine (mg/dL)	1.5 ± 0.7	1.3 ± 0.7	1.4 ± 1	.13
History of cigarette use	96 (31%)	76 (42%)	3597 (43%)	.003
Hemodynamics				
sPAP (mmHg)	43.3 ± 10.3	45.8 ± 12.7	44.3 ± 13.9	.16
dPAP (mmHg)	21.3 ± 6.3	23.6 ± 7.3	22.1 ± 8.9	.03
mPAP (mmHg)	29.8 ± 6.8	32.1 ± 9.2	30.5 ± 10.2	.05
PCWP (mmHg)	21.0 ± 5.9	21.8 ± 7.0	20.5 ± 9.0	.11
CO (L/min)	3.9 ± 1.1	4.1 ± 1.4	4.3 ± 1.4	< 0.001

Values are n, n (%), or mean ± SD.

ACM = amyloid cardiomyopathy; BiVAD = biventricular assist device; BMI = body mass index; CO = cardiac output; DCM = dilated cardiomyopathy; dPAP= diastolic pulmonary artery pressure; ECMO = extracorporeal membrane oxygenation; IABP = intra-aortic balloon pump; LVAD = left ventricular assist device; MCS = mechanical circulatory support; mPAP = mean pulmonary artery pressure; PCWP = pulmonary capillary wedge pressure; RCM = restrictive cardiomyopathy; sPAP = systolic pulmonary artery pressure.

*Status 7: patients who are inactive on the waiting list.

$P < .05$ was considered statistically significant, without adjustment for multiple comparisons.

RESULTS

We identified 306 patients with ACM, 183 with idiopathic RCM and 8416 with DCM (Table 1). Patients with ACM were older (61 years vs RCM 49 years and DCM 51 years, respectively, $P < 0.001$) and were more likely to be male (82% vs RCM 60% vs DCM 73%, $P < 0.001$). Patients with ACM were least likely to be listed as Status 1A (16% vs RCM 18% vs DCM 23%, $P < 0.001$) but were more likely to be listed as Status 2 (59% vs RCM 45% vs 27% DCM, $P < 0.001$). Inotrope use was most common in patients with DCM (35%) vs RCM (28%) vs ACM (25%), $P < 0.001$. Patients with DCM were also most likely to have a left ventricular assist devices (25% vs RCM 6.6% vs ACM 1.6%, $P < 0.001$). There were no significant differences in the use of intra-aortic balloon pumps (IABP) or extracorporeal membrane oxygenation among the groups (Table 1).

Waitlist Mortality and Waitlist Mortality/Delisting

Patients with ACM had increased cumulative incidence of both WLM and WLM/D compared to patients with RCM and DCM (Fig. 1). Of patients with ACM, 32 (10.5%) died while on the transplant waitlist during our study period, in contrast to 613 (7.3%) patients with DCM ($P < .001$ by log-rank test) and 13 (7.1%) patients with RCM ($P = .18$ vs ACM by log-rank test). Additionally, 28 (9.2%) patients with ACM were delisted during the same period, compared to 20 (10.9%) patients with RCM ($P = .79$ by log-rank test) and 541 (6.4%) patients with DCM ($P < 0.001$ vs ACM, by log-rank test).

The most common cause of death on the waitlist among ACM patients were cardiovascular causes (n = 12, 37.5% of ACM deaths) and multiorgan failure and cardiac arrest (n = 7, 21.8% of ACM deaths). Compared with ACM, 174 patients with DCM (28.3% of DCM deaths, $P = .001$ by log-rank test when compared with ACM) died of cardiovascular causes, and 136 (12% of DCM deaths when compared with ACM) died of multiorgan failure ($P = 0.11$ by log-rank test when compared with ACM). Compared to ACM, 5 patients with RCM died of cardiovascular causes ($P = .44$ by log-rank test), while 3 died of multiorgan failure ($P = .61$ by log-rank test when compared with ACM).

The overall waitlist mortality was higher for patients with ACM compared to patients with DCM (HR 1.96 [1.37−2.80]) but not RCM (HR 1.55 [0.81−2.96]) (Table 2). Unadjusted WLM/D was also higher for patients with ACM compared to patients with DCM (HR 1.97 [1.52−2.56]) but not to patients with RCM (HR 1.17 [0.77−1.80]) (Table 2). Table 2 also lists WLM/D stratified by listing UNOS status.

After adjusting for baseline characteristics, ACM was associated with increased risk of mortality and mortality/delisting compared with DCM (HR 2.03 [1.36−3.04], $P = .001$ for WLM; HR 2.07 [1.55−2.78], $P < .001$ for WLM/D) but not compared with other RCM (HR 1.28 [0.54−3.02], $P = .58$ for WLM; HR 0.97 [0.56−1.69], $P = .91$ for WLM/D).

Among patients with ACM, use of an IABP (HR 19.8 [6.22−63.23], $P < 0.001$) and lower cardiac output (HR 0.64 [0.45−0.92] per 1 L/min, $P = .015$) were associated with increased waitlist mortality. Both use of inotropes (HR 2.98 [1.63−5.44], $P < 0.001$) and IABP (HR 9.61 [3.3−28.2], $P < 0.001$) were associated with increased risk

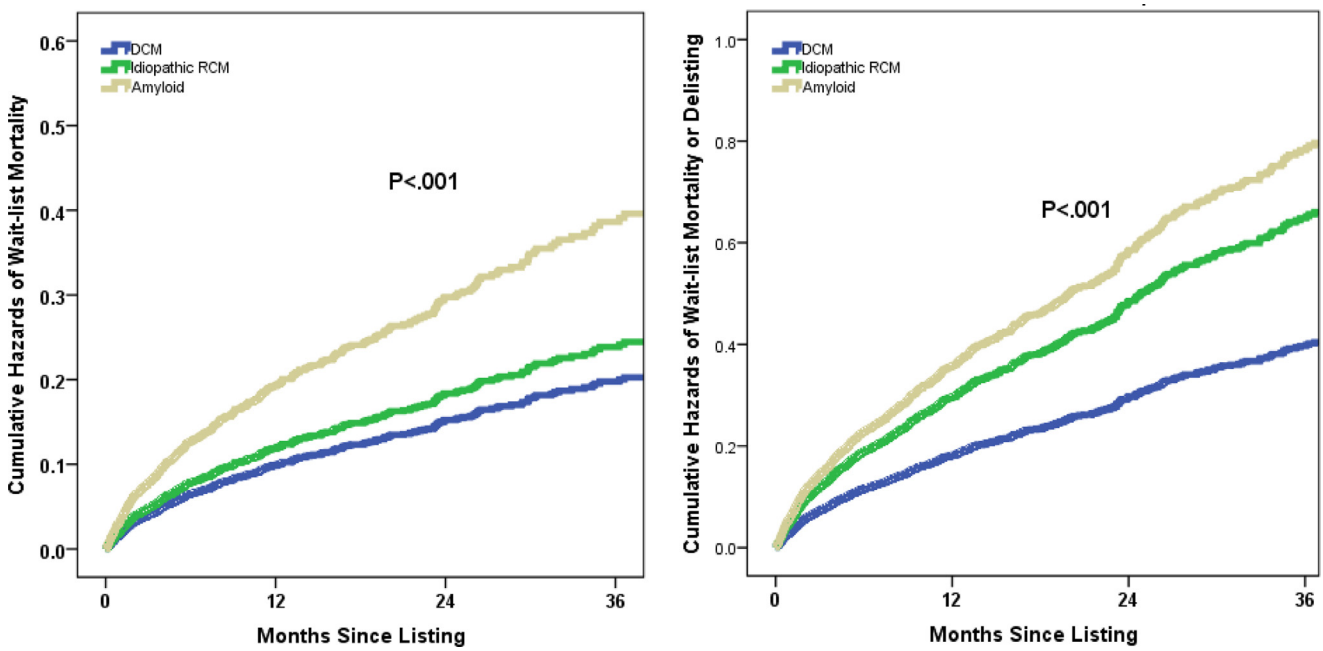

Figure 1. Cumulative incidence of waitlist mortality (left) and waitlist mortality or delisting (right) by type of cardiomyopathy. DCM = dilated cardiomyopathy; RCM = restrictive cardiomyopathy.

Table 2. Comparison of Waitlist Mortality and Waitlist Mortality/Delisting by Etiology and Status (Univariable Models)

	ACM vs DCM (OR [95%CI])	ACM vs RCM (OR [95%CI])
Waitlist mortality		
All	1.96 [1.37−2.80], $P < .001$	1.55 [0.81−2.96], $P = .19$
Status 1A	1.45 [0.46−4.55], $P = .53$	0.59 [0.12−2.93], $P = .52$
Status 1B	4.23 [2.08−8.60], $P < .001$	10.3 [1.25−84.8], $P = .03$
Status 2	2.15 [1.35−3.43], $P = .001$	1.97 [0.74−5.25], $P = .18$
Waitlist mortality/delisting		
All	1.97 [1.52−2.56], $P < .001$	1.17 [0.77−1.80], $P = .46$
Status 1A	2.27 [1.16−4.41], $P = .016$	0.98 [0.34−2.81], $P = .98$
Status 1B	4.75 [2.87−7.85], $P < .001$	2.75 [1.14−6.67], $P = .025$
Status 2	1.99 [1.40−2.84], $P < .001$	1.18 [0.63−2.21], $P = .60$

CI = confidence interval; HR = hazard ratio. Remaining abbreviations per Table 1.

of WLM/D (Supplementary Table 1). It is important to note that only 10 patients with ACM had IABP at listing; 4 had died on the waitlist and none had ben delisted.

DISCUSSION

Our study demonstrates that patients with ACM listed for HT have higher waitlist mortality than patients with other types of cardiomyopathies. In similar work consistent with our results, Hsich et al showed that patients with all restrictive cardiomyopathies (including ACM) fared worse on the waitlist than patients with dilated cardiomyopathies, (mortality odds ratio 1.7 [95% CI 1.43−2.02]).[5] The older UNOS organ allocation system wherein patients were listed according to their acuity, regardless of the etiology, poses several challenges to patients with ACM while awaiting transplantation. This issue is particularly relevant given the recently adopted changes in the UNOS organ allocation system,[6] and our results highlight the importance of considering the etiology of the cardiomyopathy in prioritization.

Currently, transplantation in cardiac amyloidosis is a Class IIA recommendation from the International Society for Heart & Lung Transplantation.[7] A major concern has been historically poor outcomes post-HT in patients with ACM, which are thought to be due to recurrence of amyloid post-transplant, with the risk being higher in light chain amyloidosis amyloidosis.[8−10] However, with advances in amyloid treatment, including chemotherapy and stem cell transplantation, the outcomes of these patients have improved.[11,12] Patients with transthyretin amyloidosis amyloidosis (either familial or wild-type) fare better than their counterparts with light chain amyloidosis, mainly because of the slower progression of the disease.[13]

The most common cause of waitlist mortality in patients with ACM has been documented to be primarily cardiac, resulting from poor systemic perfusion due to end-stage heart failure,[14] similar to our finding that the most common causes of death among patients with ACM were multiorgan failure and cardiac arrest. This is likely to be contributed to by the limited use of left ventricular assist devices as bridges to transplantation in this population. This is reflected in our study, in which only 1.6% patients on the HT waitlist had a left ventricular assist device compared to 25% of patients with DCM. This also highlights the importance of early listing of patients with ACM compared to patients with DCM because of the limited options for support in the advanced stages. It is interesting that under the proposed new allocation system for heart transplantation,[6] patients with ACM would fall under Status 4, which would be represented by current Status 1B. Whether this new allocation system would actually lead to reduced waitlist time for patients with ACM remains to be seen. It is an area of interest for future studies.

We acknowledge several important limitations of our study. First, registries provide large numbers of patients, but that is at the expense of granularity and accuracy. Therefore, our analysis of registry data may not be as robust as that of prospective studies. However, our study has the largest number of patients with ACM to have been studied to date. Second, the UNOS registry does not differentiate between patients with transthyretin amyloidosis vs light chain amyloidosis amyloidosis. We acknowledge transthyretin amyloidosis and light chain amyloidosis amyloidosis as distinct entities, but we were unable to assess that difference in our study population due to the lack of data concerning specific amyloidosis type. We also acknowledge that some patients with ACM may have been misclassified into the idiopathic RCM group. However, compared to the enrichment of ACM cases in the ACM cohort, these are likely to be only a few cases and would not drive the results seen in our study. Finally, all baseline characteristics were obtained at the time of listing. We acknowledge that some of these characteristics, such as listing status and hemodynamic parameters, are dynamic and may have changed over the course of the study since the time of listing.

CONCLUSION

Patients with ACM listed for HT have higher waitlist mortality than patients with other types of cardiomyopathies. Further studies are needed to identify whether special prioritization should be considered for patients with ACM who have been listed for HT.

STATEMENT OF AUTHORSHIP

Category 1

(a) Conception and Design: Muhammad Siyab Panhwar and Sadeer G. Al-Kindi devised the study design.

(b) Acquisition of Data: Sadeer G. Al-Kindi acquired the data and conducted statistical analyses.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.cardfail.2019.04.011.

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