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Outcomes in Patients With Cardiac Amyloidosis Undergoing Heart Transplantation

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ABSTRACT

OBJECTIVES The purpose of this study is to report outcomes after heart transplantation in patients with cardiac amyloidosis based on a large single-center experience.

BACKGROUND Cardiac amyloidosis causes significant morbidity and mortality, often leading to restrictive cardiomyopathy, progressive heart failure, and death. Historically, heart transplantation outcomes have been worse in patients with cardiac amyloidosis compared with other heart failure populations, in part due to the systemic nature of the disease. However, several case series have suggested that transplantation outcomes may be better in the contemporary era, likely in part due to the availability of more effective light chain suppressive therapies for light chain amyloidosis.

METHODS This study examined all patients seen between 2004 and 2017, either at the Stanford University Medical Center or the Kaiser Permanente Santa Clara Medical Center, who were diagnosed with cardiac amyloidosis and ultimately underwent heart transplantation. This study examined pre-transplantation characteristics and post-transplantation outcomes in this group compared with the overall transplantation population at our center.

RESULTS During the study period, 31 patients (13 with light chain amyloidosis and 18 with transthyretin [ATTR] amyloidosis) underwent heart transplantation. Patients with ATTR amyloidosis were older, were more likely to be male, had worse baseline renal function, and had longer waitlist times compared with both patients with light chain amyloidosis and the overall transplantation population. Post-transplantation, there were no differences in post-operative bleeding, renal failure, infection, rejection, or malignancy. There was no significant difference in mortality between patients who underwent heart transplantation for amyloid cardiomyopathy and patients who underwent heart transplantation for all other indications.

CONCLUSIONS In carefully selected patients with cardiac amyloidosis, heart transplantation can be an effective therapeutic option with outcomes similar to those transplanted for other causes of heart failure.
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Amyloidosis is a disease characterized by deposition of insoluble protein fibrils in tissues, which leads to toxic effects and progressive organ dysfunction (1–4). Amyloid fibrils in cardiac amyloidosis are most frequently derived from immunoglobulin light chains (AL) or transthyretin (ATTR) (4). AL amyloidosis occurs in the setting of clonal plasma cell dyscrasias that result in

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the *JACC: Heart Failure* author instructions page.

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ABBREVIATIONS AND ACRONYMS

AL = immunoglobulin light chain amyloidosis

ATTR = transthyretin amyloidosis

ASCT = autologous stem cell transplantation

UNOS = United Network for Organ Sharing

dysregulated production and secretion of aberrant light chains (5–7). ATTR amyloidosis occurs from deposition of misfolded transthyretin protein, in either a wild-type form or associated with inherited mutations (8–12).

AL amyloidosis most commonly affects multiple vital organs; common organ involvement includes the heart, kidneys, the gastrointestinal tract, liver, and nerves (6,8,13–15). Vital organ involvement in ATTR amyloidosis is typically primarily limited to the heart (wild-type form) or the heart and peripheral nerves (hereditary variant forms). Amyloid fibril deposition in the myocardium can result in restrictive cardiomyopathy, arrhythmias, and conduction system disease (16–21). Of all organs affected by systemic amyloidosis, cardiac involvement portends the worst prognosis. Both AL and ATTR cardiac amyloidosis are associated with high rates of mortality (22–26).

One challenge in treating cardiac amyloidosis is that biventricular restrictive physiology frequently leads to intolerance of traditional guideline-directed medical therapies for heart failure. No cardiac medications or implantable devices have been shown to improve mortality for patients with amyloid cardiomyopathy (16,27–31). Heart transplantation is 1 option for treating amyloid cardiomyopathy, but its use has been controversial due to early reports of poor post-transplantation outcomes (32). In a system that lacks sufficient organs to meet demand, offering heart transplantation for cardiac amyloidosis has been hypothesized by some to be a poor allocation of a limited resource (33,34).

Despite initial concerns about poor outcomes in patients with amyloidosis who are undergoing heart transplantation, multiple amyloid centers have continued pursuing this therapy with promising results (32,35,36). We previously reported the early results of our first 19 heart transplantations for amyloid cardiomyopathy and attributed improved outcomes to careful patient selection, along with advancements in therapies for controlling light chain production in AL amyloidosis (37,38). This report offers an extended perspective of our clinical experience with a greater number of transplantation recipients and significantly longer patient follow-up.

TABLE 1 Baseline Characteristics

	All Amyloid Patients (N = 31)	AL (n = 13)	ATTR (n = 18)	p Value
Age at diagnosis (yrs)	61 (56–67)	56 (49–61)	66 (60–69)	<0.001
Age at transplant (yrs)	61 (57–67)	57 (49–61)	66 (61–70)	0.042
Male	22 (71)	6 (46)	16 (89)	0.017
Race				
White	16 (52)	8 (62)	8 (44)	
Black	10 (32)	1 (8)	9 (50)	
Other	5 (16)	4 (31)	1 (6)	
TTR genotype				
WT/WT			9 (50)	
V122I/WT			7 (39)	
V122I/V122I			1 (6)	
V1221/G6C			1 (6)	
Pathological light chain				
Kappa		2 (15)		
Lambda		11 (85)		
Mayo stage				
II		2 (15)		
III		5 (39)		
IV		6 (46)		
ASCT after heart transplantation		5 (38)		
Median pre-transplant labs				
Troponin I (ng/ml)	0.10 (0.04–0.20)	0.10 (0.05–2.00)	0.10 (0.02–0.20)	0.964
BNP (pg/ml)*	436 (254–757)	680 (366–1,205)	260 (182–453)	0.023
NT-proBNP (pg/ml)*	4,828 (3,223–7,530)	4,828 (4,300–10,349)	5,506 (2,158–8,399)	0.635
Creatinine (mg/dl)	1.3 (1.0–1.7)	0.9 (0.7–1.1)	1.6 (1.4–1.9)	<0.001
Alk phos (IU/l)	108 (78–157)	98 (75–129)	112 (77–161)	0.708
Albumin (g/dl)	3.7 (3.1–4.0)	3.7 (2.9–4.1)	3.7 (3.1–3.9)	0.953
Total bilirubin (mg/dl)	1.0 (0.8–1.2)	0.8 (0.7–1.1)	1.1 (0.9–1.3)	0.022
UNOS status				
1A	5 (16)	3 (23)	2 (11)	0.371
1B	22 (71)	10 (77)	12 (67)	0.535
2	4 (13)	0 (0)	4 (22)	0.069
Days to transplantation	42 (19–108)	23 (16–41)	81 (24–144)	0.01

Values are median (interquartile range) or n (%). *Brain natriuretic peptide (BNP) (n = 16), NT-proBNP (n = 16).
AL = light chain amyloidosis; ASCT = autologous stem cell transplantation; ATTR = transthyretin amyloidosis; TTR = transthyretin; UNOS = United Network for Organ Sharing.

METHODS

All patients treated between 2004 and 2017 at Stanford University Medical Center or Kaiser Permanente Northern California for amyloid cardiomyopathy and who ultimately underwent heart transplantation were evaluated. In all cases, the diagnosis of cardiac amyloidosis was confirmed by endomyocardial biopsy with hematoxylin and eosin and/or Congo red staining. Amyloid subtyping was confirmed with immunohistochemical staining and/or mass spectrometry. All patients were evaluated by a multidisciplinary team at the Stanford Amyloid Center and underwent standard institutional pre-transplantation screening protocols for patients with AL or ATTR amyloidosis (Supplemental Table 1).

Standardized screening included evaluation for extracardiac amyloidosis, which could adversely affect post-transplantation recovery and survival. Patients with signs of organ dysfunction were

evaluated with an organ-specific biopsy to assess for amyloid deposits. Amyloid deposits on an extracardiac biopsy, in addition to signs of significant organ dysfunction, generally constituted an absolute contraindication to heart transplantation. Mild neuropathy, smoldering myeloma, and low-grade proteinuria were not contraindications to transplantation. For patients with vascular or mucosal amyloid on gastrointestinal biopsy, decisions regarding transplantation candidacy were made by evaluating clinical symptoms. Patients were still considered for transplantation if they lacked evidence of dysmotility, bleeding, or malabsorption. For patients with AL amyloidosis, pre-transplantation response to light chain–reducing therapies was seen as favorable when assessing candidacy but was not an absolute requirement for heart transplantation. The Stanford University Heart Transplant Committee made a final consensus decision regarding eligibility for cardiac transplantation in all cases. While awaiting transplant, patients were monitored clinically at regular intervals to assess functional capacity and to evaluate for development of progressive extracardiac amyloidosis. No patient was removed from the transplantation list due to disease progression, and no patient died while awaiting heart transplantation for cardiac amyloidosis. After heart transplantation, patients were monitored and treated according to standard institutional protocols. Post-transplantation immunosuppression regimens were not systematically altered for patients with cardiac amyloidosis.

Autologous stem cell transplantation (ASCT) was performed in select patients with AL amyloidosis after they had achieved clinical stability following heart transplantation. The timing for ASCT was no sooner than 6 months after heart transplantation. The decision to pursue ASCT was influenced by multiple factors, such as medical stability following heart transplantation and adequacy of light chain control with medical therapy. ASCT was performed according to standard institutional protocols and was preceded in all cases by light chain-directed therapies followed by melphalan for bone marrow conditioning. Because non-ASCT light chain therapies have improved over the last decade, our center stopped performing routine ASCT after cardiac transplantation midway through the study period; after 2013, no patient who underwent heart transplantation for AL amyloidosis received subsequent ASCT. Aside from ASCT, no patients were considered for multiorgan transplantation for amyloidosis at this institution.

Data were collected retrospectively via chart review. Baseline laboratory values and information regarding extracardiac amyloidosis were obtained. Patients were evaluated for post-operative complications, including bleeding, renal failure, rejection, infection, malignancy, graft failure, and death. Definitions for post-operative bleeding and renal failure were previously described (38). The Stanford University Institutional Review Board and Kaiser Permanente Northern California Institutional Review Boards approved the data collection protocol used in this study.

TABLE 2 Extracardiac Amyloidosis in Patients Who Underwent Heart Transplantation for Amyloid Cardiomyopathy

	All Amyloid Patients (N = 31)	AL (n = 13)	ATTR (n = 18)	p Value
Peripheral nervous system involvement	6 (19)	0 (0)	6 (33)	0.02
Autonomic nervous system involvement	2 (7)	1 (8)	1 (6)	0.811
Carpal tunnel syndrome	19 (61)	3 (23)	16 (89)	<0.001
Bone marrow biopsy performed	20 (65)	13 (100)	7 (39)	<0.001
Median % plasma cells by IHC		15 (12–18)		
Amyloid present	1 (3)	1 (8)	0 (0)	0.485
EGD performed	19 (61)	13 (100)	6 (33)	<0.001
Vascular amyloid deposits	4 (13)	3 (23)	1 (6)	0.75
Mucosal amyloid deposits	5 (16)	5 (39)	0 (0)	0.077
Both vascular and mucosal	2 (7)	2 (15)	0 (0)	0.31
Colonoscopy performed	24 (77)	13 (100)	11 (61)	0.011
Vascular amyloid deposits	4 (13)	4 (31)	0 (0)	0.044
Mucosal amyloid deposits	7 (23)	6 (46)	1 (6)	0.047
Both vascular and mucosal	3 (10)	3 (23)	0 (0)	0.089
Renal biopsy performed	4 (13)	2 (15)	2 (11)	0.726
Amyloid present	2 (7)	2 (15)	0 (0)	0.046
Fat pad biopsy performed	16 (52)	10 (77)	6 (33)	0.017
Amyloid present	3 (10)	1 (8)	2 (11)	0.247
Liver biopsy performed	1 (3)	0 (0)	1 (6)	0.388
Amyloid present	0 (0)	0 (0)	0 (0)	

Values are n (%) or median (interquartile range).
EGD = esophagogastroduodenoscopy; IHC = immunohistochemistry; other abbreviations as in Table 1.

STATISTICAL ANALYSIS. Patients with amyloid cardiomyopathy were initially divided into 2 groups—those with AL amyloidosis and those with ATTR amyloidosis. Baseline characteristics and heart transplantation outcomes were summarized for all patients with amyloid cardiomyopathy, then compared between groups. Continuous variables were listed as medians and interquartile ranges and compared using the Mann-Whitney *U* test. Categorical variables were listed as percentages and compared using Fisher exact test. Survival curves for patients who underwent cardiac transplantation for amyloid and non-amyloid cardiomyopathy were then created using the Kaplan-Meier method. Unadjusted survival rates were compared by log-rank analysis. All calculations were completed using SPSS version 24 (IBM, Armonk, New York).

TABLE 3 Post–Heart Transplantation Outcomes for Patients With Amyloid Cardiomyopathy

	All Amyloid Patients (N = 31)	AL (n = 13)	ATTR (n = 18)	p Value
Post-operative bleeding	2 (6)	2 (15)	0 (0)	0.085
Post-operative renal failure	5 (16)	3 (23)	2 (11)	0.371
No infections requiring readmission	14 (45)	5 (38)	9 (50)	0.524
1 infection requiring readmission	6 (19)	3 (23)	3 (17)	0.656
>1 infection requiring readmission	13 (42)	6 (46)	7 (39)	0.727
Site of infection				
Bacterial pneumonia	12 (39)	6 (46)	6 (33)	0.47
CMV infection	6 (19)	1 (8)	5 (28)	0.162
Fungal infection	2 (6)	0 (0)	2 (11)	0.214
Urinary tract	3 (10)	1 (8)	2 (11)	0.751
Skin and soft tissue	2 (6)	1 (8)	1 (6)	0.811
C. difficile	1 (3)	0 (0)	1 (6)	0.388
Endocarditis	1 (3)	1 (8)	0 (0)	0.232
Bacteremia	3 (10)	3 (23)	0 (0)	0.032
Other	3 (10)	2 (15)	1 (6)	0.361
ISHLT rejection >1R				
No episodes	15 (48)	5 (38)	10 (56)	0.347
1 episode	11 (35)	5 (38)	6 (33)	0.768
>1 episode	5 (16)	3 (23)	2 (11)	0.371
Antibody-mediated rejection	1 (3)	0 (0)	1 (6)	0.388
Malignancy				
Total	11 (35)	5 (38)	6 (33)	0.768
Skin	7 (23)	3 (23)	4 (22)	0.955
PTLD	1 (3)	0 (0)	1 (6)	0.388
Other	3 (10)	2 (15)	1 (6)	0.361
Recurrent graft amyloidosis	1 (3)	1 (8)	0 (0)	0.232
Graft failure	0 (0)	0 (0)	0 (0)	
Ejection fraction on most recent echo	63 (60–65)	65 (60–65)	62 (60–66)	0.812
Follow-up yrs	4.0 (2.0–6.0)	4.3 (1.4–7.6)	3.8 (2.0–5.3)	0.54
Death	4 (13)	1 (8)	3 (17)	0.484

Values are n (%) or median (interquartile range).

CMV = cytomegalovirus; ISHLT = International Society for Heart and Lung Transplantation; PTLD = post-transplant lymphoproliferative disorder; other abbreviations as in Table 1.

RESULTS

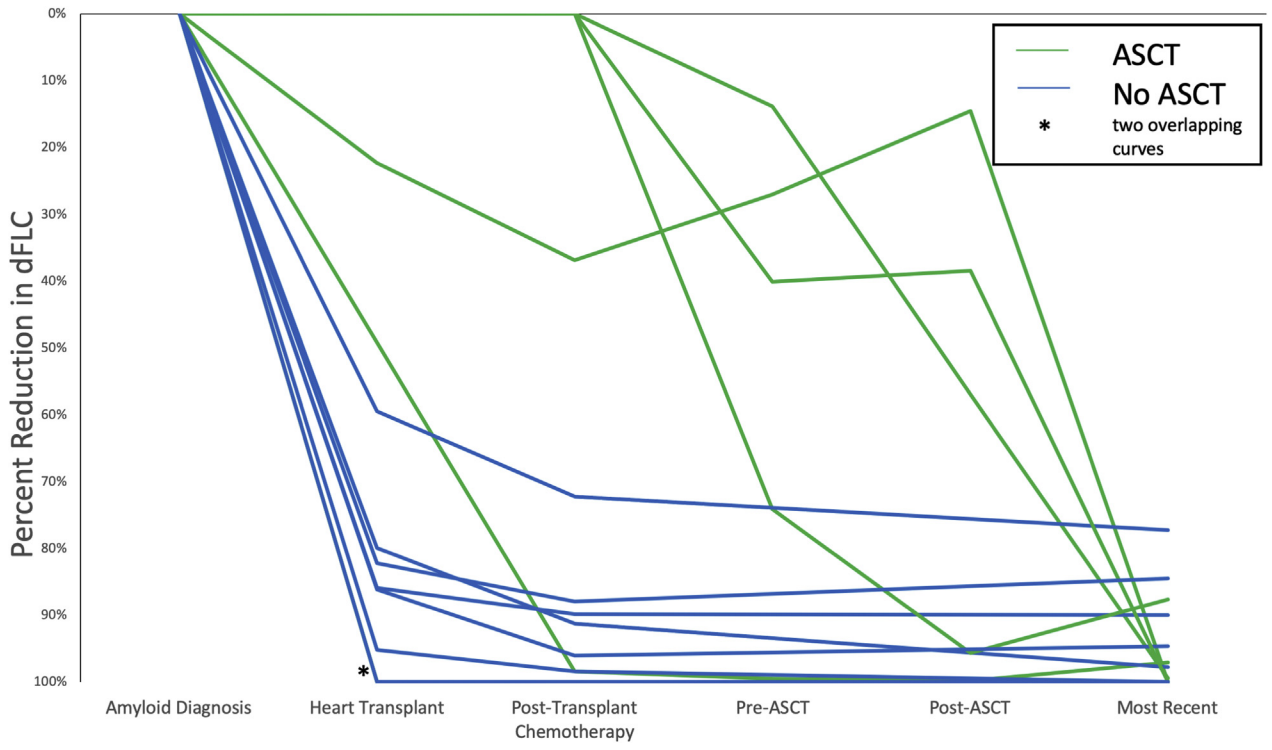
During the study period, 31 patients underwent heart transplantation for amyloid cardiomyopathy. Of these patients, 13 had AL amyloidosis and 18 had ATTR amyloidosis. Of the patients with AL amyloidosis, 2 had Mayo stage II disease, 5 had Mayo stage III disease, and 6 had Mayo stage IV disease. Patients with ATTR amyloidosis tended to be older at the time of diagnosis and transplantation, were more frequently male, waited longer for heart transplantation once listed, and had worse baseline renal function than patients with AL amyloidosis (Table 1). Baseline characteristics were otherwise similar between the groups. Median waitlist times did not differ between patients who underwent heart transplantation for cardiac amyloidosis (42 days) and non-cardiac amyloidosis indications (42 days).

Screening for extracardiac amyloidosis was performed in all cases (Table 2). Patients with ATTR amyloidosis were significantly more likely to present with carpal tunnel syndrome and symptoms of peripheral neuropathy. In total, 6 patients were noted to have peripheral neuropathy before transplantation. Of those patients, 5 had mild symptoms that were not considered likely to affect post-transplantation recovery. One patient was formally evaluated by neurology for moderate symptoms and was found to have symmetrical sensory neuropathy without motor weakness. For patients with autonomic neuropathy (n = 2), symptoms were mild, and no formal testing was performed. Patients with AL amyloidosis were more likely to undergo screening endoscopy before heart transplantation and were more frequently found to have gastrointestinal amyloid deposits. Four patients underwent renal biopsy for elevated creatinine and/or proteinuria (<1 g/day), and 2 were determined to have renal amyloidosis. Renal dysfunction was not severe enough (glomerular filtration rate >60 ml/min) to be a contraindication for cardiac transplantation in these 2 patients.

Patients with AL amyloidosis were treated with systemic therapy aimed at reducing the burden of serum free light chains and clonal plasma cell proliferation. Nine patients received proteasome inhibitor therapy before cardiac transplantation. After transplantation, 2 patients had normalized plasma free light chain ratios and did not require further chemotherapy or ASCT, 5 patients underwent ASCT, and 6 patients were treated medically with a proteasome inhibitor and/or daratumumab-based regimen. All patients showed significant decline in the difference in plasma free light chain ([kappa - lambda]) concentration from the time of diagnosis (Figure 1).

Post-transplantation outcomes were similar between AL and ATTR groups (Table 3). Two patients had significant difficulty with post-transplantation hemostasis, and 5 patients developed post-transplantation renal dysfunction that required temporary or permanent renal replacement therapy. Rates of post-transplantation infection and organ rejection were similar. One patient with gastrointestinal amyloid deposits developed post-operative ileus, which was mild and resolved with addition of an appropriate bowel regimen. Of the 2 patients with renal amyloidosis, 1 developed progressive renal dysfunction that required dialysis approximately 7 years post-transplantation. There was no significant difference in mortality between 31 patients who underwent heart transplantation for cardiac amyloidosis and 599 patients who underwent heart transplantation for all other indications (Central Illustration).

FIGURE 1 Percent Reduction of dFLc Concentration



Percent reduction of difference in plasma free light chain (dFLc) concentration ([kappa − lambda]) since the time of light chain (AL) amyloid diagnosis. ASCT = autologous stem cell transplantation.

There were 4 deaths after transplantation in our cohort of patients with cardiac amyloidosis. The earliest death occurred on post-transplantation day 71 in a patient with ATTR amyloidosis, with the cause of death determined on autopsy to be acute bacterial pneumonia. The second death occurred at 351 days post-transplantation in a patient with ATTR amyloidosis; death was attributed to multifactorial respiratory failure caused by bacterial pneumonia and diaphragmatic paralysis. The third death occurred on post-transplantation day 2,107 in a patient with AL amyloidosis, who died in hospice from complications of advanced non-small cell lung cancer. The final death occurred on post-transplantation day 3,039 in a patient with ATTR amyloidosis who developed pancreatic cancer and cholangitis. No deaths were attributable to patients' amyloidosis or amyloidosis therapy complications.

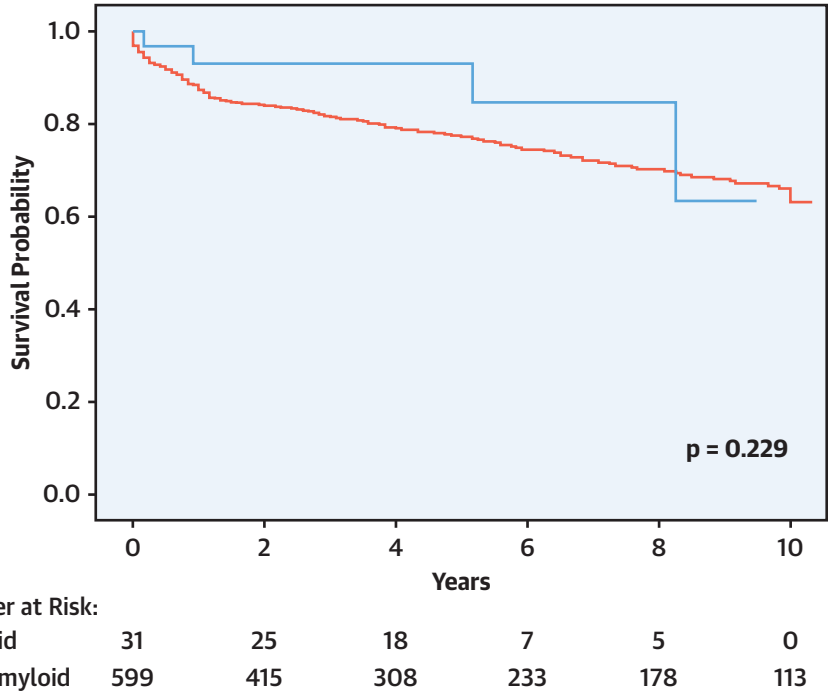
DISCUSSION

This analysis of 31 patients who underwent heart transplantation for cardiac amyloidosis is one of the largest single-center studies reported to date. Our data suggested that carefully selected patients with cardiac amyloidosis had acceptable mortality outcomes compared with patients who underwent cardiac transplantation at this institution for non-amyloid conditions, regardless of amyloid etiology (AL or ATTR). Survival data for our cohort also appeared favorable in comparison to data for overall mortality published in the International Society for Heart and Lung Transplantation 2017 Annual Adult Heart Transplant Report (39).

Because cardiac transplantation is a costly, labor-intensive, and organ-limited resource, appropriate patient selection is crucial for determining which patients may benefit most from this therapy. A rigorous selection process takes place before listing patients for organ transplantation at our institution, and it is likely that our favorable post-transplantation outcomes are in large part due to careful patient screening. To guide appropriate selection, our institution adheres to specific guidelines (Supplemental Table 1).

Our institution's screening policy is notable in that extracardiac amyloidosis is not considered to

CENTRAL ILLUSTRATION **Survival After Heart Transplantation for Patients With Amyloid and Non-Amyloid Cardiomyopathy**



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Survival after heart transplantation for cardiac amyloidosis was not significantly different than survival after heart transplantation for all other indications

be an absolute contraindication to cardiac transplantation. Specifically, patients with AL amyloidosis who were found to have limited gastrointestinal, renal, or bone marrow involvement were not immediately disqualified from transplantation if non-cardiac organ dysfunction was not thought to be life-limiting. Similarly, patients with smoldering myeloma were still considered for transplantation. This was likely because the efficacy and tolerability of light chain–directed therapies allowed patients with a higher monoclonal plasma cell burden to achieve adequate control of pathologic light chains. Furthermore, patients with systemic AL amyloidosis were not required to undergo ASCT following cardiac transplantation if pathologic light chains could be appropriately controlled with medical therapies. Less than one-half of our patients who underwent heart transplantation for cardiac AL amyloidosis underwent subsequent ASCT, all of whom required proteasome-based therapy after ASCT for ongoing pathologic light chain control.

Most patients who underwent cardiac transplantation at our institution were listed as United Network for Organ Sharing (UNOS) status 1a or 1b exceptions. Exceptions were generally taken for these patients due to the nature of their disease, an inability to tolerate inotropes, and the poor efficacy of mechanical circulatory support devices in this population. High transplantation listing status, coupled with relatively high availability of organs for transplantation in the region, led to low median time to transplantation after listing. UNOS has subsequently updated heart allocation criteria for cardiac transplantation in October 2018. UNOS eliminated the existing 2-tiered listing system and established status 1 to 6 categories (40), aiming to better prioritize certain heart failure populations who were previously disadvantaged despite having significant waitlist morbidity and mortality. Cardiac amyloidosis is

now designated as status 4 under the new listing criteria; it remains to be seen how these new criteria will affect transplantation wait times and cardiac outcomes for patients with amyloid cardiomyopathy.

STUDY LIMITATIONS

Though this report is one of the largest single-center studies reported to date, the numbers are relatively small compared to the much larger number of patients transplanted for other cardiomyopathies. In addition, local treatment practices and transplant eligibility policies vary between institutions and could lead to different results at other centers.

CONCLUSIONS

In a large single-institution experience, transplantation of carefully selected patients with AL and ATTR cardiac amyloidosis resulted in acceptable post-transplantation outcomes, with survival similar to patients who underwent transplantation for all other conditions.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Heart transplantation for patients with cardiac amyloidosis has historically been considered controversial due to poor post-transplantation outcomes. This institution's experience demonstrated that post-transplantation outcomes can be similar between amyloid and non-amyloid cardiomyopathy. The diagnosis of amyloid cardiomyopathy should not disqualify patients or limit their ability to receive heart transplantation, even if limited extracardiac involvement is present.

TRANSLATIONAL OUTLOOK: Evaluation of larger cohorts of patients who undergo transplantation for amyloid cardiomyopathy would provide more precise information regarding post-transplantation survival and other key outcomes.

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KEY WORDS amyloidosis, cardiac amyloidosis, heart transplantation, infiltrative cardiomyopathy

APPENDIX For a supplemental table, please see the online version of this paper.