Effect of Depressive Symptoms on Survival After Heart Transplantation

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Objective: This study explored the value of preoperative self-reported assessment for depression and anxiety in patients who had undergone heart transplantation (HTx). The initial sample was divided into subgroups of patients with ischemic (ICMP) and dilated cardiomyopathy (DCMP). Patient depression and anxiety scores were measured in both subgroups and their impact on pre- and postoperative mortality investigated. Method: An initial sample of 152 patients with either ICMP (N = 57) or DCMP (N = 95) and end-stage heart disease awaiting heart transplantation were assessed in a multidimensional longitudinal study, including psychological and somatic variables. One hundred and three patients received a HTx and were followed up for a mean of 4.4 years. Proportional hazard models were computed to test for the influence of psychosocial and somatic factors on outcome. Results: Preoperative depression and state anxiety scores were significantly higher in the ICMP group. In addition to donor and recipient age, ICMP patients in the preoperative high depression group also showed a significantly higher mortality after HTx. This result remained significant even after controlling for sociodemographic and somatic variables. Conclusions: Patient self-reported depression, but not anxiety, can contribute to the identification of subgroups of patients with an unfavorable outcome after HTx. It therefore may be helpful to screen for depression, particularly in patients with an ischemic cause of their end-stage heart disease. Specific intervention programs should be further developed and evaluated. Key words: heart transplantation, depression, anxiety, survival prediction, cardiomyopathy.

HTx = heart transplantation; ICMP = ischemic cardiomyopathy; DCMP = dilated cardiomyopathy; NYHA functional class = New York Heart Association functional class; DS = Depression Scale; STAI = State and Trait Anxiety Inventory; GBB = Giessen Complaints List; RR = risk ratio; LDL = low-density lipoprotein.

INTRODUCTION

There is growing evidence that major depression and even subthreshold depression are associated with elevated morbidity and mortality in patients with established cerebrovascular (1) and coronary heart disease (2–4). In addition, depression has been shown to be a predictor of mortality in medical inpatients (5, 6). The evidence for panic disorder (7) and effects of anxiety on mortality in patients with coronary artery disease are conflicting (8).

Symptoms of depression and anxiety are frequently encountered in patients awaiting a heart transplantation, with prevalence rates for major depression of 23.7% (9) and a further significant increase in depressive symptoms during the waiting period (10). Up to 60% of patients awaiting heart transplantation (HTx) met criteria for at least one Axis I diagnosis (depression and/or anxiety disorders) (11). Even in the first year after successful HTx, prevalence rates for major depression of 15.8% have been reported (9). Recent studies show an increasing deterioration of emotional well being in the long-term course after transplantation (12). There is a growing body of literature in the field of psychosocial research in HTx focused on predicting morbidity and mortality in the course of transplantation. Early studies demonstrated that psychosocial factors, particularly coping style and social support, may be significant predictors of morbidity and mortality in patients awaiting HTx (13, 14) and in the intermediate term after successful HTx (15–17).

According to the registry of the International Society of Heart and Lung Transplantation, the two major indications for adult heart transplantation are 1) ischemic cardiomyopathy (ICMP), caused by coronary heart disease, and 2) dilated cardiomyopathy (DCMP), which could be caused by genetic, viral, immune, toxic, or unknown factors (18). Although both patient groups with end-stage heart failure share common symptoms, mainly marked dyspnea, recent studies have shown different clinical prognostic factors for these two major groups (19). Even after successful HTx, patients with an initial ICMP had a significantly higher prevalence rate of graft atherosclerosis as early as 2 years after having received a HTx, indicating the systemic nature of atherosclerosis (20). Recent studies in the field of psychology have demonstrated signifi-
cantly higher depression rates in patients with ICMP (21) and a reduced resistance to stress (22) compared with DCMP patients. Based on these findings, the two-fold purpose of the current study was: 1) to assess whether different patterns of psychological distress exist in the two major diagnostic groups of patients with terminal heart failure awaiting a heart transplantation (HTx) and 2) to investigate the prognostic utility of depressive and anxiety symptoms for survival before and after HTx, adjusting for well-established somatic risk factors for fatal postoperative outcome.

**METHOD**

**Subjects**

Participants were patients referred to the Department of Cardiology, University of Heidelberg from January 1990 to January 1997 for heart transplantation evaluation. Inclusion criteria for the study were a minimum age of 18 years, sufficient command of the German language, and no bridging with an artificial heart. Only the subset of patients who were subsequently put on the waiting list were initially contacted and asked to participate in the study. A complete set of data was obtained from 160 patients, an incomplete dataset was obtained for 7 patients, and 9 patients refused to participate (participation rate 90.0%). A small heterogeneous subgroup of N = 8 (5%) patients had cardiomyopathy due to other causes (hypertrophic and restrictive cardiomyopathy, congenital heart disease, and valvular heart disease) and was not included in this study, leaving a total sample of N = 152 patients. The major diagnostic subgroups were patients with ischemic cardiomyopathy ICMP (N = 57, 35.6%) and dilated cardiomyopathy DCMP (N = 95, 59.4%). All diagnoses were made by a senior cardiologist. Ischemic cardiomyopathy (ICMP) was diagnosed by the presence of a severely reduced left ventricular ejection fraction (<25%), determined by ventriculometry, and concurrent significant coronary artery narrowing on the coronary angiogram (>50%). Patients with dilated cardiomyopathy (DCMP) had a similar diagnosis of severely reduced left ventricular ejection fraction. DCMP was diagnosed after exclusion of the following cardiac diseases: ischemic, valvular, congenital, and hypertrophic cardiomyopathy.

During the waiting period, N = 32 (21.2%) patients died, N = 1 (0.7%) developed a somatic contraindication for HTx, and N = 16 (10.5%) showed marked improvement and were taken off the waiting list. Thus, a total sample of N = 103 patients received a heart transplantation.

**Procedure**

After being placed on the waiting list, the patient was asked to participate in the study and informed consent was obtained. A 45- to 60-minute structured face-to-face interview, focusing particularly on coping skills, social support, and compliance behavior, was conducted by trained clinicians with a masters or doctoral degree in psychiatry or psychotherapy. Results of these interviews were reported previously (23). In addition, patients were asked to complete questionnaires assessing depression, anxiety, and physical complaints.

Patients were seen routinely by a cardiologist immediately before the psychosocial interview in order to review the actual somatic condition and medication. During this visit, the New York Heart Association (NYHA) functional class was assessed. According to Givertz et al. (24), NYHA Class is defined as follows: Class II—slight limitation of physical activity; such patients are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea or angina. Class III—marked limitation of physical activity; although patients are comfortable at rest, less than ordinary activity will lead to symptoms. Class IV— inability to carry on any physical activity without discomfort. Symptoms of congestive failure are present even at rest. With any physical activity increased discomfort is experienced.

Additional cardiac-related history data were obtained from hospital medical records, including coronary angiography and ventriculography. Ischemia time was defined as the duration between explantation and implantation of the donor heart. Patients were followed up until May 1, 2000, totaling a minimum follow-up period of 2 years and a mean time of postheart transplantation survival of 4.4 ± 0.9 years. Outcome on the waiting list consisted of either death or removal from the list because of worsening condition or clinical improvement. Outcome after successful transplantation was classified as either death or survival. Data were obtained from the Heidelberg Transplantation Center Database. In case of missing data, the personal physician was contacted.

**Psychological Assessment**

In addition to a short questionnaire concerning sociodemographic data, a subsequent set of questionnaires was administered to patients after being listed for a HTx.

**Depression.** The Zerssen depression scale (DS) is a one-dimensional questionnaire consisting of 16 items used for the self-evaluation of a patient’s depressive mood. In Germany, this is a widely used standardized measure with high reliability and validity (25).

**State and trait anxiety inventory.** Patients answered the 20-item German version of the state (STAI-I) and trait inventory (STAI-II), for which high reliability and validity have also been reported (26).

**Giessen Complaints List.** Giessen Complaints List (GBl) by Brähler and Scheer (27) is one of the instruments most frequently and widely used in Germany to explore the subjective limitations experienced by patients due to their physical symptoms. The questionnaire is comprised of 24 items that evaluate the areas of exhaustion, stomach ache, arthralgia, and cardiac symptoms. In addition, a total score from all four scales reflects the individual’s level of personal stress caused by physical symptoms. To investigate whether a difference existed between the ICMP and DCMP groups in their cardiac-related symptomatology, we compared cardiac scale results at both the individual-symptoms level and the complete-scale level. The six-item cardiac scale included palpitation, dizziness, tightness of throat, heart burn, shortness of breath, and heart complaints. According to Brähler and Scheer (27), the response range is defined as 0 = absent to 4 = very marked.

**Statistical Analysis**

All data were entered into a computerized database and analyzed using SPSS version 10.0/PC software. Univariate comparisons were performed using χ² statistics or Fischer exact tests (two-tailed) for categorical data and independent sample t tests (two-tailed) for continuous data. To control for type 1 error, a Bonferroni adjustment was done, as needed. To assess global mortality and differences between groups in outcome, we used the Kaplan-Meier method, including the log rank test. Before transplantation, variables known to be associated with mortality in heart transplant patients, according to the registry report of the International Society of Heart and Lung Transplantation (18) (donor and recipient age, gender, diagnosis, ischemia time), were entered into the Cox proportional hazards
statistics to evaluate their predictive power in relation to outcome mortality. Pulmonary vascular resistance was not regularly assessed at this time at our transplant center and therefore was not included in the analysis. In addition, separate analyses were conducted with questionnaire scores of the depression (DS) and state anxiety (STAI-I) inventory, dichotomized at the median. For each variable, relative risks are presented as univariate or multivariate risk ratios, with their respective 95% confidence intervals (CI). A risk ratio (RR) of greater than one indicates an increased relative risk for mortality for each one-unit increase in the predictor variable (eg, age), or in the case of dichotomized predictor variables (eg, depression), RR indicates the increased risk of mortality for those groups with high levels compared with those with low levels. Standardized mortality rates were calculated using the subjects-years method (28) and the German death statistics.

**RESULTS**

**Patients’ Baseline Characteristics**

Table 1 shows that ICMP patients were slightly but significantly older compared with the group of patients with a dilated cardiomyopathy. No group differences were seen in terms of further baseline sociodemographic characteristics and illness severity assessed using the New York Heart Association (NYHA) functional class. With the exception of a longer waiting period before transplantation, immediate inpatient stay after HTx and total days of survival after HTx did not differ significantly. Donor characteristics (donor age and cold ischemic time) were comparable for both diagnostic subgroups. Posttransplant patients were directly transferred, after the necessary time in the intensive care unit, from the Department of Cardiothoracic Surgery to the Department of Cardiology for posttransplant care and immediate rehabilitation.

**Assessment of Baseline Depression, Anxiety, and Physical Complaints**

Four ICMP patients (7.0%) and two DCMP patients (2.1%) had an earlier history of major depression, whereas two ICMP patients (3.5%) and five DCMP patients (5.3%) had a history of substance (mainly alcohol) abuse. None of the patients were on antidepressants at the time of listing. Baseline depression scores for the group of ICMP and DCMP patients were significantly higher compared with the data for healthy group with values in the normal range (Table 2). Patients with an ischemic cardiomyopathy had a significantly higher baseline depression score compared with DCMP patients. State anxiety scores were also significantly elevated in the ICMP group compared with the healthy norms and DCMP patients. A tendency in the same direction was found for trait anxiety. Regarding the level of physical complaints, both cardiomyopathy groups showed significantly increased scores in exhaustion, stomach ache, cardiac symptoms, and total score compared with the healthy German control group (29). Although the level of complaints tended to be higher for ICMP patients compared with the DCMP group in nearly every dimension, none of these were statistically significant. The

<table>
<thead>
<tr>
<th>TABLE 1. Baseline Demographic and Clinical Data by Diagnostic Group</th>
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<tbody>
<tr>
<td><strong>Ischemic Cardiomyopathy</strong> (N = 57)</td>
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<tr>
<td>Mean age ± SD (years)</td>
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<tr>
<td>Gender (%)</td>
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<tr>
<td>Male</td>
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<tr>
<td>Female</td>
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<tr>
<td>Partner status (%)</td>
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<tr>
<td>No partner</td>
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<tr>
<td>Partner</td>
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<tr>
<td>Employed status (%)</td>
</tr>
<tr>
<td>Not employed</td>
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<tr>
<td>Employed</td>
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<tr>
<td>Days waiting for HTx ± SD</td>
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<tr>
<td>Days after HTx ± SD</td>
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<tr>
<td>Days at hospital after HTx ± SD</td>
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<tr>
<td>NYHA status (%)</td>
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<td>NYHA Class II</td>
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<td>NYHA Class III</td>
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<tr>
<td>NYHA Class IV</td>
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<tr>
<td>Donor age ± SD (years)</td>
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<tr>
<td>Ischemia time ± SD (minute)*</td>
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</tbody>
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* Ischemia time was defined as the duration between explantation and implantation of the donor heart.
only difference approaching statistical significance was the comparison of cardiac symptoms \( (p = .07) \). Item analyses of the cardiac scale revealed a significantly higher symptom load \( (p = .02) \) on the item heart burn (the equivalent of angina pectoris) in the ICMP group. Depression \( (r = .102; p = .20) \), state and trait anxiety \( (r = .039; p = .63 \text{ and } r = -.047; p = .564, \text{ respectively}) \), and the total score of physical complaints \( (r = -.021, p = .88) \) were not associated with age.

Outcome on the Waiting List

During the waiting period, 32 (21.1%) patients died, all due to cardiovascular reasons. However, a subset of 16 (10.5%) patients showed a marked improvement in their physical status and were taken off the waiting list. One patient (0.7%) developed somatic contraindications for a heart transplantation. Overall, there was no significant difference in survival rates between the two diagnostic subgroups on the waiting list \( \chi^2 \text{ (log rank): } 4.92, p < .0001 \). NYHA functional class at baseline was a significant predictor of survival on the waiting list \( \text{RR} 1.75; 95\% \text{ CI, } 1.07–2.87; p = .024 \), although only for the subset of DCMP patients. Preoperative psychological variables (depression and anxiety) were not predictive of survival on the waiting list. Although the mean waiting period was approximately 1 year, it was significantly longer for ICMP patients \( (t = 2.31, p = .022) \).

Outcome After Transplantation

There were no significant differences in mortality rates between the diagnostic groups \( \chi^2 = .389, p = .533 \). Twenty-one (33.3%) DCMP patients and 10 (25.0%) ICMP patients died after transplantation, leading to an overall probability of survival at 1 year of 76.7% and at 4.4 years of 70.0%. In addition, there were no gender-dependent differences in survival after HTx \( \chi^2 (\text{log rank): } 1.1, p = .564 \). Though the observed standardized mortality rate in our patient sample was 15.2 times greater for women and 7.7 times greater for men compared with the expected mortality rate according to the German population, this difference was due to naturally lower death rates for women in this age group in the general population. Causes of death over the posttransplant period differed over time, with predominantly acute graft failure occurring in the early period and an increased prevalence of tumors over the long-term course. However, causes of post-HTx death (acute graft failure, infection, rejection, tumor) for the diagnostic groups did not differ significantly \( \chi^2 = 4.4, p = .223 \).

Due to the relatively small sample size with skewed distributions of the depression and anxiety scores, the sample was dichotomized at the median to create a low- vs. high-risk group of equal size. After the median split, the group with low depression scores was within the normal range \( (\text{low-depression group, } 6.05 \pm 2.27, \text{ vs. healthy population sample, } 5.46 \pm 4.74; t = 1.24, p = .11) \), whereas the mean of the high-depression group was more than two standard deviations (SD) above the normal mean \( (\text{high-depression group, } 15.84 \pm 5.90 \text{ vs. healthy population sample, } 5.46 \pm 4.74; t = 8.58, p < .0001) \). A similar distribution was found for the dichotomized state anxiety scores. The group with low anxiety scores was not significantly different from the healthy population sample \( (35.27 \pm 7.15 \text{ vs. } 34.45 \pm 8.83; t = 0.045, p = .325) \), whereas the high-state anxiety group scored more than 2 SD above the normal mean \( (53.44 \pm 7.94 \text{ vs. } 34.45 \pm 8.83; t = 10.44, p < .0001) \).

The unadjusted relative risks for mortality after

**TABLE 2. Comparison of Psychological Data and Physical Complaints Between Patients With Ischemic Cardiomyopathy (ICMP), Dilated Cardiomyopathy (DCMP), and Controls**

<table>
<thead>
<tr>
<th></th>
<th>Controls M ( (SD) )</th>
<th>ICMP M ( (SD) ) ( N = 57 )</th>
<th>DCMP M ( (SD) ) ( N = 95 )</th>
<th>( \rho^b )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depression (DS)</td>
<td>5.5 ± 4.7</td>
<td>10.9 ± 6.6</td>
<td>7.6 ± 5.0</td>
<td>1c, 2c, 3c</td>
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<tr>
<td>Anxiety (STAI)</td>
<td></td>
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<td></td>
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<tr>
<td>State anxiety (STAI I)</td>
<td>34.4 ± 8.8</td>
<td>44.4 ± 11.8</td>
<td>40.3 ± 10.6</td>
<td>1c, 2c, 3a</td>
</tr>
<tr>
<td>Trait anxiety (STAI II)</td>
<td>36.8 ± 9.8</td>
<td>42.2 ± 10.5</td>
<td>39.3 ± 8.7</td>
<td>1c, 2b, 3d</td>
</tr>
<tr>
<td>Physical complaints (GBB)</td>
<td></td>
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<tr>
<td>Exhaustion</td>
<td>3.9 ± 4.0</td>
<td>10.9 ± 4.7</td>
<td>9.7 ± 4.7</td>
<td>1c, 2b</td>
</tr>
<tr>
<td>Stomach ache</td>
<td>2.6 ± 3.1</td>
<td>3.9 ± 3.4</td>
<td>3.9 ± 3.5</td>
<td>1b, 2b</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>5.4 ± 4.6</td>
<td>7.0 ± 4.8</td>
<td>6.0 ± 4.4</td>
<td>1a</td>
</tr>
<tr>
<td>Cardiac symptoms</td>
<td>2.2 ± 3.2</td>
<td>9.0 ± 5.3</td>
<td>7.5 ± 4.8</td>
<td>1c, 2c, 3d</td>
</tr>
<tr>
<td>Total score</td>
<td>14.0 ± 12.7</td>
<td>30.1 ± 13.9</td>
<td>27.1 ± 13.7</td>
<td>1c, 2c</td>
</tr>
</tbody>
</table>

* DS = depression scale (25); STAI I and II = German version of state and trait anxiety inventory (26); GBB = Giessen Complaints List (27).

\( a \), ICMP vs. controls; \( b \), DCMP vs. controls; \( c \), ICMP vs. DCMP. \( a, p < .05; b, p < .01; c, p < .001; d, p = 0.07 \).
heart transplantation for basic variables are summarized in Table 3 for both diagnostic groups. Higher age of the recipient as well as higher donor age were associated with an increased risk of posttransplant mortality in the subgroup of ICMP patients. Only ICMP patients in the high-depression subgroup had significantly increased post-HTx mortality rates compared with the low-depression group (RR 5.06; 95% CI 1.07–23.89; \( p < .05 \)). The dichotomized state anxiety scores were not a predictive factor in postoperative outcome. For the DCMP patients, none of the variables reached the level of significance.

Using the method of Hosmer and Lemeshow (30), those variables reaching a level of \( p < .05 \) were included in a multivariate model. For the ICMP subgroup, the results of the multivariate Cox’s proportional hazard statistic after adjusting for age, donor age, and cold ischemic time of the donor organ remained significant (multivariate RR 5.38; 95% CI, 1.04–27.85; \( p < .05 \)).

Figure 1 illustrates the course of post-HTx survival in patients with ischemic cardiomyopathy for the preoperative dichotomized subgroups of high vs. low depression. The log-rank test showed a significantly different course of survival after transplantation for both subgroups (log rank: \( \chi^2 = 5.18, p = .023 \)). ICMP patients in the low-depression group had a mean time of posttransplantation survival of 1644.1 ± 121.3 days compared with the high-risk group of 1339.3 ± 172.2 days. In an additional analysis, patients with an earlier psychiatric history (major depression \( N = 2 \) and substance abuse \( N = 1 \)) were excluded from the analysis. The subgroups of patients with high depression scores continued to have significantly higher post-HTx mortality (log rank: \( \chi^2 = 5.11, p = .024 \)).

**DISCUSSION**

Based on the growing evidence that psychological factors play an important role in the development and expression of heart disease (31–33), this is the first study investigating the extent and impact of psychological distress separately for the subgroups of patients with end-stage ischemic (ICMP) and dilated (DCMP) cardiomyopathy. These two subgroups comprise the major distinct entities of patients with terminal heart failure awaiting heart transplantation (18).

Although both cardiomyopathy subgroups showed significantly increased levels of psychological distress compared with healthy controls, the direct comparison between both patient subgroups showed significantly increased levels of depression and anxiety among ICMP patients along with increased levels of physical complaints in both patient groups. ICMP patients with an underlying coronary heart disease (CHD) showed a higher symptom load of angina pectoris compared with the DCMP patients. Thus, in the first part of our study, we were able to demonstrate that these two major diagnostic subgroups of patients with severe cardiomyopathy showed differences in

<table>
<thead>
<tr>
<th>Variable</th>
<th>Ischemic Cardiomyopathy (( N = 40 ))</th>
<th>Dilated Cardiomyopathy (( N = 63 ))</th>
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<tbody>
<tr>
<td></td>
<td>RR (95% CI)</td>
<td>( p )</td>
</tr>
<tr>
<td>Age (years)</td>
<td>1.15 (1.01–1.31)</td>
<td>.038*</td>
</tr>
<tr>
<td>Donor age (years)</td>
<td>1.06 (1.01–1.11)</td>
<td>.029*</td>
</tr>
<tr>
<td>Ischemia time (min)*</td>
<td>.99 (0.98–1.01)</td>
<td>.162*</td>
</tr>
<tr>
<td>Depression (high vs. low)</td>
<td>5.06 (1.07–23.89)</td>
<td>.041*</td>
</tr>
<tr>
<td>State anxiety (high vs. low)</td>
<td>1.63 (0.46–5.79)</td>
<td>.449</td>
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</tbody>
</table>

* Ischemia time was defined as the duration between explantation and implantation of the donor heart.

\* \( p < .01 \).
psychological distress and, in some cases, in cardiac-related complaints in pretransplant evaluation. However, due to our study design, we were not able to explain whether these findings are a primary feature of differences in psychopathology or symptomatology or whether ICMP patients are more prone to depression and anxiety in the course of their illness. Similar to our study, Trunzo et al. (21) found increased levels of depression among ICMP patients awaiting heart transplantation (HTx) compared with a nonischemic group. Majani et al. (22) investigated the relationship between psychological profile and cardiological variables in a sample of patients covering the whole range of severity of chronic heart failure. Compared with DCMP patients, the subgroup of ICMP patients in their study reported lower satisfaction scores with physical functioning and physical appearance. In addition, the authors found a significantly reduced resistance to stress among ICMP patients.

In a second step, similar to a number of studies on CHD showing the influence of depression (3, 4) and, to a minor extent, anxiety (33) on outcome, we investigated the influence of preoperatively assessed clinical and psychological data on pre- and posttransplant outcome. Twenty-one percent of the entire sample died while waiting for a donor organ. With the exception of the NYHA functional class for the DCMP subgroup, we could find no additional somatic or psychological predictors of survival before HTx. The percentage of survival at 1 year and 4.4 years for the entire sample was 76.7% and 70.0%, respectively, and was therefore slightly higher than the survival rates of both a representative German survey with a 1-year survival rate of 71% (34) and a recently published 1-year survival rate of 62% from a French transplant center (35). Our survival rates were lower, however, compared with the 81% survival rate recently published by the International Society of Heart and Lung Transplantation (18). With standardized mortality rates in our patient sample of 15.2 for women and 7.7 for men, it is obvious that, even after HTx, patients had a significantly shorter life expectancy than their age- and sex-matched counterparts. In our sample, higher recipient and donor age were both associated with an increased risk of postransplant mortality in ICMP patients.

In addition, the level of preoperative depression (Figure 1), but not anxiety, was a significant predictor of survival in the subgroup of ICMP patients. This result remained stable after adjusting for basic sociodemographic and somatic factors of both recipient and donor. To our knowledge, this is the first report linking preoperative depression scores with postransplant survival. This might be due to the fact that the few other studies (16, 17) using hazard proportional models to predict postransplant survival in heart transplantation failed to subdivide their initial sample into the underlying diagnostic groups. Although our study provides the largest sample of patients to date, assessing and linking preoperative psychosocial factors and postoperative long-term outcome, we were not able to detect a specific pattern of deaths associated with an increased level of depression. This was most likely due to the relatively small sample size in the various subgroups and a variety of different causes of death after transplantation. Therefore, it remains speculative as to whether an increased level of depression is associated with a specific pathogenic pathway.

Dew et al. (9), however, recently showed that postoperative depression was an independent predictor for cardiac allograft disease. Although transplant vasculopathy and native atherosclerosis are clinically and pathologically different entities, the pathogenesis of both diseases exhibits some common mechanisms. Deng et al. (36) stated that both may be regarded as responses to injury within a broadened concept of the immune system. Alloantigens (eg, on donor endothelial cells) or autoantigens (eg, oxidized LDL cholesterol) are presented by antigen-presenting cells to the T cells of the body’s immune system. This may be one reason why Aziz et al. (20) found a markedly higher incidence of CHD in patients with a former ICMP compared with DCMP patients, even 10 years after transplantation.

Over the past few years, an increasing number of studies have identified specific mechanisms known to increase the risk of death in patients with CHD, such as decreased vagal and increased sympathetic tone (37, 38) as well as affection of the platelets (39) or an association with inflammation processes (40). However, heart transplant patients with a history of ischemic cardiomyopathy differ in many ways from patients with CHD. Shapiro et al. (41) showed that, in HTx-patients with a denervated heart, no functional reinnervation or other compensatory adaptation occurred up to 1 year after heart transplantation. Salmon et al. (42) found that the disrupted responses to a psychological stressor after HTx were due to the functional deficit in the innervation of the heart and a greater reliance on a hormonal response. Nevertheless, recent findings (43) have shown significant sympathetic as well as parasympathetic reinnervation in long-term transplant patients.

A general point that applies to all patients with organ transplantation is the need for life-long immnosuppression as a prerequisite for good graft function. However, rates of noncompliance range between 20% and 50% in these patients, often leading to graft loss and death (44). In a recent meta-analysis, it was...
shown that depressed patients had a threefold greater risk of noncompliance with medical treatment recommendation compared with nondepressed patients (45). In particular, Ziegelstein et al. (46) found that patients with depression are less likely to follow recommendations to reduce cardiac risk factors during recovery from myocardial infarction. These findings may in part explain why ICMP patients with high depressive symptoms may experience a higher risk of post-HTx mortality. However, they do not explain the difference in susceptibility for depression and mortality between the two groups of cardiomyopathy patients.

One major limitation of our study is the relatively small number of patients in each subgroup, reflected by the relatively wide confidence intervals. Because of declining numbers of organ transplants worldwide (18), we have initiated an ongoing prospective European multicenter study to replicate and expand our findings to a larger sample (47).

The purpose of any pretransplant assessment should be the early identification of patients experiencing increased psychosocial distress and who thus may be at risk for a poor psychosocial or somatic outcome. Therefore, the additional evaluation of depressive symptoms, especially in the subgroup of patients with an ischemic cardiomyopathy, might be helpful for early intervention strategies.

REFERENCES