Improving contemporary outcomes following heart transplantation for cardiac amyloidosis

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Abstract

Background: The incidence of systemic amyloidosis is rising, and there is a concomitant rise in heart transplant for an indication of cardiac amyloidosis.
Methods: We utilized the Organ Procurement and Transplantation Network (OPTN) database to retrospectively assess survival and outcomes in adult patients undergoing heart transplant for cardiac amyloidosis from 1999 to 2019. We also compared survival among four distinct time periods: 1999–2001, 2002–2008, 2008–2015, 2016–2019.
Results: Of 41,103 patients, 425 (1.03%) were transplanted for an indication of restrictive cardiomyopathy due to cardiac amyloidosis (RCM-Amyloidosis). The percent of all transplants occurring for RCM-Amyloidosis increased from 0.25% in the 1999–2001 era to 1.74% in the 2015–2019 era (p < .001). Across eras, Kaplan–Meier survival functions were comparable between RCM-Amyloidosis and non-RCM patients at 1 year (88% vs. 89%, p = .56) and at 5 years (72% vs. 77%, p = .092), but worse for RCM-Amyloidosis patients at 10 years (44% vs. 59%, p = .002). With adjustment for other clinical variables in multivariable Cox regression model, RCM-Amyloidosis was not associated with increased risk of death at 1 year (hazard ratio [HR] = 1.11, p = .56) or at 5 years (HR = 1.20, p = .18), but it was associated with increased risk of death at 10 years (HR = 1.35, p = .01). Cardiac amyloidosis was not associated with any morbidity outcomes following transplant, including graft failure, acute rejection, or hospitalization for infection or rejection.
Conclusions: Our data suggest a trend of improving survival among RCM-Amyloidosis patients compared with non-RCM patients across transplant eras, with current similarities in 1- and 5-year survival but a persistent, increased risk of mortality at 10 years.

KEYWORDS
cardiac amyloidosis, transplant
1 | INTRODUCTION

Cardiac amyloidosis most commonly results from two variants of the systemic disease: immunoglobulin light chain (AL) amyloid or transthyretin-related (TTR) amyloid. Most cases (85%) result from AL amyloidosis, which produces cardiac manifestations in 40%–70% of patients and causes more disseminated systemic disease than its TTR counterpart. Regardless of etiology, symptoms of cardiac amyloidosis are generally consistent with infiltrative cardiomyopathy: right-sided or biventricular heart failure with early preserved ejection fraction, thickening of the heart walls, reduced contractility, and eventual reductions in cavity size resulting in diastolic dysfunction.

Once cardiac amyloidosis becomes symptomatic, disease progression is rapid and leads to death in a matter of months (AL amyloidosis) or years (TTR amyloidosis). Standard approaches to the management of heart failure such as beta blockers, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers are poorly tolerated. Instead, treatment focuses on limiting amyloid production and deposition. In AL amyloidosis, this entails chemotherapy, autologous stem cell transplant (ASCT), and pharmacologic treatments such as bortezomib, which acts as an anti-plasma cell therapy through proteosome inhibition. A number of novel approaches to pharmacotherapy are also being studied in clinical trials, including additional proteosome inhibitors (izaxomib), anti-CD38 monoclonal antibodies (daratumumab), immunomodulators (lenalidomide), and monoclonal amyloid-directed therapies (NEOD001, CPHPC). Pharmacotherapy for TTR amyloidosis remains focused on transthyretin tetramer stabilizers, including tafamidis and alternatives now in clinical trials. These include diflunisal, a repurposed nonsteroidal anti-inflammatory drug (NSAID), tolcapone, which has been previously Food and Drug Administration (FDA) approved for Parkinson disease, and AG10, which is being studied specifically for amyloid cardiomyopathy. In patients with advanced heart disease who cannot tolerate medical therapy, heart transplant with standard immunosuppression (calcineurin inhibitor, anti-metabolite such as mycophenolate mofetil, and prednisone) is the gold standard. Transplant requires an experienced center with collaboration among cardiac surgery, hematology, nephrology, and other specialists to coordinate induction chemotherapy (often with bortezomib), transplant, and subsequent conditioning chemotherapy (usually with melphalan) and ASCT.

Despite the increasing use of transplant for cardiac amyloidosis patients, data regarding outcomes remain mixed. Previous studies of the Organ Procurement and Transplantation Network (OPTN) database have demonstrated higher mortality for RCM-Amyloidosis patients compared with all others at up to 10 years while more recent studies have demonstrated comparable survival between these two groups at up to 5 years. Recent single-center studies have observed comparable 1-year and 5-year survival among patients both with and without ASCT to manage light chain production, and one study has demonstrated comparable outcomes at up to 10 years. Long-term survival following transplant has not been re-explored at the database level, despite mounting evidence of positive outcomes in single-center studies (largely at up to 5 years) and the significant risk of posttransplant amyloid recurrence, which may occur gradually over more than 5 years. Considering the increasing use of transplant for advanced cardiac amyloidosis, we sought to characterize long-term survival outcomes among RCM-Amyloidosis patients and to assess how outcomes have changed across transplant eras.

We queried the OPTN database to assess how survival among RCM-Amyloidosis patients at 1, 5, and 10 years compared with that of patients undergoing transplant for all other indications. While prior studies

![Figure 1](image-url)
analyzed, all database years and separated data into two transplant eras, if at all, we limited our study to the past 20 years (1999–2019) and separated transplant eras into four periods based on International Society for Heart and Lung Transplantation (ISHLT)-defined year ranges (1999–2001, 2002–2008, 2009–2015, 2016–2019) to gain a better insight into contemporary trends in survival.

2 | MATERIAL AND METHODS

2.1 | Study population

The OPTN database was reviewed for adult patients (≥18 years of age) receiving a first time orthotopic heart transplant between January 1, 1999 and December 31, 2019. This range of years was selected to ensure at least 20 years of follow-up for the earliest transplants and to exclude patients who did not undergo transplant with more recent immunosuppression regimens. Patients were also excluded if they had undergone previous transplant, if multiple organs were transplanted, if they were collisted for pancreas or liver transplant, or if no follow-data were available. Variables were excluded from analysis if missing data were >20%, with exception of up to 25% for clinically relevant variables—this process only resulted in exclusion of several recipient and donor substance use variables. Institutional review board approval was obtained for analysis of the OPTN database in a prognostic study of survival following heart transplant, with no requirement to obtain informed consent.

Patients were sorted into two groups based on primary indication for transplant: restrictive cardiomyopathy due to cardiac amyloidosis (RCM-Amyloidosis) and all other non-RCM indications. Patients undergoing transplant for restrictive cardiomyopathy due to other etiologies (RCM-Other) were included as a third group for survival analyses. Transplant eras were defined by ISHLT-determined year ranges: 1999–2001, 2002–2008, 2009–2015, 2016–2019.

**FIGURE 2** Number of transplants for cardiac amyloidosis by year (A) and percent of all transplants performed for an indication RCM-Amyloidosis, by era (B)
2002–2008, 2009–2015, 2016–2019. Linear regression was used to determine whether the number of transplants increased by year. Logistic regression was used to determine whether the proportion of all transplants performed for RCM-Amyloidosis increased by era. Pearson’s $\chi^2$ and Fisher’s exact test were used to measure differences in variables between groups. Differences in continuous variables with normal distribution were assessed using analysis of variance while those with non-normal distribution were assessed with the Kruskal–Wallis $H$ test.

2.2 | Survival analysis

Kaplan–Meier analysis with predicted survival functions was used to compare outcomes of RCM-Amyloidosis and non-RCM patients at 1, 5, and 10 years. Patients were censored at 10 years of survival, at the time of retransplantation, or at the time of last contact if lost to follow-up.

Log-rank tests and univariable Cox Proportional Hazards regression models were used to assess the associations of clinically relevant categorical and continuous variables, respectively, with posttransplant 1-year survival. All variables with $p \leq .2$, and one with $p > .2$ (gender) were

### Table 1: Demographic characteristics of heart transplant recipients (1999–2019) by primary indication for transplant

|                | Non-RCM indications | RCM-Amyloidosis |
|----------------|---------------------|-----------------|
| N = 39,974     | N = 425             |                 |
| Recipient age  | 56 (46–62)          | 64 (57–68)      | <.001 |
| Male gender    | 30,235 (76%)        | 346 (81%)       | .02   |
| Days on waitlist| 90 (25–261)         | 39 (16–117)     | <.001 |
| Race (N, % within column) |             |                 |
| White         | 27,971 (70%)        | 259 (61%)       | <.001 |
| Black         | 7610 (19%)          | 137 (32%)       | .40   |
| Hispanic      | 3105 (8%)           | 24 (6%)         | .96   |
| Asian         | 1171 (3%)           | 11 (3%)         | <.001 |
| American Indian/Alaskan Native | 124 (~0%) | 0 (0%)         | .28   |
| Pacific Islander | 113 (~0%) | 2 (~0%)        | .17   |
| Multiracial   | 206 (1%)            | 0 (0%)          | .17   |
| Initial transplant status$^a$ |             |                 |
| Status 1A     | 8486 (23%)          | 67 (18%)        | .04   |
| Status 1B     | 14,747 (40%)        | 117 (32%)       | .002  |
| Status 2      | 13,708 (37%)        | 181 (50%)       | <.001 |
| Final transplant status$^b$ |             |                 |
| Status 1A     | 19,014 (51%)        | 203 (56%)       | .06   |
| Status 1B     | 13,158 (36%)        | 116 (32%)       | .18   |
| Status 2      | 4764 (13%)          | 41 (11%)        | .40   |

Note: Categorical variables presented as n (%) and continuous variables are presented as median (interquartile range). Significant $p$-values are shown in bold.

### Table 2: Clinical characteristics of heart transplant recipients and allograft donors (1999–2019) by primary indication for transplant

|                | Non-RCM indications | RCM-Amyloidosis |
|----------------|---------------------|-----------------|
| N = 39,974     | N = 425             |                 |
| Recipient BMI  | 27.1 (4.8)          | 25.3 (3.7)      | <.001 |
| Diabetes       | 10,280 (26%)        | 52 (12%)        | <.001 |
| Dialysis before Tx | 986 (2%)  | 9 (2%)         | .60   |
| Malignancy before Tx | 2661 (7%) | 68 (16%)      | <.001 |
| Cerebrovascular disease | 2054 (5%) | 13 (3%)        | .05   |
| Prior cardiac surgery | 15,743 (39%) | 34 (8%)        | <.001 |
| Life support at Tx | 30,414 (75%) | 302 (70%)      | .01   |
| ECMO at Tx     | 340 (1%)            | 6 (1%)          | .22   |
| Intra-aortic balloon pump at Tx | 3105 (8%) | 59 (14%)       | <.001 |
| On-ventilator at Tx | 799 (2%)  | 6 (1%)         | .37   |
| Hospitalized at transplant | 19,367 (48%) | 292 (69%)      | <.001 |
| Serum creatinine at Tx | 1.3 (0.6) | 1.3 (0.5)      | .04   |
| Chronic seroid use | 3016 (8%)    | 25 (6%)        | .18   |
| History of cigarette use | 14,433 (36%) | 118 (28%)      | <.001 |

|                | Donor characteristics |             |
|----------------|----------------------|----------------|
| N = 39,974     | N = 425              |                 |
| Recipient age  | 30 (22–41)           | 34 (24–46)     | <.001 |
| Calculated donor BMI | 27.0 (5.7) | 27.3 (6.0)     | .26   |
| Ischemic time (hours) | 3.2 (1.0) | 3.1 (1.0)      | .13   |
| HLA mismatch level | 5 (4–5)        | 5 (4–6)        | .04   |
| Donor history of diabetes | 1195 (3%) | 22 (5%)        | .01   |
| Donor history of cigarette use | 7532 (19%) | 78 (18%)      | .81   |
| Donor history of hypertension | 5628 (14%) | 89 (21%)      | <.001 |
| Donor history of MI | 319 (1%)       | 4 (1%)         | .75   |
| Donor history of cancer | 647 (2%)  | 13 (3%)        | .02   |

Note: Categorical variables presented as n (%) and continuous variables are presented as median (interquartile range) or mean (standard deviation). Significant $p$-values are shown in bold.

Abbreviations: BMI, body mass index; ECMO, extracorporeal membrane oxygenation; HLA, human leukocyte antigen; MI, myocardial infarction; Tx, transplant.

### Additional Notes:
- The data encompasses 94% of all patients in the dataset.
- Transplant status data before the heart allocation policy change in 2018.
- Race categories include White, Black, Hispanic, Asian, American Indian/Alaskan Native, Pacific Islander, and Multiracial.
- Donor characteristics include age, BMI, ischemic time, HLA mismatch level, donor history of diabetes, cigarette use, hypertension, MI, and cancer.
- Kaplan–Meier analysis was used to compare outcomes of different indications.
included in a multivariable Cox model. The association of RCM-
Amyloidosis with risk of 1-, 5-, and 10-year mortality in each era and
across eras was then assessed while adjusting for each other variable in
this model. The Schoenfeld Residuals test was used to confirm that the
proportionality of hazards assumption was satisfied in our model.

Logistic regression was used to assess the incidence of secondary
outcomes in each group, including coronary artery disease, stroke, new
pacemaker requirement, acute rejection, treatment for rejection, hospi-
talization for rejection or infection, and graft failure.

Statistical analyses were performed using Stata 15/SE.31 Tests were
performed with a 0.05 level of statistical significance.

3 | RESULTS

3.1 | Demographics

A total of 52,578 individuals received a heart transplant between
January 1, 1999 and December 31, 2019, of which 2117 (4.03%) were
excluded for multiple organ transplant and 44 (0.08%) were
then excluded due to concurrent listing for additional organs (-
Figure 1). After application of additional exclusion criteria, 41,103
adult, first-time transplant patients remained in our study population,
425 of whom (1.03%) were transplanted for cardiac amyloidosis.

The number of yearly transplants for RCM-Amyloidosis in-
creased over the study period from 8 (0.4%) in 1999 to 59 (2.2%)
in 2019 (p < .001) (Figure 2A). The proportion of transplants for
RCM-Amyloidosis compared with all other indications also in-
creased from 0.24% in 1999–2001 to 0.59% in 2002–2008
(1.21% in 2009–2015, and 1.74% in 2016–2019 (p < .001 be-
tween first and last eras) (Figure 2B). Compared with those with
non-RCM indications, patients with RCM-Amyloidosis were more
likely to be male (81% vs. 76%, p = .02), black (32% vs. 19%,
p < .001), and older (median 64 [57–68] vs. 56 [46–62], p < .001)
(Table 1). RCM-Amyloidosis patients were less likely than non-
RCM patients to receive Status 1A (18% vs. 23%, p = .04) or 1B
listing (32% vs. 40%, p = .002), and more likely to be assigned to
Status 2 (50% vs. 37%, p < .001). However, RCM-Amyloidosis
patients were also more likely to change status while on the
waitlist (56% vs. 51%, p = .01) and there were no differences in
status at the time of surgery. Following the 2018 heart allocation
policy change, RCM-Amyloidosis patients were more likely to be
assigned to Status 4 (51% vs. 30%, p = .001), and similarly likely to
be assigned to all other statuses, compared with non-RCM
patients.

Compared with non-RCM patients, RCM-Amyloidosis patients spent
fewer days on the waitlist [39 (16–117) vs. 90 (25–261), p < .001] and
were less likely to have a history of diabetes (12% vs. 26%, p < .001), prior
cardiac surgery (8% vs. 39%, p < .001), or cigarette use (28% vs. 36%,
p < .001) (Table 2). Before transplant, RCM-Amyloidosis patients were
less likely to be hospitalized (69% vs. 48%, p < .001) or to require life
support (70% vs. 75%, p = .01), including ventricular assist devices, intra-
aortic balloon pumps, extracorporeal membrane oxygenation, inotropes,
ventilators, or inhaled nitric oxide.

3.2 | Survival analysis

Compared with non-RCM patients, Kaplan–Meier survival functions
of RCM-Amyloidosis patients at 1-year were worse in the
1999–2001 era (54% vs. 85%, p = .003), but comparable in sub-
sequent eras and across the 1999–2019 study period (88% vs. 89%,
p = .56) (Table 3). Five-year survival functions for RCM-Amyloidosis
patients were worse up to the 2002–2008 era (54% vs. 75%,
p < .001), but comparable in the subsequent era and across the
1999–2019 study period (72% vs. 77%, p = .09). Ten-year survival
functions were worse for RCM-Amyloidosis patients in all eras, with a
15% difference in predicted 10-year survival across eras (44% vs.
59%, p = .002) (Figure 3). Survival estimates of RCM-Amyloidosis
patients were observed to improve across eras (Figure 4).

| Table 3 | Survival functions associated with RCM-amyloidosis and non-RCM indications at each time point and in each transplant era |
|---------|--------------------------------------------------|--------|--------|--------|--------|--------|
|         | 1999–2001 | 2002–2008 | 2009–2015 | 2016–2019 | All Eras |
|         | SF | p   | SF | p   | SF | p   | SF | p   |
| One year |     |      |     |      |     |      |     |      |
| RCM-Amyloidosis | 54% | .003 | 83% | .21 | 90% | .65 | 92% | .84 |
| Non-RCM | 85% |        | 88% |      | 91% |      | 92% |      |
| Five year |     |      |     |      |     |      |     |      |
| RCM-Amyloidosis | 54% | .08 | 54% | .001 | 79% | .89 | 72% | .09 |
| Non-RCM | 73% |        | 75% |      | 79% |      | 77% |      |
| Ten year |     |      |     |      |     |      |     |      |
| RCM-Amyloidosis | 15% | .001 | 44% | .002 | 35% | .02 | 44% | .002 |
| Non-RCM | 54% |        | 59% |      | 61% |      | 59% |      |

Note: Significant p-values are shown in bold.
Abbreviations: RCM, restrictive cardiomyopathy; SF, survivor function.
FIGURE 3 Kaplan–Meier curve of 10-year survival, by indication for transplant (1999–2019)

FIGURE 4 Kaplan–Meier curves of 10-year survival in the 1999–2001 (A), 2002–2008 (B), and 2009–2015 (C) transplant eras
Twenty-six variables were found to be associated with 1-year survival in univariable Cox regression, and all were included in a multivariable model (representative model for 1-year survival across eras in Table 4). When adjusting for all other variables and including patients from all eras (1999–2019), RCM-Amyloidosis was not associated with increased risk of mortality at 1 year (HR = 1.11, p = .56).
or at 5 years (HR = 1.2, p = .18) (Table 5), but remained associated with increased risk at 10 years (HR = 1.35, p = .01). When including only patients from each era in this multivariable model and continuing to adjust for all other variables, RCM-Amyloidosis was associated with a trend of increased mortality risk for RCM patients at all time points in the 1999–2001 era, at 5 and 10 years in the 2002–2008 era, and only at 10 years in the 2009–2015 era (Table 5).

3.3 Secondary outcomes

The incidence of retransplantation was comparable among RCM-Amyloidosis and non-RCM patients (0.7% vs. 1.5%, p = .17). Loss to follow-up at any time point was less common among RCM-Amyloidosis patients compared with non-RCM patients (0.7% vs. 3.6%, p = .001). No secondary morbidity outcomes following transplant were associated with RCM-Amyloidosis across eras.

4 CONCLUSIONS

In our study of 41,103 adult heart transplant patients in the OPTN database, including 425 who underwent transplant for the primary diagnosis of cardiac amyloidosis, we found that RCM-Amyloidosis patients now experience similar 1- and 5-year survival compared with non-RCM patients, but that 10-year mortality remains higher among this group. We also observed a near 10-fold increase in the proportion of transplants for any form of cardiac amyloidosis—from 0.24% in the 1999–2001 era to 1.74% in the 2015–2019 era, with a peak of 2.22% of all transplants in 2019. In consideration of this growth and of ongoing concerns regarding donor heart allocation, our data may inform future allocation practices and postoperative management. Despite worse long-term survival among cardiac amyloidosis patients, outcomes continue to improve for this group and the disease should not be considered a contraindication to transplant in an appropriate hospital setting.

We found that patients undergoing heart transplant for RCM-Amyloidosis were more likely to be male, black, and older than non-RCM patients, reflecting known demographics of patients with TTR amyloidosis. RCM-Amyloidosis patients also had fewer comorbidities at transplant than non-RCM patients, with a lower average body mass index (BMI) and lower likelihood of prior diabetes, prior cardiac surgery, or cigarette use. RCM-Amyloidosis patients were also less likely to be hospitalized or to require life support at the time of transplant. Although RCM-Amyloidosis patients enjoyed fewer comorbidities and were initially assigned a less urgent transplant status (both pre- and post-allocation change), their significantly shorter waitlist times and similar status at the time of transplant suggest a more rapid progression of heart failure compared with non-RCM patients. Given existing literature on the rapid progression of heart failure in cardiac amyloidosis, shorter waitlist times may not be surprising.

In unadjusted Kaplan–Meier analyses of all patients (1999–2019), estimated survival for RCM-Amyloidosis patients was similar to those of non-RCM patients at 1 and 5 years, but reduced by 15% at 10 years. This trend persisted when adjusting for other clinically relevant variables in multivariable cox regression, where RCM-Amyloidosis was not associated with increased risk of mortality at 1 or 5 years, but with a 35% increased risk of mortality at 10 years. These data suggest that 1- and 5-year survival are now comparable among RCM-Amyloidosis and non-RCM patients, although 10-year survival is still worse among RCM-Amyloidosis patients. This long-term risk is likely the result of progressive systemic manifestations of amyloidosis or recurrence in the allograft. As general management of amyloidosis continues to improve, however, this disparity may disappear altogether—one single-center study has already found comparable outcomes between cardiac amyloidosis and all other patients at up to 10 years following transplant. Furthermore, we have added to clinical knowledge regarding improving survival trends for transplanted cardiac amyloidosis patients at the national level and set the stage for future studies that will assess long-term survival of patients transplanted in the most recent eras.

There were several limitations to this study. Although this is the largest database study of transplant outcomes among cardiac amyloidosis patients to date, a high proportion of transplants occurred in the most recent years of OPTN data collection, when outcomes were best. It is possible that long-term outcomes of patients most recently transplanted will be increasingly comparable between RCM-
Amyloidosis and non-RCM patients, but our study cannot make this conclusion due to limitations in the current length of follow-up data. Our analysis of outcomes in the 1999–2001 era, where follow-up time was adequate for analysis of long-term outcomes, was limited by a low number of patients transplanted for RCM-Amyloidosis (n = 13). This likely accounts for nonsignificant hazard ratios at all time points in the 1999–2001 era, despite a trend of increased risk of mortality and significant differences in survival functions at 1 and 10 years. In addition, we were unable to distinguish between AL and TTR cardiac amyloidosis patients due to the absence of this information in the OPTN database. Finally, transplant outcomes in this patient subset may be affected by the 2018 OPTN heart allocation policy change, but we did not address this possibility in our study.

We have found that 1- and 5-year survival is now comparable between RCM-Amyloidosis and non-RCM patients, but that RCM-Amyloidosis is still associated with a 15% difference in survival functions at 10 years. Future database studies may reflect comparable survival at 10 years which has, at this point, only been observed at the institutional level. In light of these findings and other recent studies, heart transplant should be considered an effective form of treatment among select patients with advanced cardiac amyloidosis, although the posttransplant longevity of this population does not yet match that of non-RCM patients nationwide.

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Conflict of interests

The authors declare that there are no conflict of interests.

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