Outcomes after heart transplantation in patients with cardiac sarcoidosis

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Abstract

Background  The number of patients with sarcoidosis requiring heart transplantation (HT) is increasing. The aim of this study was to evaluate outcomes of isolated HT in patients with sarcoid cardiomyopathy and compare them to recipients with non-ischaemic restrictive or dilated cardiomyopathy.

Methods and results  Adult HT recipients were identified in the UNOS Registry between 1990 and 2020. Patients were grouped according to diagnosis. The cumulative incidences for the all-cause mortality and rejection were compared using Fine and Gray model analysis, accounting for re-transplantation as a competing risk. Rejection was evaluated using logistic regression analysis. We also reviewed characteristics and outcomes of all HT recipients with previous diagnosis of sarcoid cardiomyopathy from a single centre. A total of 30,160 HT recipients were included in the present study (n = 239 sarcoidosis, n = 1411 non-ischaemic restrictive cardiomyopathy, and n = 28,510 non-ischaemic dilated cardiomyopathy). During a total of 194,733 patient-years, all-cause mortality at the latest follow-up was not significantly different when comparing sarcoidosis to non-ischaemic dilated cardiomyopathy [adjusted subhazard ratio (aSHR) 1.46, 95% confidence intervals (CIs): 0.9–2.4, P = 0.12] or restrictive cardiomyopathy (aSHR 1.12, 95% CI: 0.65–1.95, P = 0.67). Accordingly, multivariable analysis suggested that 1 year mortality was not significantly different between sarcoidosis and non-ischaemic dilated cardiomyopathy [aSHR 1.56, 95% CI: 0.9–2.7, P = 0.12] or restrictive cardiomyopathy [aSHR 1.15, 95% CI: 0.61–2.18, P = 0.66]. No differences were observed regarding 30 day mortality, treated and hospitalized acute rejection, and 30 day death from graft failure after HT. Thirty-day mortality did not improve significantly in more recent HT eras whereas there was a trend towards improved 1 year mortality in the latest HT era (P = 0.06). Data from the single-centre case review showed excellent long-term outcomes with sirolimus-based immunosuppression.

Conclusions  Short-term and long-term post HT outcomes among patients with sarcoid cardiomyopathy are similar to those with common types of non-ischaemic cardiomyopathy.

Keywords  Cardiac sarcoidosis; Heart transplantation; Restrictive cardiomyopathy; Dilated cardiomyopathy; Outcomes

Introduction

Sarcoidosis is a rare, multisystem, inflammatory, granulomatous disease with unpredicted course. When it involves the heart, sarcoidosis manifests with conduction abnormalities, ventricular arrhythmias and heart failure (HF), with the latter requiring extensive cardiac involvement.¹ Disease progression is associated with infiltrates that are replaced by fibrotic scar. Cardiac sarcoidosis (CS) can ultimately lead to end-stage HF requiring advanced treatments, such as left
ventricular assisting device (LVAD) support or heart transplantation (HT). Although LVADs have been shown to be an effective treatment for advanced HF in the general population with ischaemic or non-ischaemic dilated cardiomyopathy, they are sub-optimal in the case of CS due to recurrent VT arrhythmias. This limitation can be overcome with HT by replacing the diseased heart with compromised electrical conduction system by a new well-functioning graft.

Current data derived from case series suggest the feasibility and efficacy of HT in the CS population. A previous analysis of the United Network for Organ Sharing (UNOS) Scientific Registry of Transplant Recipients including 148 CS patients and over 30 000 non-CS patients who underwent HT between 2006 and 2015 showed non-inferior outcomes of the CS arm compared to non-CS patients in terms of 5 year mortality. In the current study, we sought to investigate the short-term and long-term outcomes in a contemporary cohort of HT patients with CS from the UNOS database. We additionally performed a case series analysis of HT recipients with CS from a single centre to obtain further insight using more granular data.

Methods

Study population

A retrospective analysis was performed using the UNOS Registry Standard Analysis and Research database. The UNOS Registry administers the Organ Procurement and Transplantation Network (OPTN) under contract with the United States (US) Department of Health and Human Services. This database contains data on all transplant candidates undergoing listing for solid organ transplantation in the US since October 1987. The data set used for this investigation included all recipients who were transplanted with a heart between 1990 and 2020. This database contains de-identified information of included patients; hence it is considered institutional review board exempt.

Additionally, we performed a single-centre retrospective analysis of 529 patients who underwent HT at the Mayo Clinic, Rochester, Minnesota, during the period 1994 through February 2015. Demographic, clinical follow-up and laboratory data were obtained by review of the patients’ medical records and from the prospectively collected clinical database. Immunosuppressive medications were reviewed and recorded at each outpatient visit post HT. The main characteristics of this cohort have been described in detail previously. The data collection was approved by the Institutional Review Board of Mayo Clinic College of Medicine.

Study design and objectives

In the analysis of the UNOS registry, all adult patients with a diagnosis of CS or non-ischaemic restrictive or dilated cardiomyopathy who received an isolated HT during the study period were included. Exclusion criteria included candidates <18 years old, those undergoing simultaneous lung, liver, or abdominal transplantation, and those with incomplete outcomes data. The study population was then grouped based on diagnosis into sarcoidosis, non-ischaemic restrictive cardiomyopathy, or non-ischaemic dilated cardiomyopathy. The main outcomes were all-cause mortality during follow-up, 30 day mortality, 1 year mortality, and treated acute allograft rejection in the first hear after HT.

Statistical analyses

Continuous variables were checked for normality using the Shapiro–Wilk test and are presented as mean ± SD. Differences between groups were assessed using the ANOVA test. Categorical variables were expressed as frequency (%) and compared with the χ² test. Because re-transplantation is a competing event for all-cause mortality, the cumulative incidence function (CIF) was used to estimate the cumulative incidence of all-cause mortality and rejection. The CIF keeps patients who experienced the competing risk event (in this case re-transplantation) in the risk set using inverse probability weighting; therefore, once patients have undergone re-transplantation, they contribute less to the risk set than those who did not and are still at risk of the event. Nelson–Aalen cumulative-hazard plots were used to describe all-cause mortality. Subsequently, 30 day mortality, 1 year morality, and mortality at latest follow-up were compared between groups based on diagnosis using the Fine and Gray model, and these were presented as subdistribution hazard ratios (SHR) with 95% confidence intervals (CIs). The multivariable models included age, race, diabetes mellitus, body mass index, calculated panel reactive antibody (CPRA) values, UNOS status, induction therapy, serum creatinine at the time of HT, extracorporeal membrane oxygenation (ECMO), intra-aortic balloon pump (IABP), LVAD support as a bridge to HT, ischaemic time, mechanical ventilation at the time of HT, donor age, and donor gender. The 1 year risk of rejection was analysed with logistic regression analysis after adjusting for the same covariates, and results were presented as odds ratios (ORs) with 95% CI. The effects of three HT eras (1990–1999, 2000–2009, and 2010–2020) on outcomes were tested. Analyses were performed using Stata 17.0 (College Station, Texas, USA). All tests were two-sided, and P < 0.05 was considered as statistically significant.
Results

Patient characteristics

In the UNOS registry, there were 62,970 patients who underwent HT between 1990 and 2020. We identified three groups of HT recipients: 239 diagnosed with sarcoidosis, 1,411 with non-ischaemic restrictive cardiomyopathy, and 28,510 with non-ischaemic dilated cardiomyopathy. Baseline characteristics are presented in Table 1. Male patients were the predominant gender without differences among groups (P = 0.234). Black race was more prevalent in the sarcoidosis group (28%) compared with the other groups (P < 0.001). Patients with CS had significantly lower creatinine as well as lower pulmonary capillary wedge pressures (PCWP) and systolic pulmonary artery pressures (sPAP) both at listing and at HT times (P < 0.001). Similarly, they had a lower need for inotropes at the time of listing and HT (P < 0.001). Among CS patients, 191 underwent transplant between 2009 and 2020, 33 between 2000 and 2009, and 15 between 1990 and 1999.

Regarding the case series from the Mayo Clinic in Rochester, MN, USA, we identified 14 patients with CS prior to HT (2.64%) who were also confirmed in the explanted hearts. Within the sarcoidosis group, most patients were men (57.1%) and 9 (64.3%) patients had dilated cardiomyopathy (Table 2). One patient underwent combined heart and kidney transplant. Regarding the classic cardiovascular risk factors, 4 (28.6%) had hypertension, one patient had diabetes and the overall kidney function was reasonable [eGFR, 60 (23.6) mL/min/1.73 m²]. All patients were receiving statins, whereas only one patient was receiving aspirin. From the immunosuppression (IS) perspective, all patients were treated with the combination of calcineurin inhibitor (CNI) (71% with tacrolimus and the remaining patient with cyclosporine) and antimetabolite (85.7% with mycophenolate mofetil (MMF) and the remaining with azathioprine) early post-HT. Subsequently, most patients (85.7%) were converted from CNI-based IS to sirolimus (SRL)-based IS and the median time to SRL conversion was 0.8 [interquartile range (IQR): 0.61–1.17] years. The median duration of treatment with SRL was 3.7 years (IQR: 1.9–6). All patients were treated with steroids with mean duration of 3.1 (2.1) years post-HT. Two patients had The International Society of Heart and Lung Transplantation (ISHLT) grade 2R acute cellular rejection and two patients had antibody mediated rejection. However, only one patient developed haemodynamically significant rejection (defined as allograft rejection causing significant allograft dysfunction with haemodynamic derangement). Three patients (23%) had mild allograft vasculopathy (ISHLT Grade 1). Moreover, 2 patients had cytomegalovirus (CMV) infection and 3 patients had Epstein–Barr virus (EBV) infection. No patients developed a solid or haematologic malignancy. However, 5 patients had skin cancer (3 with squamous cell carcinoma and 2 with basal cell carcinoma). During a follow time of 5.1 (IQR: 3.2–7.6) years, one patient died. After reviewing all endomyocardial biopsies obtained post HT, no recurrence of CS was observed in any of the patients included in the study during follow-up.

Outcomes of heart transplantation in patients with cardiac sarcoidosis

We assessed whether outcomes after HT differed between patients with CS and those with restrictive or dilated cardiomyopathy using a CIF, accounting for re-transplantation as a competing risk. All-cause mortality occurred in 11,684 (38.7%) patients and re-transplantation in 662 (2.2%) of our study population. Total patient follow-up time in this cohort was 194,733 patient-years. The incidence rate of all-cause mortality was 5.3 per 1000 patient-years in patients with CS, 6.8 in those with non-ischaemic restrictive cardiomyopathy, and 5.9 in those with non-ischaemic dilated cardiomyopathy. The median survival was 15.8 years for CS HT recipients, 13 years for non-ischaemic dilated cardiomyopathy and 11.7 years for restrictive cardiomyopathy. The median survival was 15.8 years for CS HT recipients, 13 years for non-ischaemic dilated cardiomyopathy and 11.7 years for restrictive cardiomyopathy. In unadjusted univariate analyses, CS was not associated with significantly different all-cause mortality rates compared with restrictive and non-ischaemic dilated cardiomyopathy (P = 0.07 and P = 0.32, respectively). In multivariate regression analyses with adjusting for potential confounders, all-cause mortality at latest follow-up remained similar between CS and restrictive cardiomyopathy and between CS and non-ischaemic dilated cardiomyopathy [adjusted subhazard ratio (aSHR) 1.12, 95% CI: 0.65–1.95, P = 0.67; and aSHR 1.46, 95% CI: 0.9–2.4, P = 0.12, respectively] (Figure 1). Thirty-day mortality did not improve significantly in more recent HT eras (6.7% between 1990 and 1999, 12.1% between 2000 and 2009, 4.7% between 2010 and 2020, P = 0.24) whereas there was a trend towards improved 1 year mortality in the latest HT era (26.7% between 1990 and 1999, 18.2% between 2000 and 2009, 9.4% between 2010 and 2020, P = 0.06).

Within 30 days after transplantation, 1222 (4%) patients died. Multivariate regression analysis revealed that 30 day mortality was not significantly different in CS compared with restrictive (aSHR 1.45, 95% CI: 0.55–3.8, P = 0.45) or dilated cardiomyopathy (aSHR 2, 95% CI: 0.89–4.56, P = 0.095). Within the first year after transplantation, 3118 (10.3%) patients died. In a multivariate regression analysis, 1 year mortality was not significantly different between CS and restrictive (aSHR 1.15, 95% CI: 0.61–2.18, P = 0.66) and between CS and non-ischaemic dilated cardiomyopathy (aSHR 1.56, 95% CI: 0.9–2.7, P = 0.12) (Figure 2).

A total of 32 (32/163 [19.6%]) patients with CS experienced allograft rejection within the first year after HT. The
| Variable                              | Cardiac sarcoidosis (n = 240) | Non-ischaemic restrictive (n = 1431) | Non-ischaemic dilated (n = 29 203) | P value |
|---------------------------------------|-------------------------------|-------------------------------------|-----------------------------------|---------|
| **Recipient characteristics**         |                               |                                     |                                   |         |
| Male gender, n (%)                    | 154 (64)                      | 971 (68)                            | 20 092 (69)                       | 0.234   |
| Age, years                           | 52.2 ± 9.4                    | 53.9 ± 12.8                         | 49.8 ± 12.9                       | <0.001  |
| **Race**                              |                               |                                     |                                   |         |
| White, n (%)                          | 160 (67)                      | 1034 (72)                           | 17 933 (61)                       | <0.001  |
| Black, n (%)                          | 66 (28)                       | 282 (20)                            | 7827 (27)                         |         |
| Other, n (%)                          | 14 (5)                        | 115 (8)                             | 3443 (12)                         |         |
| **BMI, kg/m²**                        | 27.6 ± 4.9                    | 25.9 ± 4.5                          | 26.9 ± 5.1                        | <0.001  |
| **Induction therapy**                 |                               |                                     |                                   |         |
| None, n (%)                           | 142 (59)                      | 779 (54)                            | 16 509 (57)                       | <0.001  |
| Antithymocyte globulin, n (%)         | 51 (21)                       | 291 (20)                            | 5197 (18)                         |         |
| IL-2 inhibitors, n (%)                | 44 (19)                       | 266 (18)                            | 6211 (21)                         |         |
| Alemtuzumab, n (%)                    | 0 (0)                         | 8 (1)                               | 226 (1)                           |         |
| OKT3, n (%)                           | 3 (1)                         | 87 (6)                              | 1060 (3)                          |         |
| **UNOS status**                       |                               |                                     |                                   |         |
| 1A, n (%)                             | 88 (37)                       | 490 (34)                            | 11 240 (38)                       | <0.001  |
| 1B, n (%)                             | 52 (22)                       | 294 (21)                            | 6791 (23)                         |         |
| 1C, n (%)                             | 9 (4)                         | 19 (1)                              | 503 (2)                           |         |
| 2, n (%)                              | 33 (14)                       | 122 (9)                             | 1973 (7)                          |         |
| 3, n (%)                              | 14 (6)                        | 40 (3)                              | 830 (3)                           |         |
| 4, n (%)                              | 14 (6)                        | 53 (4)                              | 671 (2)                           |         |
| 5, n (%)                              | 0 (0)                         | 0 (0)                               | 26 (0)                            |         |
| 6, n (%)                              | 1 (0)                         | 5 (0)                               | 150 (1)                           |         |
| 7, n (%)                              | 0 (0)                         | 0 (0)                               | 6 (0)                             |         |
| 1 (old allocation), n (%)             | 4 (1)                         | 172 (12)                            | 3447 (12)                         |         |
| 2 (old allocation), n (%)             | 25 (10)                       | 236 (16)                            | 3566 (12)                         |         |
| **Device type**                       |                               |                                     |                                   |         |
| None, n (%)                           | 164 (69)                      | 947 (66)                            | 11 718 (40)                       | <0.001  |
| LVAD, n (%)                           | 46 (20)                       | 65 (5)                              | 7933 (27)                         |         |
| RVAD, n (%)                           | 0 (0)                         | 0 (0)                               | 73 (0)                            |         |
| BiVAD, n (%)                          | 4 (1)                         | 17 (1)                              | 244 (1)                           |         |
| TAH, n (%)                            | 3 (1)                         | 10 (0)                              | 988 (4)                           |         |
| BiVAD/TAH/other, n (%)                | 3 (1)                         | 37 (3)                              | 1192 (4)                          |         |
| Missing data, n (%)                   | 20 (8)                        | 355 (25)                            | 7055 (24)                         |         |
| **ABO group**                         |                               |                                     |                                   |         |
| A, n (%)                              | 103 (43)                      | 589 (41)                            | 11 285 (39)                       | 0.007   |
| B, n (%)                              | 45 (19)                       | 206 (15)                            | 4315 (15)                         |         |
| AB, n (%)                             | 19 (8)                        | 78 (5)                              | 1500 (5)                          |         |
| O, n (%)                              | 73 (30)                       | 558 (39)                            | 12 103 (41)                       |         |
| **Prior cardiac surgery, n (%)**      | 28 (12)                       | 90 (6)                              | 4525 (15)                         | <0.001  |
| **Creatinine, mg/dL**                 | 1.2 ± 0.5                     | 1.4 ± 0.9                           | 1.3 ± 0.9                         | 0.029   |
| **CPRA value**                        | 13.5 ± 24.3                   | 9.3 ± 20.8                          | 11.8 ± 23.9                       | 0.093   |
| **Cardiac output, L/min**             |                               |                                     |                                   |         |
| At listing                            | 3.9 ± 1.1                     | 3.9 ± 1.3                           | 4.1 ± 1.4                         | <0.001  |
| At HT                                 | 4.2 ± 1.4                     | 4.2 ± 1.5                           | 4.4 ± 1.5                         | <0.001  |
| **PCWP, mmHg**                        |                               |                                     |                                   |         |
| At listing                            | 16.7 ± 8.2                    | 21.4 ± 7.1                          | 20.6 ± 9.1                        | <0.001  |
| At HT                                 | 16.2 ± 8.5                    | 20.4 ± 7.6                          | 19.1 ± 9.1                        | <0.001  |
| **sPAP, mmHg**                        |                               |                                     |                                   |         |
| At listing                            | 35.7 ± 13.3                   | 44.2 ± 12.6                         | 43.7 ± 13.9                       | <0.001  |
| At HT                                 | 34.6 ± 13.1                   | 42.9 ± 12.7                         | 41.3 ± 13.8                       | <0.001  |
| **IABP, n (%)**                       |                               |                                     |                                   |         |
| At listing                            | 24 (10)                       | 74 (5)                              | 1764 (6)                          | 0.014   |
| At HT                                 | 27 (3)                        | 136 (10)                            | 2505 (9)                          | 0.168   |
| **ECMO, n (%)**                       |                               |                                     |                                   |         |
| At listing                            | 4 (2)                         | 8 (1)                               | 326 (1)                           | 0.098   |
| At HT                                 | 6 (3)                         | 27 (2)                              | 425 (1)                           | 0.178   |
| **Inotropes, n (%)**                  |                               |                                     |                                   |         |
| At listing                            | 69 (29)                       | 432 (30)                            | 10 669 (37)                       | <0.001  |
| At HT                                 | 92 (38)                       | 711 (50)                            | 12 201 (42)                       | <0.001  |
| **Mechanical ventilation, n (%)**     |                               |                                     |                                   |         |
| At listing                            | 7 (3)                         | 8 (1)                               | 608 (2)                           | <0.001  |
| At HT                                 | 5 (2)                         | 18 (1)                              | 559 (2)                           | 0.199   |

(Continues)
multivariable logistic regression model revealed that patients with CS had similar risk of rejection as compared to those with restrictive cardiomyopathy (relative risk ratio [RRR] 1.01, 95% CI: 0.48–2.1, \( P = 0.97 \)) and to those with dilated cardiomyopathy (RRR 0.7, 95% CI: 0.37–1.4, \( P = 0.24 \)). Although CS patients had less episodes of hospitalization for acute rejection episodes (19.8% vs 28.9% in dilated and 21.4% in restrictive cardiomyopathy, \( P < 0.001 \)), the multivariable logistic regression model revealed that patients with CS had similar risk of hospitalization for rejection with restrictive and dilated cardiomyopathy (RRR 0.99, \( P = 0.98 \) and RRR 0.76, \( P = 0.52 \)). We found no difference in the rates of hospitalizations for any infections (CS 30.5% vs. dilated 32.2% vs. restrictive 33.8%, \( P = 0.4 \)). Finally, post-transplant lymphoproliferative disorder rates were numerically but not significantly lower among CS patients (CS 3.5% vs. dilated 9.4% vs. restrictive 7%, \( P = 0.4 \)) without differences in the multivariable regression models.

Finally, death from severe graft failure in the first 30 days after HT did not differ significantly among groups (CS 5.9%, dilated 4.4%, restrictive 5.4%, \( P = 0.2 \)). Multivariable regression models did not suggest differences in the risk of death from graft failure in the first 30 days after HT (vs. restrictive aSHR 1.56, 95% CI: 0.6–4.1, \( P = 0.37 \), vs. dilated sSHR1.96, 95% CI 0.86–4.4, \( P = 0.1 \)).

### Discussion

The current retrospective analysis of 239 patients with CS who underwent HT in the USA between 1990 and 2020, we found no difference in short- or long-term mortality and other post HT outcomes as compared with patients with dilated or restrictive cardiomyopathy after adjusting for potential confounders. To our knowledge, this is the largest cohort used to examine outcomes of patients with CS undergoing HT. Further insight was obtained from a single centre case series analysis, where rejection was observed in rates similar to previously published studies, showing no evidence of recurrence of CS after a long-term follow-up using serial endomyocardial biopsy data.

The number of patients with end-stage CS who require HT in the USA has increased, comprising 0.5% of the total transplanted patients between 2010 and 2014 as compared with 0.1% between 1994 and 1997.1 Parallel to that, the incidence of CS appears to be increasing as well. However, this could be at least partially explained by increased clinical awareness and improved diagnostic modalities for CS, such as cardiac magnetic resonance (CMR) and 18F-fluorodeoxyglucose positron emission tomography (FDG-PET).6 Cardiac manifestations occur in about 5% of patients, whereas asymptomatic infiltration of the heart is found almost five times more frequently.7 In fact, due to diagnostic challenges, CS is occasionally diagnosed as the cause of cardiomyopathy at the time of HT or LVAD implantation by histology.2 Regardless of its epidemiology, CS may progress to end-stage HF requiring HT.

Although studies evaluating the outcomes of patients with CS have reported similar outcomes to patients with other aetologies of HF,3,8,9 these studies, however, are limited by small cohort sizes and therefore further investigation is warranted. The main concerns in these patients are the following: (i) sarcoidosis is a multisystem disease involving other organs; therefore, the long-term outcome of the disease remains unknown after HT; (ii) sarcoidosis can cause pulmonary hypertension, which can progress after HT and negatively affect the allograft via mechanisms that involve the pulmonary vasculature; and (iii) recurrence of CS or increased rejection rates may also occur following HT. Nevertheless, our findings suggest that HT is an excellent therapeutic option for selected patients with end-stage CS without evidence of increased risk of mortality, allograft rejection, or recurrence of CS after HT, thus confirming the results of prior smaller studies.

It is worth noting that pulmonary pressures were lower in patients with CS in our UNOS cohort and that we excluded patients with concomitant lung transplantation. Along these lines, Rosenthal et al. obtained follow-up invasive cardiac

### Table 1 (continued)

| Variable                          | Cardiac sarcoidosis (n = 240) | Non-ischaemic restrictive (n = 1431) | Non-ischaemic dilated (n = 29203) | \( P \) value |
|----------------------------------|-------------------------------|-------------------------------------|----------------------------------|--------------|
| Donor characteristics            |                               |                                     |                                  |              |
| Male gender, n (%)               | 158 (66)                      | 917 (64)                            | 20285 (69)                       | <0.001       |
| Age, years                       | 32.8 ± 11.5                   | 32.0 ± 12.2                         | 31.4 ± 11.7                      | 0.052        |
| Transplantation characteristics  |                               |                                     |                                  |              |
| Ischaemic time, h                | 3.1 ± 0.9                     | 3.1 ± 1.0                           | 3.1 ± 1.0                        | 0.689        |

Abbreviations: BIVAD, biventricular assist device; BMI, body mass index; CPRA, calculated panel reactive antibodies; ECMO, extra-corporeal membrane oxygenation; HT, heart transplantation; IABP, intra-aortic balloon pump; IL-2, interleukin 2; LVAD, left ventricular assist device; OKT3, muronomab CD3; PCWP, pulmonary capillary wedge pressure; RVAD, right ventricular assist device; sPAP, systolic pulmonary artery pressure; TAH, total artificial heart; UNOS, United Network for Organ Sharing.

\( P < 0.05 \) was deemed statistically significant.
Table 2 Baseline characteristics and outcomes of heart transplant patients with cardiac sarcoidosis at a single institution

| Patients with cardiac sarcoidosis (n = 14) |
|-------------------------------------------|
| Age at transplant, year                   | 49.6 (10.5) |
| Male                                      | 8 (57.1%)   |
| ICM                                       | 0           |
| DCM                                       | 9 (64.3%)   |
| CHD                                       | 0           |
| Ischaemic time, min                       | 164.6 (59)  |
| Donor age, year                           | 33.5 (112.4)|
| Concurrent transplantation                |             |
| None                                      | 1 (7.1%)    |
| Kidney                                    | 1 (7.1%)    |
| Liver                                     | 0           |
| Lung                                      | 0           |
| Bone marrow                               | 0           |
| Kidney and liver                          | 0           |
| Tacrolimus (vs. cyclosporine)             | 10 (71.0%)  |
| MMF (vs. AZA)                             | 12 (85.7%)  |
| Converted to SRL                          | 12 (85.7%)  |
| Steroids                                  | 14 (100%)   |
| Steroids duration, year                   | 3.1 (2.1)   |
| OKT3 induction therapy                    | 4 (36.3%)   |
| ATG induction therapy                     | 10 (65.7%)  |
| BMI, kg/m²                                 | 27.6 (4.8)  |
| Hypertension                              | 4 (28.6%)   |
| Diabetes                                  | 1 (7.1%)    |
| Statins                                   | 14 (100%)   |
| Aspirin                                   | 1 (7.1%)    |
| Anti-coagulant                            | 2 (14.3%)   |
| CCB                                       | 7 (50%)     |
| BB                                        | 1 (7.1%)    |
| ACE-I                                     | 2 (14.3%)   |
| Glucose, mg/dL                            | 101 (24)    |
| Creatinine, mg/dL                         | 1.4 (0.5)   |
| eGFR, mL/min/1.73 m²                      | 60 (23.6)   |
| Total cholesterol, mg/dL                  | 251 (61)    |
| Triglycerides, mg/dL                      | 174 (72)    |
| HDL cholesterol, mg/dL                    | 70 (21)     |
| LDL cholesterol, mg/dL                    | 146 (5)     |
| Graft LVEF, %                             | 65 (3)      |
| Cellular rejection grade                  |             |
| 2R (or 3A in the 1990 scheme)             | 2 (8.6%)    |
| 3R (or 3B and 4 in the 1990 scheme)       | 0           |
| Any AMR                                   | 2 (16.7%)   |
| Haemodynamically significant rejection     | 1 (9.1%)    |
| ISHLT CAV grade                           |             |
| 0                                         | 10 (77.0%)  |
| 1                                         | 3 (23.0%)   |
| 2                                         | 0           |
| 3                                         | 0 (1 missing) |
| CMV viraemia                              | 2 (14.3%)   |
| EBV viraemia                              | 3 (21.4%)   |
| Malignancy                                | 0           |
| Skin cancer                               | 9 (64.3%)   |
| SCC                                       | 3 (21.4%)   |
| BCC                                       | 2 (14.3%)   |
| Melanoma                                  | 0           |
| Death                                     | 1 (7.1%)    |

Abbreviations: ACE-I, angiotensin-converting enzyme inhibitor; AMR, antibody mediated rejection; ATG, antithymocyte globulin; AZA, azathioprine; BB, beta-blocker; BCC, basal cell carcinoma; CAV, cardiac allograft vasculopathy; CCB, calcium channel blocker; CHD, congenital heart disease; CMV, cytomegalovirus; CNI, calcineurin inhibitor; DCM, dilated cardiomyopathy; EBV, Epstein–Barr virus; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; HT, heart transplantation; ICM, ischaemic cardiomyopathy; ISHLT, International Society for Heart and Lung Transplantation; LDL, low-density lipoprotein; LVEF, left ventricular ejection fraction; MMF, mycophenolate mofetil; SCC, squamous cell carcinoma and SRL, sirolimus.

pressures in a small cohort of patients with CS who underwent HT showing no increase in pulmonary vascular resistance or development of pulmonary hypertension following HT. Studies have suggested that pulmonary hypertension may develop in approximately 6% of patients with sarcoidosis with modest pulmonary involvement. In the same study, no patients developed recurrent CS and rejection rates were comparable with other non-CS HT patients. Our results from the UNOS database confirm similar rejection rates, whereas no recurrence of CS was observed in our single-centre case series. The absence of CS recurrence has also been reported in other studies. The immunologic interplay that occurs in patients with sarcoidosis after HT is likely very complex. However, our findings suggest that contemporary immunosuppression regimens in patients who develop sarcoidosis without significant lung disease or extra-cardiac manifestations may be adequate to prohibit development of systemic inflammation and recurrence of cardiac and extra-cardiac sarcoidosis thereby ensuring similar outcomes compared to patients who undergo HT for other HF aetiologies.

Accumulating evidence suggests improvement in CAV progression, lower rates of cancer and CMV infections. In our institution we follow a protocol of early conversion to sirolimus for primary prevention of CAV. Essentially, all patients are routinely switched to a regimen which includes sirolimus and mycophenolate mofetil. Our protocol of early sirolimus conversion has been reported previously and is associated with excellent safety and efficacy compared with calcineurin inhibitor based regimens. Regarding use of mTOR antagonists, the data in UNOS represent a heterogeneous use of these medications usually as secondary prevention of CAV, calcineurin inhibitor induced nephropathy or skin cancer. The aetiology, timing and dosing of mTOR antagonists are not entirely clear. The protocols are not well described, and the number of patients on this treatment is rather low. Therefore, we did not analyse this particular patient population on mTOR antagonists in UNOS. Although, it is unknown if sirolimus would precipitate further lung-related complications in patients with pulmonary sarcoidosis, in the small case series presented here, no patients experienced this adverse event. Further studies would be necessary to confirm safety and efficacy of sirolimus in sarcoidosis patients after heart transplantation.

Our results agree with previous studies of the UNOS databases, which were focused on the effect of the new allocation system applied in 2018. However, those are data-derived from a shorter period (2013 and later), a smaller patient population and the scope of those study goes beyond

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exclusively studying the role of CS in outcomes. Thus, the smaller sample size and the different study design could potentially underpower statistical analyses of interest.\(^{12,13}\)

In conclusion, this analysis of the UNOS Registry showed that short-term and long-term all-cause mortality and rejection risks after isolated HT were not inferior in sarcoid cardiomyopathy as compared with other common types of non-ischaemic cardiomyopathy. These data suggest that HT can be safe and effective in this growing patient population with advanced HF due to CS.

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Conflict of interest

The authors declare that they have no competing interests.

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