

The Value of Psychosocial Factors in Patient Selection and Outcomes after Heart Transplantation

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Abstract Heart transplantation remains the gold standard treatment for advanced heart failure, although its use is limited by donor organ availability. To ensure that the rare resource of a donor heart is allocated appropriately, the evaluation of the heart transplant candidates includes extensive medical and psychosocial assessments. These psychosocial factors are critically important to understand pre-heart transplant because it is known that psychosocial evaluation and psychosocial comorbidities have a strong association with post-heart transplant outcomes. The critical factors to assess are psychological functioning, adherence to medical recommendations, and social support. These factors are likely inter-related and have been shown to have an effect on the health-related quality of life and overall survival. Recently, new tools have been developed to standardize the evaluation process. In this review, we will discuss the tools available to assess psychosocial factors in the transplant candidate and discuss the role these factors have on post-heart transplant outcomes.

Keywords Heart transplant · Depression · Social support · Medication adherence

Introduction

Heart transplantation remains the gold standard treatment for patients with advanced heart failure who are on maximal medical therapy and have limited long-term survival. Heart transplantation in this population improves survival and quality of life. Based on the most recent International Society of Heart and Lung Transplantation Registry (ISHLT) the worldwide survival at 1, 5, and 10 years are 81, 69, and 60 % respectively [1]. The improvement in survival over the past 40 years is due to a combination of factors such as improved organ preservation, better understanding of the immune responses to a transplanted organ, advances in immunosuppressive drugs, and individualized immunosuppressive regimen in response to comorbidities developing after heart transplantation.

Although heart transplantation is a very successful form of treatment for advanced heart failure, the number of procedures is significantly limited due to donor organ shortage. The number of patients suffering from heart failure has increased over the years, while the availability of organs has not. For this reason, it is important to select recipients for this rare resource who will benefit the most from heart transplant. As transplant centers have gained more experience, there has been an evolution in the absolute and relative contraindications to heart transplantation. There are well-known medical and surgical contraindications, but psychosocial factors also have an important influence on outcomes after heart transplantation.

This review examines recent findings and developments in the field of psychosocial evaluation pre-transplantation, with a focus on how psychosocial factors predict post-heart transplant morbidity and mortality. Research on three important

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psychosocial domains is reviewed: psychological functioning, compliance and adherence to medical regimens, and social support systems.

Specific Tools Used in the Psychosocial Evaluation of Transplant Patients

The evaluation of transplant candidates is done through a multidisciplinary approach (physicians, surgeons, nurse coordinators, dieticians, social workers, psychologists, or psychiatrists). The role of psychologists and social workers who are familiar with the stresses of end-stage heart failure and transplant has expanded and is critical to ensuring success in the post-heart transplant period. Ongoing developments in the assessment of the psychosocial functioning of the transplant patient have yielded new tools to better identify problems in psychosocial functioning domains. Psychological Assessment of Candidates for Transplantation (PACT) is a 10-item scale developed in 1988 that assesses several domains of psychosocial functioning [2]. The Transplant Evaluation Rating Scale (TERS) includes a similar set of domains [3]. Both show good inter-rater reliability and provide a uniform framework for evaluating psychosocial domains during a pre-transplant evaluation that is standardized across multiple organ systems. A new screening tool called the Stanford Integrated Psychosocial Assessment for Transplantation (SIPAT) has recently been described by Maldonado et al. [4••]. The SIPAT assesses psychosocial factors in pre-transplant patients including psychological stability and psychopathology, patient's readiness level and illness management, social support, and lifestyle/substance abuse issues. Within these domains, specific questions about medical knowledge, desire for treatment, available and functional social support systems, history of psychopathology and personality traits/disorders, and substance abuse are asked [4••].

Maldonado et al. demonstrated that the SIPAT and the PACT scores were highly correlated, but the inclusion of more specific assessments, social support, and knowledge of the details of illness and transplant in SIPAT made for an improvement over the older tests [4••]. Having adequate tools to detect psychosocial problems, pre-transplant is crucial because pre-transplant psychological evaluation has been shown to predict survival following heart transplantation [5].

Psychological Functioning and Outcomes After Heart Transplantation

One of the key areas of interest for clinicians evaluating a transplant candidate on psychosocial criteria is the presence of past or current psychopathology, particularly depression. Transplantation is a very stressful experience for candidates

and recipients, and patients must cope with significant medical and emotional challenges related to undergoing workup for listing, waiting for a donor heart to become available, undergoing surgery and post-operative recovery, and adjustment to life with a transplanted organ. Depression and anxiety are frequent in recipients awaiting heart transplantation with or without a bridge to heart transplantation with a left ventricular assist device (LVAD) [6–8]. It is estimated that prevalence rates for depression in patients awaiting heart transplant is 23.7 % [9], with approximately 60 % of candidates meeting at least one Axis I diagnosis [10]. Further, studies have confirmed that these depressive symptoms persist in the first year following successful heart transplantation [11] and on long-term follow-up [12]. Transplant teams usually express concerns that a patient with a history of or current psychopathology will likely experience an increase of symptoms through the stressors of the transplant process. Additionally, there is apprehension that this exacerbation of symptoms will negatively affect compliance, self-care, and motivation post-heart transplant which would directly impact recovery. Only a limited number of studies have examined the prognostic role of psychiatric variables in heart transplant outcomes.

The first known study we identified linking pre-operative depression levels to poorer survival post-heart transplant was conducted by Zipfel et al. [13]; however, the results only held for patients with a diagnosis of ischemic cardiomyopathy (ISCM) and not for dilated cardiomyopathy (DCM). Havik et al. [14] and Owen et al. [15] found a strong association between depression and mortality post-heart transplant at 6-year follow-up and noted that the association held across all patients and not only for ISCM patients. Both studies note that the mechanism of the relationship between depression and mortality remains unclear; whether this is likely related to a nonspecific mechanism such as noncompliance or low motivation or a specific biologic pathogenic pathway [14, 15].

While no recent studies have explored the mechanism of action in further detail, they have identified certain depressive symptoms that are linked to worse medical outcomes. Grandi et al. [16] noted that demoralization in combination with depression predicted more acute rejection episodes by 6 years post-heart transplant than each variable independently; further, Sirri et al. [17] reported that hostility was an important predictor of poor medical outcomes post-transplantation. Other identified symptoms of depression which were linked to poorer outcomes were irritability and a sense of worthlessness [18]. Conversely, positive outlook and optimism were associated with better physical health post-transplantation [19].

The studies described above and others clearly demonstrate the importance of screening and identification of patients with a current or past history of depression. Further work to determine if subsequent provision of targeted interventions to improve coping through the transplantation process is associated with improvements in post-heart transplant outcomes.

Adherence and Outcomes After Heart Transplantation

Another psychosocial factor taken into consideration when evaluating a patient's candidacy for heart transplantation is adherence. Adherence (also called "compliance") has been broadly defined by the World Health Organization as "the extent to which a person's behavior corresponds with agreed recommendations from a health care provider" [20] and thus encompasses all aspects of the therapeutic care plan including prescribed medications, diet, exercise, tobacco abstinence, and clinical follow-up (i.e., office visits, laboratory/diagnostic testing). A wealth of data exists across a variety of chronic medical diseases supporting the otherwise intuitive concept that the success or failure of a therapeutic plan is related to the degree to which it is followed [21–25].

For many medical conditions, including heart transplantation, the health consequences of non-adherence can be quite severe. Following heart transplantation, any interruption in maintenance of immunosuppressive medications and/or missing routine surveillance testing can lead to allograft rejection with potentially catastrophic results. Several prospective studies in patients with heart transplant have demonstrated that non-adherence with medications is associated with higher rates of acute rejection episodes [26–29] and cardiac allograft vasculopathy [27, 28], both of which are known independent predictors for mortality. While most studies have been small (owing to the relatively small population of heart transplant patients in general), single-center, and primarily focused on adherence to immunosuppressive agents, one large prospective multi-institutional study (2242 heart transplant patients from 26 centers) evaluating multiple areas of adherence found that adherent patients had significantly better survival at 2 years when compared to patients who were noncompliant with immunosuppressive medications (72 vs 91 %, $p < 0.0001$), clinic visits (77 vs 91 %, $p < 0.0001$), laboratory analyses (84 vs 91 %, $p < 0.009$), and self-monitoring (73 vs 91 %, $p < 0.0001$) [30]. Moreover, patients that were non-adherent in ≥ 3 areas had worse survival than those that were non-adherent in only 1 or 2 areas (68 vs 85 %, $p < 0.01$) [30]. There have not been any randomized studies evaluating the effect of patient adherence on outcomes following heart transplantation for obvious reasons.

Despite the evidence that post-operative adherence affects outcomes and health care providers' attempts to educate patients to that end, non-adherence in heart transplant patients remains high. The most extensively studied component of non-adherence—non-adherence with immunosuppressive medications—has been observed in up to 20 % of patients within 1 year of transplant [27]. The overall incidence varies per report depending on case finding methods, patient demographics, adherence component(s) assessed, and method of measurement (i.e., patient self-reporting, pill counting, blood assays, medication event monitoring system [MEMS]) with

studies that utilize patient self-reporting typically demonstrating lower rates of non-adherence than those that utilize blood assays, MEMS, or combinations of multiple methods of measurement. While substantially less studied, the incidence of non-adherence with follow-up evaluations and blood testing appears to be in the order of 3–15 %, smoking abstinence 5–19 %, diet 18–28 %, and exercise 24–48 % [27].

Given these persistently high rates of non-adherence, studies of patient adherence following heart transplantation have focused on identifying its predictors, underlying factors, and barriers. Several psychosocial factors including pre-transplant non-adherence, age (particularly adolescents), education level, lower social support, lower perceptions about the necessity of medications, weaker beliefs that medications can prevent rejection, higher concerns about the harms of medications, and lower overall "conscientiousness" have been identified as predictors of post-operative non-adherence [26, 29, 31, 32]. Additional factors that may be equally as important include interpersonal dynamics of the physician-patient relationship, level of patient involvement and participatory decision-making, cultural variations, and emotional health challenges (i.e., anxiety and depression) [33]. However, while many of these psychosocial factors have been shown to predict non-adherence with a relatively high degree of probability, none have been shown to be *fully reliable* predictors [34], and as such, they generally do not represent absolute contraindications to heart transplantation during the candidate selection process. Instead, their greatest value at the present time is to identify patients that may benefit most from both preventative and restorative adherence-enhancing interventions prior to and following transplantation.

Social Support and Outcomes After Heart Transplantation

As noted above, the psychosocial factors such as psychological functioning and medication adherence are clearly associated with better post-heart transplant outcomes, including survival. Social support is also a critical factor in predicting post-heart transplant outcomes. Social support (or lack of support) has been shown to be associated with wellness and quality of life in numerous disease processes including heart failure [35], cancer [36], and coronary artery disease [37]. Gottlieb and Bergen define social support as "the social resources that persons perceive to be available or that are actually provided to them by non-professionals in the context of both formal support groups and informal helping relationships" [38]. Support may be provided in the realms of advice giving, financial assistance, transportation, and medical help. The support network takes into account the number of support people available and the nature of the relationship between the individuals [38].

In their meta-analysis of studies of qualitative psychosocial factors in heart transplant patients, Conway et al. found that social support—including support from a variety of sources—was one of the most critical components of the post-heart transplant psychosocial experience for many patients [39]. This finding is important because this meta-analysis included studies performed in a variety of cultural settings making this generalizable to a broad range of transplant patients. Interestingly, one of the most beneficial areas of support for heart transplant patients in their analysis was the availability of support and connections with other transplant patients, highlighting the need to consider the importance of support system outside of the family unit.

Other work has shown that the degree of social support at the time of transplant may change in the period post-heart transplant. Bohachick et al. studied 30 heart transplant patients and assessed social support and other psychosocial variables at the time of transplant and 6 months later [40]. Social network understanding, advice, and information seeking remained stable over the 6-month period but social network helpfulness declined. The authors suggest that this may be related to the decreased contact that the patient has with the health care team which occurs as a natural component of post-operative recovery. This information is critical for health care providers to consider when setting post-heart transplant expectations for patients.

A patient's spouse is often considered the lynchpin of the social support network, although there is conflicting data as to the effect and importance of marital status on post-transplant outcomes. Dobbels et al. found that lack of partnership (spouse) was the only predictor of graft loss (in a population of lung, liver, and heart transplant patients) between 6 and 12 months (OR 4.88; CI 1.10–21.7) even when accounting for non-adherence and other psychosocial variables [29]. This suggests that social support systems/partnerships do more than simply reinforce compliance. Tam et al. also found that marital status was associated with post-transplant survival [41]. In their single institution study of 260 patients receiving a heart transplant between 1995 and 2010, married patients had a 5-year survival of 84 % and unmarried patients 69 % ($p < 0.01$) with no significant difference found between men and women. In a multivariable model including age, marital status, whether or not a patient had children or not, diabetes, body mass index, creatinine, and CMV mismatch (all from time of listing for transplant), only marital status as “married” (HR 0.47; CI 0.23–0.97) and creatinine (HR 1.8; CI 1.2–2.8) were significantly associated with 5-year survival. Despite this compelling data, Farmer et al. found that in a study of 555 post-heart transplant patients, marital status was not associated with death at 5 to 10 years after heart transplant (marriage was actually associated with a trend toward *worse* survival, $p = 0.055$) [42]. It is unclear why marriage was not associated with survival in this study, but the authors note that they were unable to quantify the nature of the marriage or recent marital transitions. The effect of marriage on

post-heart transplant survival may depend on the quality of the partnership, not just its presence.

In addition to having an effect on post-heart transplant quality of life and survival, social support has a very important effect on morbidity and mortality while the patient waits on the transplant list. As part of the “Waiting for a new heart study,” Spaderna et al. prospectively studied 318 heart transplant patients from the time of initial listing through 12 months [43]. They found that a combination of depression and social isolation was strongly associated with death or deterioration while waiting on the transplant list and that non-isolated/non-depressed patients were more likely to see improvement sufficient enough to warrant removal from the transplant list. Social support network size was associated with clinical improvement even when controlling for heart failure severity.

Conclusions and Future Directions

This review clearly establishes the important role of the pre-heart transplant psychosocial evaluation in the heart transplant work-up. Psychological functioning, particularly depression, medication adherence, and social support, are all associated post-heart transplant outcomes including quality of life and survival. Although, as we have shown, there is a great deal of literature detailing the associations between these factors and transplant outcomes, much less is known about the role of interventions to address problem areas that are identified in the evaluation process. Further work to determine the role of targeted interventions early in the transplant process (e.g., psychotherapy, pharmacotherapy, family meetings, and support groups) is needed.

Compliance with Ethics Guidelines

Conflict of Interest Erin E. Coglianese, Mekhala Samsi, Max J. Liebo, and Alain L. Heroux declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- Of major importance

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