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Role of psychological factors in the clinical course of heart transplant patients

See companion article on page 247.

Depression is an increasingly recognized risk factor for adverse clinical outcomes and mortality in heart transplant patients.[1–4] These increased cardiovascular risks associated with depression are consistent with observations in patients with heart failure,[5] coronary artery disease[6] and in the general population.[6,7] In a comprehensive meta-analysis of 146,538 individuals participating in 54 studies, depression was found to be consistently predictive of mortality in patients with a known diagnosis of cardiovascular disease as well as new-onset myocardial infarction and cardiovascular mortality in cardiovascular disease-free participants.[6] Reported risk ratios associated with depression are comparable to well-established coronary artery disease (CAD) risk factors such as hypertension, hypercholesterolemia and obesity.[8,9] Depression often coincides with social isolation (i.e., lack of social integration and low social support) and other psychological factors involving negative affect (e.g., hostility anxiety, and distress specifically related to the transplant episode), which may further increase the risk of adverse long-term outcomes.[4] The potential impact of psychological factors in heart transplant patients has been recognized for over 4 decades.[10] However, the joint predictive value and treatment of depression, social isolation and other psychological factors in the heart and lung transplant population require further investigation.

Four critical phases in the clinical course of heart transplant patients are relevant in the evaluation of psychosocial risk factors for adverse post-transplant outcomes (Table 1): (1) pre-transplant referral; (2) wait-list period; (3) early post-transplant follow-up (within 1 year); and (4) long-term transplant follow-up (>1 year). In general, prevalence estimates of depression in pre- and post-transplant patients range from 15% to 30%, but substantial differences within and across patients have been observed.[1-4]

During the "pre-transplant referral" phase, psychological characteristics and patient adherence behaviors need to be considered in the context of progressive heart failure, and these factors require attention because of their predictive value for pre- and post-transplant survival, post-transplant adherence to medical and behavioral guidelines and post-transplant quality of life. Depression is common in heart failure patients (prevalence ≈20%) and is a significant risk factor for mortality and secondary events in heart failure (relative risk [RR] = 2.1; 95% confidence interval [CI] 1.7 to 2.6).[5] In addition, depression in heart failure is associated with poor medication adherence and substance abuse. Social and other resources are often taken into consideration when patients and their treating physicians consider referral for transplantation. Little is known about the role of these psychosocial and behavioral factors in the initial referral for cardiac transplantation. Systematic early evaluation of potential transplant candidates for psychological and behavioral measures relevant to treatment adherence may optimize patient selection for transplant waiting lists and improve pre-emptive risk modification.

The "wait-list period" is of particular importance to heart transplant candidates given the high levels of psychological distress related to the potential unavailability of a donor heart and the patient's life-threatening medical condition. The waiting time can be long, exceeding 1 year in approximately 40% of patients, which may further contribute to increases in levels of distress.[11] The lack of control over these major challenges may result in sustained distress in patients and their families, leading to depression and other adverse psychological outcomes. The article by Spaderna et al. in this issue of the journal supports the predictive value of depression and social isolation in patients who are on the waiting list for heart transplantation.[12]

The "early post-transplant follow-up" period (<1 year) is generally characterized by substantial improvements in physical functioning, but many patients experience sustained or new-onset depression and other psychological problems that interfere with quality of life and maintenance of medication

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Table 1 Critical Phases in the Psychosocial Evaluation of Heart Transplant Patients

Phase	Psychosocial factors
I. Pre-transplant referral	Adherence to medication and healthy lifestyle Depression and distress Social network/resources Rule-out of current substance abuse and cognitive impairment Patient and physician expectations of transplant outcome
II. Wait-list period	Distress–uncertainty of availability–life-threatening disease Prolonged waiting time → further increases in distress, depression and anxiety Social support and coping resources
III. Early follow-up (<1 yr)	Adjustment to new medical regimen: clinic visits, biopsies and immunosuppressive medications Learning to incorporate improved physical function in daily life Coping with rumination about wait-list patients and organ donor
IV. Long-term follow-up (>1 yr)	Adjustment to continued medication adherence Demands related to sustained healthy lifestyle requirements Common gradual increase or new-onset depressive symptoms

adherence and optimal health behaviors.[13,14] Post-transplant depressive symptoms and other psychological factors involving negative affect (e.g., hostility and distress specifically related to the transplant episode) are associated with adverse long-term outcomes (vasculopathy, graft rejection and/or mortality).[1–4,15]

The "long-term transplant follow-up" (>1 year) requires continued monitoring for psychological well-being and health behaviors. A few studies suggest that depression may gradually increase in the post-transplant period. It will be of interest to conduct further follow-up analyses of heart transplant cohorts, examining trajectories of pre- and post-transplant psychological and behavioral factors as predictors of long-term outcomes.

Spaderna et al. in this issue of the journal found that mortality and clinical deterioration occur disproportionately more often in patients with a combination of depression and a small social network (defined as usual contact with <4 close friends and relatives during 1 month) vs those without depression and a relatively large social network (>11 friends or relatives) (19% vs 6%; 1-sided $p = 0.048$). Similarly, de-listing as a consequence of improvement was *not* observed in patients with a combination of depression and a small social network and occurred only in patients without depression and a relatively large social network (0% vs 17%, 1-sided $p = 0.004$). It remains to be determined, however, which of the multiple outcome categories were predicted by depression and social isolation. Specifically, a small network was present in 11 of 42 (26%) patients who died or deteriorated during follow-up, 19 of 83 (23%) in those with urgent transplantation, 9 of 30 (30%) with elective transplantation, 23 of 142 (16%) for those still on the waiting list, and 3 of 17 (18%) of those who were de-listed after clinical improvements.

Consistent with prior research,[15] depression was also associated with these outcomes (depression-related percentages for the aforementioned outcomes were 43%, 45%, 37%, 38% and 6%, respectively ($p = 0.054$). It can therefore be inferred that the predictive value of these psychological factors was primarily attributable to the lower incidence of improvements in patients who were socially isolated and/or depressed, although the sample size of the improved group was very small ($n = 17$). Patients who are de-listed patients for reasons of clinical improvements tend to be more often female, younger, and on the waiting list for a longer period of time.[16] These three factors are typically associated with more severe depression scores, and hence the present findings may represent an underestimation of the association between depression and clinical outcomes in waitlisted transplant patients. Results are less clear for the prediction of adverse outcomes (mortality, deterioration or urgent transplantation) because the significance of results may differ depending on which group is chosen as the reference group (i.e., patients still on the waiting list or those with elective transplantation).

Strengths of the study by Spaderna and colleagues include the multi-site setting, the prospective design, the relatively high effective participation rate (318 of 380, or 84%) and assessment of multiple psychological and behavioral measures. The short duration between wait-listing and return of questionnaires (median 15 days) may have underestimated the general level of depressed mood in wait-listed patients as depressive symptoms tend to increase over the course of the waiting period.[11] Reliance on mailed questionnaires may reveal sub-optimal assessments of depression and social isolation measures, but this limitation is largely outweighed by the high participation rate and the use of validated questionnaires.

Placing the findings by Spaderna et al. in a broader

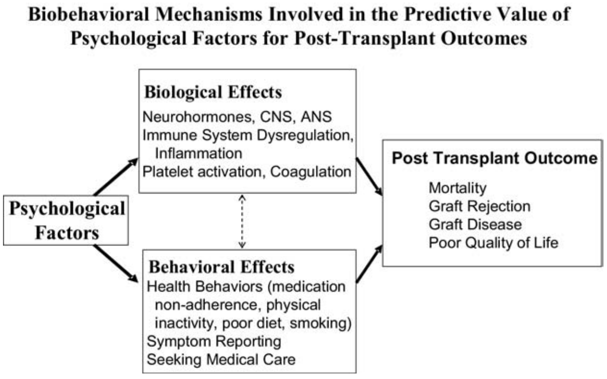

Figure 1 Biobehavioral mechanisms involved in the predictive value of psychological factors for post-transplant outcome. CNS = central nervous system; ANS = autonomic nervous system.