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Should UNOS Status 2 Patients Undergo Transplantation?

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ABSTRACT

Background. With recent improvements in medical and device therapy, the benefit of cardiac transplantation for UNOS Status 2 patients has been questioned. No randomized trial has been performed to compare transplantation versus contemporary medical therapy.

Methods. Between January 1996 and December 2003, 203 patients were listed at our institution for heart transplantation as UNOS Status 2. We performed a retrospective review to determine outcomes in these patients.

Results. Demographics of this cohort revealed a mean age of 52 years, female sex in 28%, and ischemic etiology in 47%. Eighty-one patients (40%) had an implantable cardiac defibrillator. A total of 64 patients (32%) had to be upgraded in their UNOS status, with 9 requiring a left ventricular assist device. Of the entire group, 95 (47%) underwent transplantation at a mean time of 303 days, 45 (22%) died while waiting at a mean time of 397 days, and 24 (12%) were removed from the waiting list due to deterioration in medical condition such that transplantation was no longer an option. The remaining patients continue to wait or have been removed from consideration due to improved condition. Survival at 1- and 3-years postlisting was 94% and 87% for patients who received transplants compared to 81% and 57% for patients who did not receive transplants ($P < .01$).

Conclusion. A significant number of patients listed as Status 2 are upgraded in UNOS status or die while on the waiting list. Early and midterm survival is significantly better with transplantation. Identification of variables associated with deterioration may allow for better risk stratification in the future. At this point, transplantation offers the best outcome.

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INTRODUCTION

Heart transplantation is considered the gold standard treatment for endstage heart failure that has become refractory to continued medical therapy [Mudge 1993]. The United Network for Organ Sharing (UNOS) currently stratifies heart transplantation candidates to one of two status categories based on mortality risk [UNOS Policy section 3.7.3]. Status 1 patients are deemed to have worse heart failure and generally require continuous intravenous inotropic support or the use of a mechanical assist device. Status 2 is assigned to all other patients who have been optimized with current medical therapy as outpatients but still have a predicted survival of less than 1 year without transplantation. Given the significant imbalance between supply and demand for donor hearts, questions have been raised whether the current system of heart allocation provides the best method of ensuring that the sickest patients derive the greatest benefits from available organs [Copeland 2001]. The Comparative Outcome and Clinical Profiles in Transplantation (COCPIT) Study showed that only patients on the waiting list who have a high risk of dying have a survival benefit with heart transplantation, whereas patients with a low to medium risk of death have no reduction in mortality with transplantation [Deng 2000]. It has been suggested that by restricting heart transplant listing to patients with refractory or progressive heart failure, survival of all heart failure patients would increase due to earlier transplantation of the sickest patients [Frigerio 1997].

With the continued organ donor shortage and the success of ventricular assist device (VAD) therapy as bridge to transplantation, there is an emerging need to address whether Status 2 patients have a survival benefit from heart transplantation. We sought to evaluate the overall outcomes of all Status 2 patients listed at our institution to determine if transplantation still confers a survival benefit to this group.

MATERIALS AND METHODS

The study was a retrospective review of adult patients listed as Status 2 at our institution between January 1, 1996, and December 31, 2003. Clinical data from the UNOS/Organ Procurement and Transplantation Network database were supplemented from the inpatient records of each patient.

Table 1. Clinical Characteristics of Status 2 Patients (N = 203)

Variable	Value	%
Age, y, mean ± standard deviation	52.17 ± 10.5	
Female sex	57	28.1
Diagnosis		
Ischemic cardiomyopathy	96	47.3
Dilated cardiomyopathy	85	41.9
Congenital cardiomyopathy	7	3.5
Hypertrophic cardiomyopathy	3	1.5
Retransplantation	5	2.5
Valvular	3	1.5
Other	4	2.0
Implantable cardiac defibrillator	81	40.0

Relevant variables included age, sex, diagnosis, and any intervention employed, including implantation of a VAD or automated implantable cardiac defibrillator (ICD). All patients were maximized on medical therapy according to established guidelines, prior to being listed. Relevant events in the time course of the patient included transplantation, death of any cause, upgrade in UNOS status, or removal from the transplant waiting list. Upgrade was defined as from Status 2 to 1 prior to 1999 and to Status 1B or 1A after the newer UNOS criteria were implemented [Abraham 2000]. All data were analyzed using Pearson χ^2 test for nominal variables and Kaplan-Meier survival curves for dichotomous characteristics using SYSTAT (SYSTAT Software, Richmond, CA, USA). The study was approved by the Institutional Review Board of the Washington University School of Medicine.

RESULTS

Between January 1, 1996, and December 31, 2003, 203 adult patients were listed for heart transplantation as Status 2 at our institution. Table 1 presents the demographic characteristics of these patients. The average age was 52 ± 11 years, and the majority of patients were male. The most common indication for transplantation was ischemic cardiomyopathy followed by dilated cardiomyopathy. A smaller percentage of the population comprised other diagnoses. At the time of listing, 39% of patients had an ICD. The mean maximum oxygen consumption was 11.7 mL/min per kg (range, 7-20) for the 68 patients (34%) for whom these data were available.

A total of 64 patients (32%) had an upgrade in their UNOS status at a mean time of 220 days, with 9 requiring a left VAD.

Table 2. Outcomes of Status 2 Patients (N = 203)

Event	n	%
Upgrade in Status		
Status 1	24	11.8
Status 1B	41	20.2
Status 1A	9	4.4
Final outcome		
Transplantation	95	46.8
Death	45	22.2
Removal, improved	26	12.8
Removal, other	24	11.8
Still waiting	13	6.4

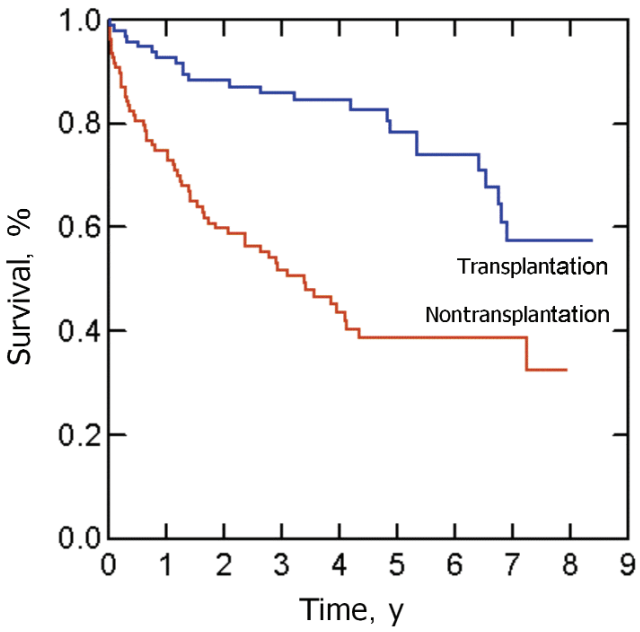

Figure 1. Survival of all patients, transplantation versus nontransplantation. Period of follow-up began at time of initial listing on the transplant registry ($P < .01$).

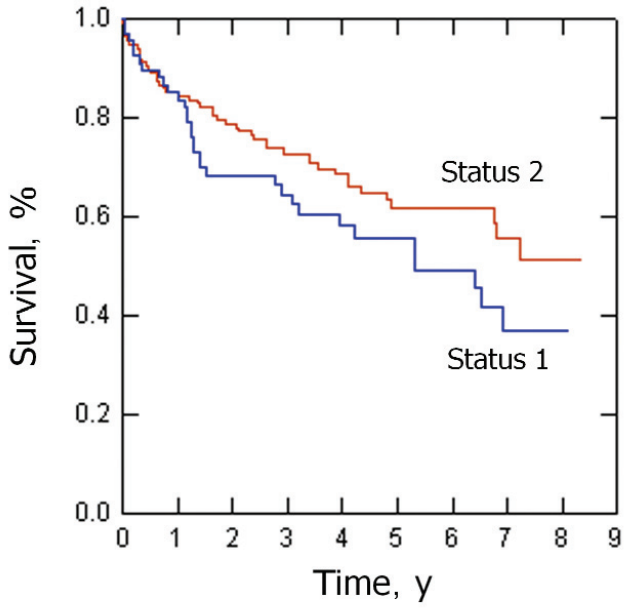

Figure 2. Survival of the nontransplantation patients, Status 1 versus Status 2. Period of follow-up began at time of initial listing on the transplant registry ($P < .01$).

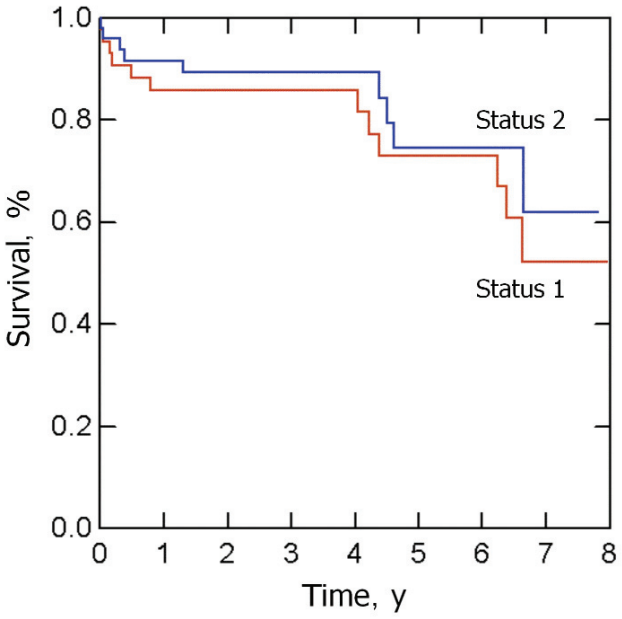

Figure 3. Survival of transplantation patients, Status 1 versus Status 2 at time of transplantation. Period of follow-up began at time of transplantation ($P > .05$).

Of this group, 24 were upgraded to Status 1, 41 to Status 1B, and 9 to Status 1A (7 of whom were initially upgraded to Status 1B). Overall, transplantation was performed in 95 patients (47%) at a mean time of 303 days, 45 patients (22%) died while waiting for a suitable donor at a mean time of 397 days, and 24 patients (12%) were removed from the waiting list due to deterioration in medical condition such that transplantation was no longer an option. The remaining patients continue to wait for an appropriate allograft or have been removed from consideration due to improved condition (Table 2).

Of the 45 patients who died while waiting for a suitable allograft, 12 died at our institution, and the cause of death could be definitively ascertained. Cause of death was sudden cardiac death in 4 (33%). None of these patients had an ICD placed, 3 had a diagnosis of ischemic cardiomyopathy, 1 had dilated cardiomyopathy. The other 8 patients (67%) died from heart failure exacerbation with progression to multisystem organ failure. In this group, diagnosis was ischemic cardiomyopathy in 4, dilated cardiomyopathy in 3, and hypertrophic cardiomyopathy in 1 patient. In this latter group, 7 had previous ICD placement.

Of all patients, survival at 1 and 3 years was 87% and 71%, respectively. Patients who received transplants fared much better than those who did not. Survival from the time of listing for the 95 transplant recipients was 94% at 1 year and 87% at 3 years. Similar analysis for the 108 patients who did not receive transplants was 81% and 57% at 1 and 3 years, respectively (Figure 1).

Figure 2 compares survival between all patients who were upgraded to Status 1 (including Status 1A and 1B) to all patients who remained Status 2. In the long term, patients who remained Status 2 fared better than those who required an upgrade in status. Survival of Status 2 patients was 85% at 1 year and 69% at 3 years. Upgraded patients had a survival of 85% and 59% in the same time frame.

Figure 3 shows posttransplantation survival according to status at transplantation of all patients initially listed as Status 2. At 1 year after transplantation, survival was 85.0% for patients who underwent transplantation as Status 1 and 89% as Status 2. There was no statistical difference in survival between the 2 groups ($P = .57$).

Figure 4 shows patient survival in the cohort that did not receive transplants according to any UNOS status changes. Patients who had an upgrade in status had an extremely poor prognosis with a 1-year mortality of 50%. Upgrade in status occurred at a mean time of 302 days with a mean time of 55 days to death (n = 19) or removal due to clinical deterioration (n = 3). Survival for patients who remained Status 2 (n = 86) was 76% at 1 year and 55% at 3 years ($P < .01$).

Figure 5 shows time-dependent survival of patients who had remained Status 2 for a period of at least 6 months. Survival from 6 months postlisting was 83% at 1 year and 57% at 3 years for patients who did not receive transplants (n = 77). Survival for the transplant recipients (n = 45) was 93% and 83% at 1 and 3 years, respectively ($P < .05$).

DISCUSSION

In this retrospective study, we sought to determine the survival of patients initially listed for heart transplantation as UNOS Status 2 candidates. Although a subgroup of patients continued to remain stable or even experienced

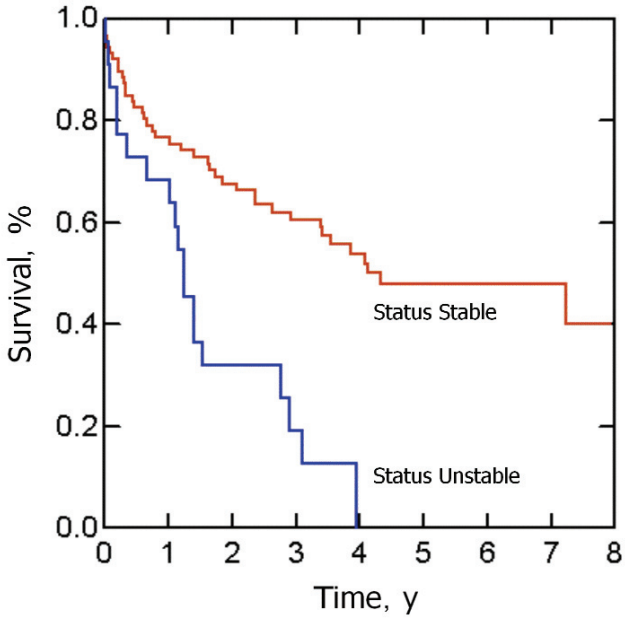

Figure 4. Survival of patients remaining Status 2 for >6 months, transplantation versus nontransplantation. Period of follow-up began at time of initial listing on the transplant registry ($P < .05$).

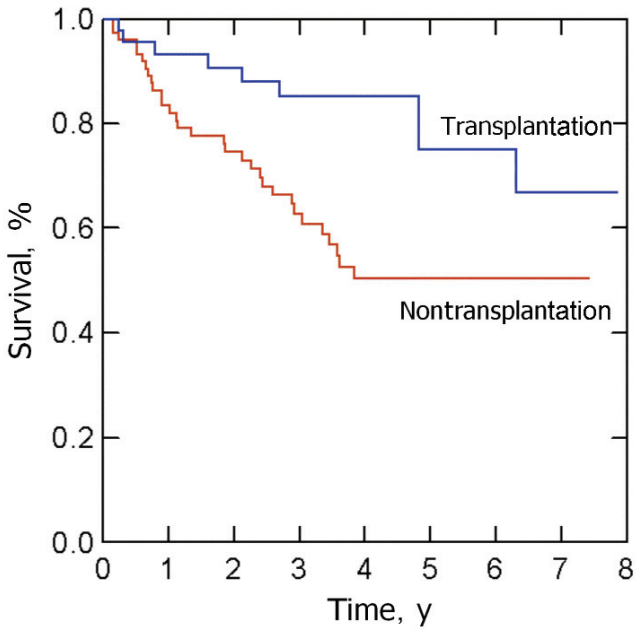

Figure 5. Survival of all patients, Status 1 versus Status 2. Period of follow-up began at time of initial listing on the transplant registry ($P < .05$).

improvement, a significant proportion worsened over time. Overall, 32% of patients deteriorated and required an upgrade in status. In addition, 22% of patients died while waiting for a suitable heart and 12% were removed from the list because significant deterioration made them ineligible for transplantation.

In agreement with previous studies, patients who deteriorated and were upgraded in status had a dismal survival rate unless they received transplants. Continued advances in the treatment of heart failure with multidrug regimens, home inotropic infusion, pacemakers, ICDs, and VADs are likely to improve the survival of heart failure patients, even without transplantation [Abraham 2000; Bristow 2000; Upadya 2004]. Recent studies have shown that medical management may be equivalent to transplantation in the current age of heart failure therapy. Rickenbacher et al determined the characteristics and survival of 116 transplant candidates with severe left ventricular dysfunction who were managed with medical treatment alone due to clinical stability [Rickenbacher 1996]. Survival in these patients was 98% and 84% at 1 and 4 years, respectively. Eight patients (7%) suffered a cardiac death while only 9 (8%) required listing for transplantation during the study period.

In a study of 160 patients who were deemed "too well" for transplantation prior to listing, Oechslin and colleagues showed no difference in midterm survival for patients treated medically (n = 160) compared with those who were listed for transplantation (n = 133) [Oechslin 1998]. Two-year survival for these 2 groups was 74% versus 70% ($P = .05$). However, 41 (25%) of the medically managed patients deteriorated clinically and required subsequent listing. This in part accounts for the 5-year, long-term survival differences in the 2 groups: 41% for the medically managed cohort and 54% for the transplant-listed cohort ($P < .001$). These studies reflect the growing consensus that medical management of a subset of heart transplantation candidates can be favorable to immediate listing.

Currently, no study has effectively established criteria to define the subset of patients who meet transplantation criteria but will remain stable and alive with medical management alone. In this study, we were unable to determine variables associated with deterioration. Peak $VO^2 \leq 12$ mL/kg per minute and cardiac index ≤ 2.0 L/min/m^2 have been previously shown to be independent prognostic indicators on multivariate analysis [Haywood 1996]. Other variables such as low serum sodium, etiology, New York Heart Association class, left ventricular end diastolic dilatation, pacemaker, pulmonary wedge pressure, and mean systolic blood pressure have also been found to be independent risk factors [Campana 1993; Saxon 1993]. Clearly, predictive risk factors for further subcategorization of Status 2 patients to better assess risk profiles and define characteristics that predict stability and survival versus progression of disease and death are desperately needed before we can answer the question of which subgroup benefits most from transplantation.

Previous studies have shown that a survival benefit to transplantation may only exist in patients listed as Status 1. Jimenez et al demonstrated that in 4255 patients initially listed as Status 2, 1-year survival analysis showed no difference in patients undergoing transplantation compared with those still waiting as Status 2 [Jimenez 2005]. At 30 months after transplantation, survival was 81% for patients undergoing transplantation as Status 1A, 77% as Status 1B, and 83% as Status 2. Deng et al determined that transplantation is associated with a survival benefit only in patients with a predicted high risk of dying based on heart failure survival scores [Deng 2000]. Of 889 adults, high-risk patients had a 51% 1-year mortality rate compared to 32% and 29% for medium- and low-risk patients, and only the high-risk cohort experienced a survival benefit from transplantation. If patients experience a mortality reduction from transplantation only when they deteriorate to a high-risk status, it may be prudent to wait for candidates to reach Status 1 before listing.

Our study confirms that survival of patients receiving transplants as Status 1 is equivalent to those receiving transplants as Status 2. Our results also suggest that up to one third of patients initially listed as Status 2 can get upgraded due to clinical deterioration. Furthermore, the survival of patients who are upgraded is worse when compared to the stable Status 2 patients. This is likely related to the fact that cardiac transplantation or mechanical support is not always an option once the patient deteriorates. At our institution, as is common in many transplantation centers across the country, the availability of suitable donor organs is limited, thus timely transplantation may not be possible. High-volume centers in major metropolitan areas may not be subject to these constraints. Although therapies such as VADs are now widespread and acceptable as bridges to transplantation, significantly

higher initial morbidity and mortality in the critically ill patient remains a problem.

In an analysis at our institution, we looked at 27 patients who were removed from the waiting list due to either clinical stability or to significantly worsening comorbidities. In the 18 patients who were removed from the UNOS waiting list due to improved clinical condition, survival was 100% at a median follow-up time of 3.7 years [Shah 2004]. Again, characteristics defining this population could not be elicited. Kao and colleagues [1994] reported no survival benefit from transplantation for patients who were on the transplant waiting list for at least 6 months. In survival analyses at 6, 12, and 18 months, heart transplantation and medical therapy patients experienced the same mortality rate [Kao 1994]. Perhaps a waiting time of >6 months on the list should be a consideration in deeming a patient too well for transplantation. However, as is discussed in Kao's report and further shown in ours, certain patients will deteriorate after the 6 month time frame and would therefore benefit from transplantation. Therefore, Status 2 patients as a whole continue to benefit from transplantation, even in the group that has been stable for 6 months postlisting.

The retrospective nature of this analysis limits the study; as such, certain variables were not available for analysis and we could not determine risk factors associated with clinical deterioration. Although numerous surgical options, including VAD and ICD implantation, have been employed at our institution during the time frame of this study, we could not appropriately evaluate the benefits or complications of these interventions. In the small analysis of causes of death, however, we did notice a trend consistent with MADIT II in that as many as one third of the deaths were related to sudden cardiac death [Moss 2002]. In addition, without data on quality of life, we are unable to determine any benefit of medical therapy or transplantation other than mortality. Finally, although our study encompasses 7 years of data, the lack of a significant number of patients precludes any analysis of changes over time due to the advent of more modern surgical or medical therapies.

Despite recent reports suggesting that patients who are eligible but are not listed for transplantation do well over the long term [Lewis 2004], we have clearly demonstrated that patients initially listed as Status 2 continue to benefit from transplantation as mortality on the waiting list and clinical deterioration is common and often unpredictable. There is clearly a need to further determine risk factors that predict outcomes in this subgroup of patients with endstage heart failure. Once these factors are determined, a randomized trial comparing medical therapy versus transplantation may be warranted [Deng 2003]. Until then, cardiac transplantation remains the best treatment option for patients currently considered as meeting Status 2 criteria.

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