Sarcoidosis, Race, and Short-term Outcomes Following Lung Transplantation*

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Background: Patients with sarcoidosis, many of whom are African American, may require lung transplantation (LT). Little is known about survival following LT for sarcoidosis.

Objective: To determine short-term mortality following LT for sarcoidosis, to evaluate if survival after LT for sarcoidosis is similar to outcomes after LT for other diseases, and to investigate the impact of race on the results of LT.

Design: Retrospective review.


Measurements: Vital status at 30 days after LT and cause of death.

Results: During the study period, 4,721 LTs were performed; of these 133 LTs (2.8%) were for sarcoidosis. Approximately 83% of patients with sarcoidosis survived following LT compared to 91% of persons undergoing transplantation for other reasons (p = 0.002). In multivariate analysis controlling both for health insurance status and other factors known to affect survival after LT, patients with sarcoidosis were no more likely to die than persons undergoing transplantation for other conditions (adjusted odds ratio for death, 1.45; 95% confidence interval [CI], 0.84 to 2.48). Significant predictors of mortality included the following: undergoing combined heart-lung transplant, need for mechanical ventilation, treatment in an ICU at time of LT, pre-LT FEV1, need for supplemental oxygen, and donor age. Both recipient race and donor race significantly affected short-term survival. African-American patients were nearly 50% more likely to die (adjusted odds ratio, 1.49; 95% CI, 1.01 to 2.20). This difference based on race persisted after excluding heart-lung recipients and after controlling for recipient-donor racial mismatch. The most frequent cause of death for patients with sarcoidosis was graft failure, while infection was the primary cause of death among other LT patients.

Conclusions: Patients with sarcoidosis do as well as patients undergoing LT for other diseases. Race is an important factor affecting survival after LT. (CHEST 2004; 125:990–996)

Key words: mortality; outcomes; race; sarcoidosis; survival; transplantation

Abbreviations: CI = confidence interval; IPF = idiopathic pulmonary fibrosis; LT = lung transplantation; MV = mechanical ventilation; OLT = orthotopic lung transplantation; UNOS = United Network for Organ Sharing

Sarcoidosis causes a wide spectrum of illness. Patients may have minimal pulmonary symptoms or acquire progressive, fibrotic lung disease.1 Sarcoidosis may also affect nonpulmonary organs systems and lead to cardiomyopathies, neurologic impairment, and bone disease. Despite the potential for extrapulmonary involvement, pulmonary disease is the major cause for morbidity and mortality in patients with sarcoidosis.2 Fortunately, most patients with sarcoidosis do well.1,2 Often they require no therapy or respond to treatment with corticosteroids. For patients who fail to improve with corticosteroids or who become intolerant of them, options include methotrexate, thalidomide, and anti-tumor necrosis factor-α therapies.3–5

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Despite these newer treatment alternatives, certain subjects with sarcoidosis are evaluated for and subsequently undergo lung transplantation (LT). Radiographically, these patients usually have parenchymal fibrosis and scarring. Clinically, persons with advanced pulmonary sarcoidosis report dyspnea, fatigue, and exercise intolerance. Little is known, however, about outcomes for patients with sarcoidosis who undergo LT. The vast majority of LTs performed are for diseases other than sarcoidosis. This limits the ability of individual transplant centers to collect sufficient numbers of patients with sarcoidosis from which to draw conclusions regarding the efficacy of LT in this setting. Prior studies describing outcomes for subjects receiving LT for sarcoidosis are inadequate in that they have mainly consisted of small case series. Walker et al described 12 patients with sarcoidosis who underwent LT and reported 3-year and 5-year survival rates of 70% and 56%, respectively. In a larger study, Arcasoy and colleagues noted that more than half of patients at their institution listed for LT died while awaiting LT. For those undergoing LT, the 1-year survival rate was 62%.

Several factors unique to the management of patients with sarcoidosis suggest that results from LTs performed for other forms of interstitial lung disease are not generalizable to those with sarcoidosis. Specifically, patients with sarcoidosis may have bronchiectasis, which in turn may be complicated by the presence of aspergillomas. While double-lung transplantation is rarely done for idiopathic pulmonary fibrosis (IPF), bronchiectasis might necessitate double LT for those with sarcoidosis. In patients listed for LT, pulmonary hypertension is also more common in persons with sarcoidosis than in those with IPF. Conversely, individuals with sarcoidosis are likely to be significantly younger than their counterparts with IPF. This age differential might convey a survival advantage to patients with sarcoidosis undergoing LT.

In short, there are limited data describing the results of LT performed for sarcoidosis. To better define outcomes for patients with sarcoidosis receiving LTs, to compare their short-term survival to those transplanted for other diseases, and to investigate the causes of mortality following LT for sarcoidosis, we conducted a retrospective analysis of all patients who received a LT in the United States between January 1995 and December 2000.

**Materials and Methods**

**Subjects and End Points**

The United Network for Organ Sharing (UNOS) maintains a registry of all patients receiving organ transplants in the United States. We reviewed this registry and identified persons who underwent LT for any cause between January 1995 and December 2000, regardless of initial listing date. We identified the underlying diagnosis leading to LT in order to compare those with sarcoidosis to subjects undergoing transplantation for other reasons (eg IPF, cystic fibrosis, COPD, etc). The primary diagnosis was based on the reports of the referring transplant centers. Patients listed for any form of possible LT (single-lung, bilateral-lung, or heart-lung transplant) were included in the study cohort. The primary end point for this study was 30-day mortality following LT. Cause of death in the 30 days following LT comprised a secondary end point.

**Study Variables**

Data regarding patient demographics (age, gender, and race) and source of payment for LT were recorded. In addition, information concerning type of LT (single-lung, double-lung, or heart-lung) functional status, and pulmonary function at time of LT was noted. Patients were categorized as either having no activity limitations, able to perform activities of daily living with assistance, hospitalized, or in the ICU for purposes of assessing functional status. For pulmonary function, both FEV1 and FVC were examined. Data regarding the diffusion of carbon monoxide were unavailable. UNOS only began noting the FEV1/FVC ratio in 1999, so this was not incorporated into our analysis. Other pulmonary variables included the need for mechanical ventilation (MV) or treatment with vasopressors at time of LT, and use of supplemental oxygen (liters per minute). We further examined the influence of donor-related factors previously shown to affect outcome following LT. We documented the lung donor’s demographics (age, gender, and race) and donor-organ cold ischemia time. To investigate changes over time and the potential for improvement in outcomes as experience with LT increased, we investigated the year of LT dichotomized into 2-year increments (from 1995 to 1996, from 1997 to 1998, and from 1999 to 2000).

For patients who died in the 30 days following LT, cause of death was grouped into one of six categories: graft failure, infection (eg pneumonia, bacteremia, sepsis, etc), cardiovascular, pulmonary, cerebrovascular, or other. Initial reports as to cause of death were based on information provided by each individual LT center. One investigator (A.F.S.) evaluated each death that was initially miscategorized as “other” by the referring LT center when in fact it was due to a cause which was already listed as an option on the transplant case report form.
data, missing information was set to the “highest” group. Data were absent in >10% for only three variables: FEV1, FVC, and ischemia time. Ninety-five percent confidence intervals (CIs) are reported where appropriate. Analyses were done using SAS version 8.0 (SAS Institute; Cary, NC).

Results

During the study period, 4,721 LTs were performed, of which 133 LTs (2.8%) were for sarcoidosis. Unadjusted 30-day survival rates differed significantly based on underlying diagnosis. Approximately 83% of patients with sarcoidosis survived following LT compared to 91% of persons undergoing transplantation for other reasons (p = 0.002). This corresponds to a nearly double unadjusted risk for mortality for those in the sarcoidosis cohort (odds ratio for mortality, 2.07; 95% CI, 1.31 to 3.28).

Patients with sarcoidosis, however, were significantly different than others undergoing LT. Table 1 demonstrates that subjects with sarcoidosis were more likely to be African American and female. Subjects with sarcoidosis were also younger, with a mean age of 45.8 ± 12.3 years vs 48.9 ± 12.3 years (mean ± SD) for other diagnosis (p < 0.001). Heart-lung transplantation was more common for sarcoidosis and accounted for 5.3% of all LTs, while only 1.4% of LTs for other diseases included combined heart transplantation (p < 0.004). Similarly, slightly more than half of individuals with sarcoidosis underwent double LT while only 40% of all other LTs were double LTs. Although no more likely to be treated with vasopressors at time of LT, there was a trend toward persons with sarcoidosis to more often be receiving MV. The overall need for MV was low in both cohorts, but 4.5% of patients with sarcoidosis needed MV in comparison to 2.2% of other individuals (p = 0.07). More patients with sarcoidosis reported some form of limitation in activities of daily living. There was no variation in the proportion of subjects in the ICU at time of LT based on underlying lung process.

In terms of spirometry, higher FVCs were seen among those with diagnoses other than sarcoidosis (mean FVC, 44.1 ± 14.9% predicted for sarcoidosis vs 50.0 ± 18.2% predicted for other conditions, p < 0.001). The FEV1, however, was higher in those with sarcoidosis (37.9 ± 17.6% predicted vs 30.8 ± 20.1% predicted for other disease states, p < 0.001). The groups were comparable with respect to functional status and need for supplemental oxygen. The annual rate of LTs performed also did not fluctuate based on underlying condition.

For donor variables, we observed that patients with sarcoidosis more often received organ(s) from female donors than did other LT subjects (p = 0.03). The distribution of donor races, however, was similar between the sarcoidosis and nonsarcoidosis groups. Therefore, since more patients with sarcoidosis were African American, subjects with sarcoidosis were more likely to experience a donor/recipient racial mismatch. Donor age and cold ischemia time did not differ based on primary pulmonary condition.

Health insurance status varied based on underlying diagnosis (Fig 1). Equal proportions of both the sarcoidosis and nonsarcoidosis cohorts had Medicare listed as their primary payer. Medicaid, though, was more often the payor for sarcoidosis LTs. Specifically, Medicaid covered 13.5% of all sarcoidosis LTs relative to 7.5% of other LTs (p = 0.019). Reflecting this pattern, private insurance coverage paid for relatively fewer LTs for sarcoidosis than for other conditions (Fig 1).

Focusing only on those receiving single LT or only those receiving double LT did not alter our findings with respect to differences between those with sarcoidosis and patients with other disease states. Among all single-lung recipients (n = 2,748), 2.1% had sarcoidosis. In this group, as was seen in the entire cohort of patients receiving orthotopic LT (OLT), persons with sarcoidosis were significantly younger, more often female, and more often African American. Patients with sarcoidosis patients also had lower FVC and higher FEV1 measures. For patients receiving double-lung OLT (n = 1,901, 3.5% sar-
coidosis), similar patterns were found in terms of significant differences with respect to the variables examined for this analysis.

In multivariate analysis to identify predictors of mortality among all subjects (both sarcoidosis and nonsarcoidosis) undergoing OLT, several variables were significantly predictive of 30-day mortality (Table 2). Underlying diagnosis after adjusting for confounders no longer correlated with outcome. Although the adjusted odds ratio for mortality among sarcoidosis patients was 1.45 (95% CI, 0.84 to 2.48), this was not statistically significant (p = 0.18). The strongest risk factor for short-term mortality was need for heart-lung transplantation. Being in the ICU at time of transplantation also increased the likelihood of mortality (adjusted odds ratio, 3.33; 95% CI, 2.23 to 4.97). Neither donor nor recipient gender related to survival. Race, however, affected LT results. African-American recipients and those receiving organs from African Americans were approximately 50% more likely to die 30 days after LT. The impact of race was independent of health insurance status. Excluding heart-lung transplant subjects from the analysis altered findings little, and sarcoidosis continued not to predict poor short-term survival (Table 2). All other variables except need for MV initially identified as associated with mortality remained significant in this adjusted model.

Because of the observation that race was significantly predictive of survival, we conducted a further multivariate assessment of donor/recipient racial mismatch among all patients undergoing OLT (both sarcoidosis and other conditions). Specifically, we attempted to determine if racial mismatch explained

Table 2—Independent Predictors of 30-Day Mortality Among All Patients Undergoing LT

<table>
<thead>
<tr>
<th>Variables</th>
<th>All Lung Transplants</th>
<th>Transplants Excluding Heart-Lung</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Odds Ratio</td>
<td>95% CI</td>
</tr>
<tr>
<td>Sarcoidosis</td>
<td>1.44</td>
<td>0.84–2.47</td>
</tr>
<tr>
<td>Heart-lung transplant</td>
<td>2.78</td>
<td>1.55–4.96</td>
</tr>
<tr>
<td>In ICU</td>
<td>2.25</td>
<td>1.26–4.01</td>
</tr>
<tr>
<td>Receiving MV</td>
<td>1.89</td>
<td>0.98–3.64</td>
</tr>
<tr>
<td>Recipient African American</td>
<td>1.49</td>
<td>1.01–2.20</td>
</tr>
<tr>
<td>Donor African American</td>
<td>1.44</td>
<td>1.10–1.88</td>
</tr>
<tr>
<td>Recipient male gender</td>
<td>1.20</td>
<td>0.98–1.47</td>
</tr>
<tr>
<td>O₂ required, per L/min from mean value</td>
<td>1.09</td>
<td>1.03–1.14</td>
</tr>
<tr>
<td>FEV₁, per unit from mean value</td>
<td>1.01</td>
<td>1.00–1.01</td>
</tr>
<tr>
<td>Donor age, per year from mean age</td>
<td>1.01</td>
<td>1.00–1.02</td>
</tr>
<tr>
<td>Year of transplant 1995–1996 (reference 1999–2000)</td>
<td>1.45</td>
<td>1.13–1.85</td>
</tr>
<tr>
<td>Year of transplant 1997–1998 (reference 1999–2000)</td>
<td>1.24</td>
<td>0.97–1.59</td>
</tr>
</tbody>
</table>
why African Americans faced a higher risk of death following LT. Both white subjects receiving organs from African American donors and African American patients with LTs from white donors had a higher probability of death at 30 days. The adjusted odds ratio for mortality in white patients with organs from African Americans was 1.43 (95% CI, 1.07 to 1.92), while African Americans receiving organs from whites were more than twofold more likely to die (adjusted odds ratio, 2.05; 95% CI, 1.02 to 4.11). Nonetheless, recipient race persistently altered survival. African Americans who had organs transplanted from African Americans faced a substantial and independent increase in the chance of dying (adjusted odds ratio, 3.07; 95% CI, 1.21 to 7.77). Of African Americans with sarcoidosis who received organs from African-American donors, the 30-day mortality rate was 30.0%.

The most common cause of death at 30 days after LT among individuals with sarcoidosis was graft failure (Fig 2). Graft failure accounted for two of every five deaths in this cohort. For other patients, graft failure was also the most frequent reason for early death. Those with sarcoidosis, though, were 2.70 (95% CI, 1.34 to 5.45) times more likely to succumb because of graft failure. Infection contributed little to death following LT in sarcoidosis (8.7% of deaths), while it was the cause of death in 22.1% of other patients. The overall distribution of causes of death was not significantly different based on primary lung condition.

**Discussion**

LT for sarcoidosis confers an increased risk for short-term mortality. This risk, however, is explained by other confounders rather than the disease state itself. Patients with sarcoidosis are more likely to require heart-lung transplantation and to be African American. Severity of illness, as measured by need for care in an ICU or MV at time of LT, is an important predictor of survival. Additionally, this large retrospective study of all LTs done in the United States reveals that graft failure is a major cause of death following LT for sarcoidosis.

Several earlier reports have described the results of LT in sarcoidosis. Walker et al noted that the 3-year mortality in LT for sarcoidosis was 30%, despite the common recurrence on nonnecrotizing granulomas in the transplanted lung. In their group of 12 subjects, 3 patients (25%) died within 30 days of transplantation. In each case, acute graft failure was the cause of death. In a series of nine patients, Nunley and colleagues observed three deaths in the first year after transplantation. All subjects survived beyond postoperative day 30. During the ensuing 5 years of follow-up, only one individual died of graft failure. Finally, Arcasoy and coworkers followed up 12 patients with sarcoidosis after LT; one half were alive at 3 years. Only one patient died in the immediate post-LT period from an aspergiloma.

Our report builds on these studies in several ways. First, we focused on a multicenter database that...
allows us to capture the entire experience in the United States with LT for sarcoidosis. Second, our sample size was significantly larger and affords the ability to explore outcomes in LT for sarcoidosis relative to survival following LT for other conditions. Only the study by Nunley et al. included a control arm. Finally, we explored variables capturing severity of illness, race, and health insurance status that have not previously been examined as to their impact on outcomes for LT for sarcoidosis.

The finding that markers of disease severity impact mortality following LT is not surprising. A recent series stated that patients receiving MV at the time of transplant had acceptable survival rates. Our results should give pause to efforts to expand the eligible recipient pool to include patients needing MV in the ICU. Our findings further suggest that patients with sarcoidosis are potentially being listed late in their disease course so that when they undergo LT they are concomitantly more severely ill. Complicating efforts to determine when to list a patient with sarcoidosis for LT are the variable natural history of the disease and the paucity of data to aid in mortality prediction. In order to improve outcomes associated with LT in sarcoidosis, it is imperative to develop better guidelines to facilitate the decision as to when to refer for LT.

The independent effect of race on survival has several potential explanations. First, race may affect access to care. However, we explored the significance of health insurance status and used this as a surrogate to control for variations in access to care. Additionally, it seems unlikely that access to care would alter short-term postoperative mortality as opposed to medium and long-term outcomes. Inability to obtain follow-up care and medications as an outpatient would be expected to play a role in survival at 3 years and 5 years after LT. Most patients, in the 30 days after LT, are closely followed up. Second, race may play an important immunologic role. In clinical trials of immunosuppressants in renal transplants, African-American patients have increased graft loss believed related to immunologic hyperresponsiveness. African Americans are also more likely to display greater major histocompatibility polymorphism. Whatever the reasons, multiple studies have documented that African Americans receiving renal transplants fare worse than white subjects. The same is seen in the setting of liver transplantation. Nair and colleagues, in a review of all liver transplants done in the United States from 1988 to 1996, noted that the 30-day mortality rate was 6% in whites compared to 9% in African Americans (p < 0.05). After controlling for possible confounders in a multivariate analysis, African-American patients were 36% more likely to die at 2 years after liver transplantation. Third, and relatedly, the issue may not be one purely of race but of donor/recipient racial mismatch. This may lead to mismatching at some level for variables not traditionally screened for and increase the risk for graft failure. However, racial mismatch cannot account for the worse mortality among African Americans who received organs from other African Americans. As a corollary, many of the antirejection medication routinely employed in transplant medicine were studied mainly in whites.

The higher rates of early graft failure in sarcoidosis are surprising. Granulomas often recur in the allograft. Traditionally, the return of granulomas is thought not to have clinical significance. Potentially, they might contribute to graft failure in an as yet undefined manner or via elaboration of tumor necrosis factor-α. Racial mismatching might promote early graft loss by predisposing to subclinical rejection. Given the absence of data on the pharmacokinetics and pharmacodynamics of many immunosuppressive in African American one can speculate that the dosages of these medication routinely employed are incorrect for this population. Each of these possible explanations, however, is hypothetical and merit more rigorous examination.

Our study has several limitations. Because of its retrospective nature there is the potential for bias. The UNOS database, however, consists of data recorded at time of transplant as opposed to information abstracted in a post hoc fashion. Therefore, recall bias is not a likely issue. Moreover, there is little room for bias in determining the incidence of the primary study end point, mortality. UNOS, though, relies on referring transplant centers for the quality of the data. Determination of cause of death is more open to interpretation that limits the strength of our conclusions in this area. Since patient management in terms of the approach to immunosuppression and other aspects of peritransplant care varies from center to center, we cannot discount that center-specific factors may explain our findings. Nonetheless, no one center has a vast experience in the care of patients with sarcoidosis requiring LT. Consequently, it seems unlikely that data from one institution skewed the results.

Another concern with the UNOS registry is that although it is robust, it still lacks information on variables that might affect mortality. Specifically, we did not have information regarding the transplant clinician’s reasoning as to why a patient underwent one form of OLT rather than another (eg, single-lung vs double-lung), the presence or absence of pleural disease, warm ischemia time, degree (if any) of pulmonary hypertension at time of OLT, or nutritional status. Any of these factors could play an
important role in determining outcomes. Similarly, we can only speculate as to why patients with sarcoidosis were more likely than others to receive heart-lung transplants. For example, some of these subjects may have acquired a cardiomyopathy as part of their sarcoidosis. Most other diseases for which patients undergo OLT do not directly affect cardiac performance. Also unavailable were descriptions of patient comorbidities. However, as we have shown earlier, the incidence of comorbidities at time of listing is low among patients awaiting transplantation. As with all analyses of large registries, we are constrained by the type and form of data UNOS collects. Again, it is important for readers to note that when faced with a relatively rare event (eg, OLT for sarcoidosis) utilization of a registry allows collection of sufficient numbers of cases to facilitate hypothesis generation in hopes of designing future, more comprehensive studies.

In conclusion, patients with sarcoidosis face higher short-term mortality following LT than persons undergoing transplantation for other conditions. This difference is explained by factors other than the disease itself. Race and severity of illness are important predictors of survival in the 30 days following LT. The importance of race in affecting outcomes from LT is likely due to multiple immunologic and nonimmunologic factors.

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