Role of Depression and Social Isolation at Time of Waitlisting for Survival 8 Years After Heart Transplantation

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Background—We evaluated depression and social isolation assessed at time of waitlisting as predictors of survival in heart transplant (HTx) recipients.

Methods and Results—Between 2005 and 2006, 318 adult HTx candidates were enrolled in the Waiting for a New Heart Study, and 164 received transplantation. Patients were followed until February 2013. Psychosocial characteristics were assessed by questionnaires. Eurotransplant provided medical data at waitlisting, transplantation dates, and donor characteristics; hospitals reported medical data at HTx and date of death after HTx. During a median follow-up of 70 months (<1–93 months post-HTx), 56 (38%) of 148 transplanted patients with complete data died. Depression scores were unrelated to social isolation, and neither correlated with disease severity. Higher depression scores increased the risk of dying (hazard ratio = 1.07, 95% confidence interval, 1.01, 1.15, P = 0.032), which was moderated by social isolation scores (significant interaction term; hazard ratio = 0.985, 95% confidence interval, 0.973, 0.998; P = 0.022). These findings were maintained in multivariate models controlling for covariates (P values 0.020–0.039). Actuarial 1-year/5-year survival was best for patients with low depression who were not socially isolated at waitlisting (86% after 1 year, 79% after 5 years). Survival of those who were either depressed, or socially isolated or both, was lower, especially 5 years posttransplant (56%, 60%, and 62%, respectively).

Conclusions—Low depression in conjunction with social integration at time of waitlisting is related to enhanced chances for survival after HTx. Both factors should be considered for inclusion in standardized assessments and interventions for HTx candidates. (J Am Heart Assoc. 2017;6:e007016. DOI: 10.1161/JAHA.117.007016.)

Key Words: depression • heart failure • psychology and behavior • social isolation, social contacts • survival analysis • transplantation
Clinical Perspective

What Is New?

• Depression and social isolation assessed at time of waitlisting were associated with reduced survival over 8 years after heart transplantation.
• Patients without depressive symptoms who were not socially isolated at time of listing had the best survival rates after transplantation compared with groups with either 1 of these 2 factors or both.
• The association of depression and social isolation with survival was independent of known demographic and medical covariates.

What Are the Clinical Implications?

• Evaluation of patients for heart transplantation may benefit from including systematic assessments of depression and social contacts.
• Psychosocial interventions to accompany medical efforts to stabilize patients at risk for health decline may be warranted early in the course of transplantation.

the field of HTx also suggest that psychosocial attributes contribute to both pre- and posttransplant outcomes. In the multisite prospective Waiting for a New Heart Study that enrolled 318 patients newly registered for HTx, we have shown that depressive symptoms and social isolation were not only prevalent among HTx candidates at time of waitlisting,10,11 but also contributed to pre-transplant outcomes such as reduced chances for delisting because of clinical improvement, reduced event-free survival, higher probabilities of mechanical circulatory support device implantation, and HTx in high-urgency status.11–14 Most importantly, of several psychosocial variables that were evaluated including anxiety, only depression and social isolation were consistently associated with the abovementioned waiting list outcomes at follow-ups of varying length. Depression and social factors also appear to play a role in post-HTx mortality.15–17 However, in these studies of transplant recipients15–17 it is unclear whether these characteristics were already present before surgery, as their assessment took place post-HTx. Therefore, these studies cannot provide any evidence whether depression and social factors present at time of waitlisting impact transplant outcomes and whether systematic assessment of these patient characteristics should already be part of the pretransplant evaluation. A recent meta-analysis of heart, liver, kidney, lung, and other solid organ transplant patients found depression in general to be related to adverse posttransplant outcomes.18 However, this meta-analysis included only 4 (smaller single-center) studies of HTx patients with a pretransplant assessment of depression, which have reported conflicting findings.19–22

Social isolation was not evaluated in these studies. Thus, the prospective role of depressive symptoms and social isolation assessed at time of waitlisting for long-term survival of HTx recipients remains elusive.

Using data from the extended follow-up of patients in the Waiting for a New Heart Study covering the post-HTx period until February 2013 (an observation period of almost 8 years) allows for a test of the hypothesis that higher scores of depressive symptoms and social isolation at time of waitlisting contribute to reduced survival rates after HTx regardless of diagnosis. The large number of HTx recipients also allows for statistical control of other factors known to influence post-HTx survival.

Methods

Procedure and Participants

The Waiting for a New Heart Study is a multisite prospective cohort study of patients newly listed for HTx in 17 hospitals (16 in Germany, 1 in Austria) between April 2005 and December 2006, carried out in collaboration with Eurotransplant International Foundation. It aims at identifying psychosocial and behavioral predictors (assessed at time of waitlisting) of pre- and posttransplant outcomes.

Analyses at varying follow-ups during the waiting period found that depression and social isolation played a consistent role for reduced chances of delisting because of clinical improvement, and for increased risks for implantation of a mechanical assist device, transplantation in high-urgency status, and for event-free survival during waiting time.11–14,23 The present report is the first to examine these 2 patient characteristics (depression and social isolation) as predictors of post-HTx survival in participants who received a transplant between study start and February 2013. Study procedures have been described previously.10,11 Exclusion criteria were aged <18 years, being listed for combined heart–lung transplantation, retransplantation, not being fluent in German, and too severely ill to participate. Of 318 participants,10 164 patients had received a transplant by the end of follow-up. Sixteen patients were lost to follow-up because of discontinuation of participation by 1 hospital. Data from 148 recipients were analyzed (Figure 1). All participants gave written informed consent. The study was approved by the ethics committee of the Landesärztekammer Rheinland-Pfalz and by local ethics committees, and carried out in accordance with the Declaration of Helsinki.

Measures

Outcome was time until death after HTx in months since transplantation with date of the event provided by hospitals.
Transplantation status (high-urgency versus elective) was documented, as was waiting time in days, rescaled that a 1-unit increase refers to 100 days. Nonmedical patient characteristics were self-reported at time of listing. Depression was measured via the Hospital Anxiety and Depression Scale, with higher scores (possible
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Survival analyses.

assessed at time of listing. Age at HTx was computed for receiving any psychological counseling (yes/no) were ing (yes/no), and education (10 years of education [yes/no]), together with smoking status (for details see [27]) and receiving any psychological counseling (yes/no) were assessed at time of listing. Age at HTx was computed for survival analyses.

Data Analyses

Analyses were conducted using SPSS 22.0 (SPSS Inc, Chicago, IL). For continuous medical variables with <30% missing, sample medians were used, according to Eurotransplant procedures. Otherwise, observations were considered missing (Table 1). Descriptive statistics are presented in absolute numbers and percentages for categorical variables, means, and SD for normally distributed continuous variables, and medians and interquartile ranges for not normally distributed variables, respectively. Pearson correlations of depression scores and number of social contacts (reverse scored) with indicators of disease severity at time of listing were computed.

To identify relevant demographic and medical predictors for post-HTx mortality (time until death in months), univariate Cox proportional hazards analyses were conducted. P values derived from reductions in the $-2 \log \text{Likelihood}$ expressed as change of $\chi^2$ are reported.28 Associations of these variables with the exposure variables “depression” and “social isolation” were examined. In addition, relationships among variables associated with time until death were examined to identify redundant predictors. Interrelationships among number of social contacts, marital status, and living alone were also inspected. To evaluate depressive symptoms and social isolation as predictors for post-HTx survival, Cox proportional hazards regression was applied to test univariate and multivariate associations with time until death. Continuous scores were used to avoid loss of power associated with dichotomization. Four multivariate models were built. First, centered depression and social isolation scores were entered, followed by their interaction term. This procedure was repeated, controlling for age and sex of recipient and donor. Additional medical covariates significantly associated with death in univariate analyses were also entered. Finally, to ensure that the results were not affected by overfitting, a model including only statistically significant predictors was run.

To further explore a significant interaction term of depression and social isolation scores, the associations of depression scores with time until death in patients at the lower and at the upper 10th percentile of social isolation were examined. To do this, social isolation was first rescaled such that the value 0 represented very low social isolation (ie, 20 social contacts per month), and secondly, that the value 0 represented high social isolation (ie, 3 social contacts per month). In addition, findings were illustrated by using dichotomous variables (Hospital Anxiety and Depression Scale-D $\geq 9$ and median split of social isolation) to plot Kaplan–Meier survival curves for patients not depressed/not socially isolated, not depressed/isolated, depressed/not isolated, and depressed/isolated. All statistical tests were 2-tailed with the significance level at $P<0.05$.

Results

Baseline Findings

Characteristics of study participants are shown in Table 1. The 16 patients lost to follow-up did not differ from the 148 recipients included in the analyses in terms of demographic and psychosocial characteristics, BMI, or medical parameters assessed at time of listing, except for being more likely to be outpatients (87.5% versus 56.1%, $P=0.016$). Fifteen patients (10.1%) out of 129 patients, for whom these data had been documented, had received antidepressants at baseline. Depressive symptoms and social isolation scores were not significantly correlated with indicators of disease severity at time of listing (Table 2), except for 2 small associations of social isolation scores with the Heart Failure Survival Score ($r=0.16$) and with the cardiac index ($r=0.17$). Depressive
symptoms and social isolation were uncorrelated, \( r(148) = 0.06, P = 0.44 \). Married and unmarried patients reported comparable numbers of social contacts (\( M = 9.4, \text{SD} = 8.8 \), versus \( M = 8.6, \text{SD} = 5.9 \), \( t[146] = 0.70, P = 0.48 \)). The same was observed for patients living alone compared with those living with others (\( M = 7.2, \text{SD} = 6.6 \), versus \( M = 9.3, \text{SD} = 7.2 \), \( t[146] = -1.4, P = 0.17 \)).

### Outcomes After Transplantation

Of the 148 HTx recipients, 107 patients (72%) had received HTx while listed in Eurotransplant high-urgency status. Patients transplanted in high-urgency status and those transplanted electively did not differ in their baseline depressive symptom (\( t[146] = 0.83, P = 0.41 \)) or social isolation scores (\( t[146] = 1.38, P = 0.17 \)).

During a median follow-up of 70 months after HTx (range <1–93 months), 56 (38%) recipients died. One-year actuarial survival for this sample was 75% and 5-year survival was 66%. In univariate analyses, a higher recipient BMI at time of listing, former or current smoking, ischemic diagnosis, longer waiting time, higher donor age, higher pulmonary vascular resistance, and stay in intensive care unit at time of transplant were each

**Table 1. Demographic, Medical, and Psychosocial Characteristics in 148 Heart Transplant Recipients**

| Characteristic | Mean (SD) or n (%)  | MD  | IQR |
|---------------|---------------------|-----|-----|
| Demographic and anthropometric characteristics at time of listing | | | |
| Age, y | 52.2 (11.7) | 54 | 45 to 62 |
| Male sex | 121 (81.8%) | | |
| Unmarried | 58 (39.2%) | | |
| Living alone | 28 (18.9%) | | |
| Currently working | 10 (6.8%) | | |
| Education \( \geq 9 \) y | 66 (44.6%) | | |
| Inpatient | 65 (43.9%) | | |
| BMI, kg/m² | 25.2 (3.9) | | |
| Medical characteristics at time of listing | | | |
| Ischemic diagnosis | 45 (30.4%) | | |
| HFSS | 7.8 (1.0) | 7.7 | 7.2 to 8.3 |
| Cardiac index (L/min per m²) | 2 (0.5) | 1.9 | 1.6 to 2.3 |
| PCWP, mm Hg | 20.9 (8.1) | 20 | 15 to 25.8 |
| Creatinine, mg/dL | 1.4 (0.5) | 1.3 | 1.1 to 1.6 |
| Pulmonary vascular resistance (n=93) (dyn·s·cm⁻⁵) | 215.2 (147.8) | 180 | 117.5 to 255.5 |
| Smoking history | | | |
| Current/former smoker | 104 (70.0%) | | |
| Never smoker | 44 (29.7%) | | |
| Comorbidities | | | |
| Previous heart surgery (n=126) | 40 (27.0%) | | |
| Atrial fibrillation (n=109) | 21 (14.2%) | | |
| ICD (n=118) | 81 (54.7%) | | |
| Psychosocial characteristics at time of listing | | | |
| HADS Depression score (0–21) | 7.5 (4.0) | 8 | 5 to 10 |
| HADS Depression score \( \geq 9 \) | 59 (39.9%) | | |
| Number of social contacts | 8.9 (7.1) | 6.5 | 4 to 10 |
| Psychological counseling | 62 (41.9%) | | |
| Characteristics at time of HTx | | | |
| Recipient age | 53 (11.8) | 55 | 46 to 63 |
| Recipient BMI (kg/m²) (n=146) | 24.9 (3.8) | | |
| Donor age (y) | 40.9 (13.0) | 43 | 32 to 48 |
| Donor male sex | 89 (60.1%) | | |
| Donor BMI, kg/m² | 25.0 (3.7) | | |

N=148, if not indicated otherwise. BMI indicates body mass index; HADS, Hospital Anxiety and Depression Scale; HFSS, Heart Failure Survival Score; Higher scores denote a lower mortality risk; HTx, heart transplantation; IABP, intraaortic balloon pump; ICD, intracardiac cardioverter-defibrillator; IQR, interquartile range in case of no normal distribution; MD, median; PCWP, pulmonary capillary wedge pressure; VAD, ventricular assist device.

**Table 1. Continued**

| Characteristic | Mean (SD) or n (%) | MD  | IQR |
|---------------|-------------------|-----|-----|
| Creatinine (mg/dL) (n=146) | 1.6 (1.3) | 1.4 | 1.1 to 1.7 |
| Panel reactive antibody level (0) (n=132) | 132 (100.0%) | | |
| Central venous pressure (mm Hg) (n=30) | 14.9 (5.6) | 13 | 10 to 19.3 |
| Pulmonary vascular resistance (n=132) (dyn·s·cm⁻⁵) | 200.8 (90.9) | 184 | 139 to 257 |
| Diabetes mellitus | 34 (23.0%) | | |
| VAD | 11 (7.4%) | | |
| IABP | 4 (2.7%) | | |
| Intensive care unit (n=144) | 70 (47.3%) | | |
| Ventilation (n=146) | 8 (5.4%) | | |
| Cold ischemic time (min), mean (SD) (n=140) | 190.4 (60.1) | | |
| Waiting time (d) | 339 (461.5) | 142 | 57.5 to 482 |

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was associated with survival (data not shown; all (Table 3). None of the medications assessed at baseline significantly associated with an increased risk of death (Table 3). None of the medications assessed at baseline was associated with survival (data not shown; all P values >0.12). Higher depression scores at time of listing predicted death (Table 3; hazard ratio [HR]=1.07, 95% confidence interval [CI] 1.01–1.15; P=0.032), but social isolation by itself did not (Table 3; HR=1.03, 95% CI, 0.98–1.07; P=0.19). Neither being unmarried nor living alone was associated with death (both P values >0.71).

Table 2. Correlations of Depressive Symptoms and Social Isolation Assessed at Time of Listing With Indicators of Disease Severity at Time of Listing

| Variable | Depression Score | Social Isolation |
|----------|------------------|-----------------|
| Ischemic diagnosis* | 0.04 | 0.08 |
| HFSS | −0.004 | −0.16† |
| Cardiac index, L/min per m² | −0.03 | 0.17‡ |
| PCWP, mm Hg | 0.13 | −0.03 |
| Creatinine, mg/dL | 0.04 | 0.03 |
| PVR, dyn×s×cm⁻⁵ | 0.00 | −0.07 |

N=148. HADS indicates Hospital Anxiety and Depression Scale; HFSS, Heart Failure Survival Score; higher scores denote a reduced risk; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance.

*Included in the Heart Failure Survival Score.
‡P value of Pearson correlation identical to P value derived from t test ([146]—0.54 and −0.94, respectively).
†P=0.05.

None of the above-identified univariate predictors was significantly associated with the exposure variables depression and social isolation. However, to evaluate whether depression and social isolation and their interaction term were associated with time until death over and above known predictors of posttransplant mortality such as donor age, ischemic diagnosis, and BMI,29–31 recipient and donor age and sex, BMI at HTx, diagnosis, and waiting time were retained as covariates. Stay in intensive care unit, pulmonary vascular resistance, and smoking history were not retained in the multivariate models, as they were significantly correlated with the other major covariates in the model.

The first model tested the interaction of depressive symptoms and social isolation, controlling for their main effects (Table 4). In the second and third multivariate models controlling for demographic characteristics (model 2), and also BMI at HTx, ischemic diagnosis and waiting time (model 3), the interaction term remained significantly associated with time until death (Table 4). This association proved robust both in a model that also adjusted for transplantation status (P=0.027; data not shown) and in a model restricted to significant predictors only (df=5; Table 4). In all of these models, depression (centered at the mean) was significantly associated with time until death, with social isolation (also

| Variable | HR | 95% CI | P Value |
|----------|----|--------|---------|
| Demographic characteristics | | | |
| Age at HTx, y | 1.02 | 0.99–1.04 | 0.199 |
| Male sex | 1.47 | 0.70–3.11 | 0.292 |
| Unmarried | 0.90 | 0.53–1.55 | 0.711 |
| Living alone | 0.90 | 0.46–1.79 | 0.767 |
| Education ≤9 y | 0.97 | 0.57–1.63 | 0.893 |
| Former or current smoking | 1.91 | 0.99–3.69 | 0.041 |

| Donor characteristics | | | |
| Donor age, y | 1.04 | 1.01–1.06 | 0.002 |
| Donor male sex | 0.76 | 0.45–1.28 | 0.302 |
| Donor BMI, kg/m² | 1.04 | 0.97–1.11 | 0.282 |

| Medical recipient characteristics at time of listing | | | |
| BMI, kg/m² | 1.09 | 1.02–1.17 | 0.015 |
| Ischemic diagnosis | 2.00 | 1.18–3.39 | 0.012 |
| HFSS | 0.93 | 0.71–1.23 | 0.623 |
| Creatinine, mg/dL | 1.49 | 0.93–2.39 | 0.114 |
| PCWP, mm Hg | 1.00 | 0.96–1.03 | 0.833 |
| Cardiac index, L/min per m² | 1.11 | 0.66–1.85 | 0.705 |
| ICD (n=118) | 0.72 | 0.39–1.31 | 0.286 |
| Previous heart surgery (n=126) | 1.56 | 0.88–2.75 | 0.135 |

| Medical recipient characteristics at time of HTx | | | |
| BMI at HTx (kg/m²) (n=146) | 1.08 | 1.00–1.16 | 0.045 |
| Creatinine at HTx (mg/dL) (n=146) | 0.97 | 0.79–1.20 | 0.773 |
| PVR* (dyn×s×cm⁻⁵) (n=132) | 1.03 | 1.00–1.06 | 0.088 |
| VAD support | 2.02 | 0.86–4.73 | 0.139 |
| ICU (n=144) | 2.01 | 1.15–3.51 | 0.012 |
| Intra-aortic balloon pump | 1.28 | 0.31–5.23 | 0.745 |
| Diabetes mellitus | 1.38 | 0.77–2.46 | 0.289 |
| Ventilation (n=146) | 1.81 | 0.72–4.55 | 0.241 |
| Inotropes (n=143) | 1.38 | 0.79–2.39 | 0.251 |
| High-urgency status | 1.26 | 0.69–2.31 | 0.447 |
| Cold ischemic time (min; n=140) | 1.00 | 0.99–1.00 | 0.752 |
| Waiting time (100 d) | 1.06 | 1.01–1.11 | 0.049 |

| Psychosocial characteristics at time of listing | | | |
| Depressive symptoms (HADS-D ≥9) | 1.62 | 0.96–2.73 | 0.075 |
| Depressive symptoms (HADS-D; 0–21) | 1.07 | 1.01–1.15 | 0.032 |
| Social isolation | 1.03 | 0.98–1.07 | 0.187 |
| Psychological counseling | 0.86 | 0.50–1.47 | 0.570 |

BMI indicates body mass index; CI, confidence interval; HADS-D, Hospital Anxiety and Depression Scale; HFSS, Heart Failure Survival Score; HR, hazard ratio derived from univariate Cox proportional hazards regression; HTx, heart transplantation; ICD, implanted cardioverter defibrillator; ICU, intensive care unit; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; VAD, ventricular assist device.

* Representing a 10-unit increase in PVR.
Social isolation was first rescaled such that the value 0 represented very low social isolation (ie, 20 social contacts per month). Among those with low social isolation, higher depression scores remained associated with a significantly increased risk of death, even when controlling for covariates (HR=1.29, 95% CI, 1.06–1.56, \( P=0.011 \)). If social isolation was high (ie, the value 0 represented only 3 social contacts per month), higher depression scores did not increase the risk (HR=0.99, 95% CI, 0.91–1.09, \( P=0.86 \)), but high social isolation was associated with death (HR=1.06, 95% CI, 1.00–1.12, \( P=0.049 \)).

Table 4. Models Displaying Multivariate Associations of Psychosocial Patient Characteristics Assessed at Time of Listing With Time Until Death Post-HTx in 148 Heart Transplant Recipients

| Variable                                           | HR   | 95% CI      | \( \chi^2 \) (df) | \( P \) Value |
|----------------------------------------------------|------|-------------|-------------------|--------------|
| 1. Model including psychosocial variables only     |      |             |                   |              |
| Depressive symptoms                                | 1.097| 1.024–1.175*|                   |              |
| Social isolation                                   | 1.048| 0.996–1.103*|                   |              |
| Depression \( \times \) social isolation           | 0.985| 0.973–0.998*| 5.23 (1)          | 0.022        |
| 2. Model controlling for demographic characteristics|      |             |                   |              |
| Recipient age                                      | 1.000| 0.974–1.026 |                   |              |
| Recipient female sex                               | 0.641| 0.286–1.440 |                   |              |
| Donor age                                          | 1.031| 1.006–1.057*|                   |              |
| Donor female sex                                   | 1.377| 0.765–2.478 |                   |              |
| Depressive symptoms                                | 1.077| 1.003–1.157*|                   |              |
| Social isolation                                   | 1.044| 0.993–1.099†|                   |              |
| Depression \( \times \) social isolation           | 0.985| 0.973–0.998*| 5.45 (1)          | 0.020        |
| 3. Model controlling for additional covariates (N = 146) |      |             |                   |              |
| Recipient age                                      | 0.983| 0.954–1.013 |                   |              |
| Recipient female sex                               | 0.695| 0.305–1.585 |                   |              |
| Donor age                                          | 1.033| 1.007–1.060*|                   |              |
| Donor female sex                                   | 1.890| 0.992–3.599†|                   |              |
| Ischemic diagnosis                                 | 1.900| 1.044–3.460*|                   |              |
| BMI at HTx                                         | 1.071| 0.989–1.160†|                   |              |
| Waiting time (100 d)                               | 1.024| 0.966–1.086 |                   |              |
| Depressive symptoms                                | 1.085| 1.007–1.169*|                   |              |
| Social isolation                                   | 1.056| 1.000–1.115*|                   |              |
| Depression \( \times \) social isolation           | 0.985| 0.971–0.999*| 4.64 (1)          | 0.031        |
| 4. Reduced model including only significant terms plus the main effects and the interaction term of depression and social isolation |      |             |                   |              |
| Donor age                                          | 1.032| 1.008–1.057*|                   |              |
| Ischemic diagnosis                                 | 1.790| 1.052–3.046*|                   |              |
| Depressive symptoms                                | 1.077| 1.003–1.156*|                   |              |
| Social isolation                                   | 1.039| 0.987–1.093 |                   |              |
| Depression \( \times \) social isolation           | 0.987| 0.974–0.999*| 4.25 (1)          | 0.039        |

Displayed are values based on centered variables of depression and social isolation. BMI indicates body mass index; CI, confidence interval; df, degrees of freedom; HR, hazard ratio; HTx, heart transplantation.

*Wald test \( P \) value <0.05.
\( \dagger \) Wald test \( P \) value <0.10.

Centered) held constant at its mean. To further explore the interaction of both variables, we examined the association of depression with survival in patients at the lower 10th percentile and at the upper 10th percentile of social isolation.

Discussion

Our analyses of survival post-HTx extended our findings observed for the pre-HTx phase: depressive symptoms and social isolation present at time of waitlisting impacted not only the prognosis of patients on the HTx waiting list, but were also important for post-HTx survival. Patients without depressive symptoms who were also not socially isolated at time of listing had the best survival rates up to 8 years after transplantation compared with groups with either 1 of these 2 factors or both. This was significant, even after adjusting for donor and recipient age and sex, and patient primary diagnosis. One-year survival in our entire sample was 75%, which is comparable to 76% reported for Germany previously.\(^\text{32}\) Thus, a 1-year survival of 86% in patients without depressive symptoms who were well socially integrated is considerably higher than the average 1-year survival in Germany.

Importantly, there was no indication that patients with increased psychosocial risk had already been sicker than patients without these risk factors at time of listing. Moreover, both depressive symptoms and social isolation...
were unrelated to factors assessed at time of HTx that predicted posttransplant survival in this sample. This finding suggests that survival of HTx recipients may not only be affected when depression and social isolation occur after HTx, but also when they are already present at time of waitlisting, indicating the opportunity for addressing these factors early in the course of transplantation.

As we have already shown, patients who reported depressive symptoms (in the clinically relevant range) and few social contacts at time of listing also reported more emotional stressors and stressors related to the domain of family and social contacts than patients without these psychosocial risk factors. These patients also had diminished chances to get delisted because of clinical improvement. Moreover, high psychosocial risk reduced event-free survival in the pre-HTx phase and contributed independently to a declining health status, indicated by an increased probability of receiving a mechanical assist device, or to receive HTx in high-urgency status. Thus, taken together, our findings from the Waiting for a New Heart Study strongly suggest that psychosocial problems present at waitlisting affect the entire course of transplantation.

While depression and social isolation are clearly related to poor prognosis in this patient population, the mechanisms linking these characteristics to poor outcomes are unclear. It has been suggested that biological and behavioral pathways appear to be involved in this relationship. For example, depression and heart failure share the dysregulation of the hypothalamus–pituitary–adrenal axis, inflammation, and oxidative stress. Similar mechanisms have been described for social isolation. Although sympathetic and parasympathetic innervation of the heart is no longer possible after transplantation, cardiac function can still be influenced by circulating catecholamine levels via activation/suppression of adrenergic receptors. Moreover, there is evidence for sympathetic reinnervation of the heart, at least in the long run. From a behavioral perspective, depression and lacking social contacts have been linked to impaired self-care and adherence to the complex regimen associated with advanced heart failure and transplantation, such as medication taking, adequate diet, physical activity, and symptom monitoring. Future studies need to assess additional variables (eg, medication adherence and behavioral and psychological distress markers) in order to explore the

**Figure 2.** Kaplan–Meier survival plot comparing 4 groups with either low or high scores in depressive symptoms (HADS-D <9 vs HADS-D ≥9) and in social isolation (median split of social isolation, median=6.5). Patients with low depression and low social isolation constitute the reference group against which each other group is compared applying the log rank test. (Overall log rank test χ²(3)=7.3, P=0.066.) HADS-D indicates Hospital Anxiety and Depression Scale-D.
mechanisms underlying the observed association of depression and social isolation with poorer outcomes.

Our findings that depressive symptoms and social isolation impair the prognosis of patients with advanced heart failure pre and post HTx underscore the need for routine screening of psychosocial problems even as early as at evaluation for waitlisting. Screenings should include reliable and well-established instruments and, in the case of social isolation, not only rely on assessing marital status or living situation. Neither marital status nor living alone were related to survival in the present study.

Because depression and lacking social integration are modifiable behavioral risk factors, psychosocial interventions to accompany medical efforts to stabilize patients at risk for health decline are warranted early in the course of the disease and during the entire clinical course of transplantation. Treatment options such as cognitive behavior therapy have shown promise for patients with heart failure, but more studies are needed in this population with more advanced disease, particularly regarding means to promote social integration.

Our study has several limitations. First, it relied on self-reports of depressive symptoms instead of a clinical diagnosis, and depressive symptoms and social contacts were assessed only at time of waitlisting. Thus, we cannot know in how many patients depression and social isolation remained stable until time of transplant. It is conceivable that depression and social isolation are particularly detrimental when present until time of transplant, as has been shown for depressive symptoms in lung transplantation. However, because depression tends to increase during the waiting period and has been shown to remain stable when present after HTx, the associations observed in the present study may actually be underestimated. Second, we had to exclude patients who were considered too ill to participate at waitlisting. Thus, depression of the entire population might have been even higher and might have had an even greater impact if critically ill patients had been permitted to participate. Third, social isolation was only based on self-reports on the number of contacts with close friends/relatives during 1 month. In spite of this, this measure proved to be more important for survival than the assessment of marital status and/or living alone. Being unmarried has also been criticized as a measure of social isolation by others, which is supported by the fact that in our sample married and unmarried patients reported comparable numbers of social contacts. The same was true for patients living alone and those living with others. Future studies might use a more comprehensive assessment of social isolation. Fourth, our focus on depression should not preclude the role of other negative emotions (e.g., anxiety) that have been shown to correlate significantly with depression. Also, future studies might assess additional variables, (e.g., medication adherence), in order to explore the mechanisms for the observed association of depression and social isolation with poorer outcomes.

Finally, to more fully understand the relevance of depression and social relationships for pre- and post-HTx survival, larger data sets, allowing for a more comprehensive evaluation of recipient and donor characteristics as well as potential mechanisms, are needed. These could also allow for investigating 3 additional issues: first, whether socioeconomic deprivation is related to these associations; second, whether these findings generalize to non-European heart transplant populations; and third, whether ethnicity and sex play a role in these associations. This was not feasible in our European sample that included only 27 transplanted women. Yet, sex-specific associations of depression, social support, and social network characteristics with outcomes have been reported previously. Therefore, we strongly recommend adding standardized measures of psychosocial patient characteristics to the evaluation of HTx candidates and relevant databases, in order to provide sufficient data to address these questions in the future.

To conclude, this first report of the Waiting for a New Heart Study to evaluate associations between pretransplant psychosocial risk factors and post-transplant survival corroborates the clinical relevance of depression and social contacts for clinical outcomes in heart transplant patients. The relative absence of depression in combination with social integration in patients newly listed for HTx benefits survival after transplantation, and both factors impact the entire clinical course of transplantation. Therefore, screening and early intervention for patients at risk is warranted.

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