Original Article

The predictive value of depression in the years after heart transplantation for mortality during long-term follow-up

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Running head: Depression and mortality after HTx

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Abstract

Objective: Current understanding of the prognostic impact of depression on mortality after heart transplantation (HTx) is limited. We examined whether depression after HTx is a predictor of mortality during extended follow-up. Subsequently, we explored whether different symptom dimensions of depression could be identified, and whether they were differentially associated with mortality.

Methods: Survival analyses were performed in a sample of 141 HTx recipients assessed for depression, measured by self-report of depressive symptoms (Beck Depression Inventory – version 1A (BDI-1A)), at median 5.0 years after HTx, and followed thereafter for survival status for up to 18.6 years. We used uni- and multivariate Cox proportional hazard models to examine the association of clinically significant depression (BDI-1A total score ≥10), as well as the cognitive-affective and the somatic subscales of the BDI-1A (resulting from principal component analysis) with mortality. In the multivariate analyses, we adjusted for relevant sociodemographic and clinical variables.

Results: Clinically significant depression was a significant predictor of mortality (hazard ratio (HR): 2.088; 95% confidence interval (95% CI): 1.366–3.192; p=.001). Clinically significant depression also was an independent predictor of mortality in the multivariate analysis (HR: 1.982; 95% CI: 1.220–3.217; p=.006). The somatic subscale, but not the cognitive-affective subscale, was significantly associated with increased mortality in univariate analyses, while neither of the two subscales was an independent predictor of mortality in the multivariate analysis.

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Conclusions: Depression measured by self-report after HTx is associated with increased mortality during extended follow-up. Clinical utility and predictive validity of specific depression components require further study.

Key words: depressive disorder; depression; heart transplantation; mortality; survival

Acronyms: ACS = acute coronary syndrome; BDI-1A = Beck Depression Inventory – version 1A; BMI = body mass index; CAD = coronary artery disease; CAV = cardiac allograft vasculopathy; eGFR = estimated glomerular filtration rate; HR = hazard ratio; HTx = heart transplantation; IQR = interquartile range; OUH = Oslo University Hospital; PCA = principal component analysis; SD = standard deviation; 95% CI = 95% confidence interval

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Introduction

Improvements in immunosuppressive therapy and management of somatic complications after heart transplantation (HTx) have led to improved survival (1). To enhance outcomes further, research has increasingly focused on potentially related psychosocial issues (2, 3), including posttransplant depression.

Although data on the association of depression with increased mortality after HTx seem robust in the medium term (i.e., median observation time of 5.4 years across studies in a meta-analysis (4)) (4-6), knowledge is limited about depression's long-term effects on mortality (7).

Furthermore, several aspects of the interplay between depression and prognosis remain unknown or poorly understood. In the setting of coronary artery disease (CAD), an integrative model of the complex interplay between depression and prognosis has been proposed (8). Within this framework, it is hypothesized that acute depression after acute coronary syndrome (ACS) reflects the psychological impact of this event (8). Persistent/recurrent depression is hypothesized to act as an indirect causal factor in the progression of CAD via behavioural pathways such as non-adherence to medication, poor diet, and limited physical activity (8). The model is based partly on findings of cognitive-affective and somatic symptom dimensions of depression in depressed CAD and ACS patients, with the somatic dimension hypothesized to be associated with less favourable prognosis (8). A meta-analysis has confirmed the stronger and more consistent association of the somatic (e.g., work difficulty, insomnia, fatigability) than the cognitive-affective (e.g., sense of failure, guilt, self-dislike) symptom dimension with cardiovascular prognosis (including all-cause mortality), based on 13 prospective longitudinal studies in patients with heart disease (9); however we lack comparable data on HTx samples.

Several sociodemographic and clinical characteristics are associated with increased mortality after HTx. Studies focusing on the interplay between depression and prognosis should therefore include these variables as covariates. Recipient age (1), recipient sex (1), reason for HTx (10), donor age (1), and allograft ischemic time (1) have been directly associated with increased mortality after HTx. Hypertension, hyperlipidemia, renal dysfunction, diabetes, and cardiac allograft vasculopathy (CAV) are important morbidities after HTx, with renal dysfunction and CAV being among the most important contributors to mortality (1). Posttransplant smoking is associated with increased mortality in solid organ transplant recipients, including HTx recipients (11). Regarding body mass index (BMI), data from samples of HTx recipients are somewhat conflicting (10, 12, 13). BMI should nevertheless be included as covariate in survival analyses because BMI values in the range indicating overweight and obesity are associated with increased mortality in never-smokers without chronic diseases (14).

In this study, we aimed to extend existing knowledge about the prognostic impact of depression after HTx on mortality. To this end, we examined whether depression, measured by self-report of depressive symptoms, at a median of 5.0 years (interquartile range (IQR): 2.1–8.4) after HTx predicted subsequent mortality during extended follow-up (i.e., up to 18.6 years). In subsequent analyses, we explored whether cognitive-affective and somatic symptom dimensions of depression could be identified in our sample of HTx recipients and, in that case, whether these two symptom dimensions were differentially associated with mortality. In multivariate analyses, we adjusted for relevant sociodemographic and clinical variables.

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Methods

Study sample

In Norway, all HTx surgery is performed at the national transplant centre located at Oslo University Hospital (OUH). Selection of HTx candidates follows international guidelines (15). After the first year, HTx recipients return annually to OUH for their follow-up assessments. Of 220 HTx recipients who returned to OUH for their annual follow-up between 1998 and 2000, 147 were included in a study focused on psychiatric symptoms and quality of life. Cross-sectional data (16), longitudinal data on the association between depressive symptoms and mortality during a mean follow-up of 6 years (5), and longitudinal data on the association between self-reported physical function and mortality during a mean follow-up of 10 years (17) have been reported earlier. For the present study, end of follow-up for survival status was June 16, 2017. Of the 147 included HTx recipients from the original cohort, 6 were excluded from the current analyses because they had insufficient data for calculating a total score of the Beck Depression Inventory – version 1A (BDI-1A) (18). Thus, we present data on 141 participants. By June 16, 2017, 100 of these 141 HTx recipients had died, 2 were re-transplanted, and 39 were still alive with the same graft (i.e., alive and not re-transplanted). Median follow-up interval from inclusion in the main study and end of follow-up for the present study was 10.7 years (IQR: 5.8–17.6; mean: 10.9; standard deviation (SD): 5.8). Maximum of follow-up was 18.6 years. Median time interval between HTx and inclusion into the main study (i.e., self-report of depressive symptoms) was 5.0 years (IQR: 2.1–8.4; mean: 5.6; SD: 3.9).

Procedures

The present study is a secondary analysis. To this end, the database of the main study was updated regarding survival status and cause of death through June 16, 2017. The regional

committee for medical and health research ethics had approved the present secondary analysis as part of the approval of the main study.

Measures

Self-report of depressive symptoms

Depressive symptoms were measured by self-report at time of inclusion (i.e., 1998–2000), at a median of 5.0 years (IQR: 2.1–8.4) after HTx, with the BDI-1A (18). The BDI-1A consists of 21 items, rated from 0 to 3 in terms of intensity (19). The total score is the sum of the scores of the single items (range: 0–63). A Cronbach's alpha of .862 in the present sample indicates good internal consistency for the total score of the BDI-1A. Standard cut-off points to identify severity of depressive symptoms have been determined by the developers of the scale (19). A total score of 10 or higher indicates clinically significant depression (19); a total score between 10 and 18 indicates mild depression and a total score of 19 or higher indicates moderate or severe depression (19). A BDI-1A total score ≥10 resulted in a sensitivity of 81.8% and a specificity of 78.7% to detect major depression in a sample of 199 CAD patients (20).

Sociodemographic and clinical characteristics

Sociodemographic and clinical characteristics from time of HTx and time of inclusion were analysed to describe the sample, including the covariates in the multivariate survival analyses (see below). Specifically, we report recipient age at time of inclusion (in years), recipient sex, time between HTx and inclusion (in years), reason for HTx, donor age (in years), cold ischemic time (in minutes), renal function at time of inclusion, presence of CAV at time of inclusion, smoking status at time of inclusion (yes/no), and BMI at time of inclusion (in kg/m^2). Reason for HTx was classified into three categories: non-ischemic cardiomyopathy (defined according to the American Heart Association (21)), ischemic cardiomyopathy, or other. Renal function was

measured by means of estimated glomerular filtration rate (eGFR) (5, 22), and renal dysfunction defined as eGFR <60 ml/min/1.73 m^2. CAV was defined as luminal narrowing in one or more of the main arteries based on the presence of any of the following: any degree of stenosis, distal tapering/pruning, or loss of tertiary vessels (5). Smoking status was based on self-report, nurses' report, or hospital medical records (5). Cause of death is reported as part of the description of the sample.

Statistical analysis

Descriptive data are presented as frequencies and proportions or means and SD, as appropriate.

Because mortality was the event of interest, re-transplanted participants were censored at the time of re-HTx in the survival analyses. Observation time started at time of inclusion in the main study (i.e., 1998–2000) and was measured in days until death or censoring (i.e., end of follow-up or re-HTx) as appropriate. No participant was lost to follow-up regarding survival status.

We used the Kaplan-Meier method to calculate survival curves and tested for differences in survival with the log-rank test between those with and without depression (i.e., BDI-1A total score ≥10 and <10) at time of inclusion.

Predictive validity of depression (i.e., BDI-1A total score ≥10), as well as the relevant covariates (see below) on mortality, was assessed with univariate Cox proportional hazard models. For the categorical variables, the category associated with lower risk for mortality was chosen as the reference category. Furthermore, we calculated a multivariate Cox proportional hazard model, considering depression and the covariates. For the presented Cox proportional hazard models, hazard ratios (HRs), 95% confidence intervals (95% CIs), and corresponding p-values are

reported. The multivariate model is based on data for all participants with complete datasets, thus incorporating data for 136 out of 141 participants.

For the reasons outlined in the introduction, the following variables were included as covariates in the multivariate analysis: recipient age at time of inclusion, recipient sex, reason for HTx, donor age, duration of cold ischemic time, presence of renal dysfunction at time of inclusion, presence of CAV at time of inclusion, smoking status at time of inclusion, and BMI at time of inclusion. In addition to these variables, we included time between HTx and inclusion as covariate because this time interval varied considerably across included participants (median: 5.0 years; IQR: 2.1–8.4).

Based on existing literature, indicating that only clinically significant depression (according to diagnostic criteria or scores above threshold for caseness on self-report scales) is consistently associated with increased mortality (4), and aiming at highest possible applicability of our results to the clinic, we used the BDI-1A as dichotomous variable (i.e., BDI-1A total score ≥10 or <10) in our primary analyses. However, to explore the possibility of a dose-response relationship, we also conducted the analyses with the BDI-1A total score as continuous variable.

To explore whether cognitive-affective and somatic symptom dimensions of depression could be identified in our sample of HTx recipients, we conducted principal component analysis (PCA) on the items of the BDI-1A and pre-specified a solution with two components, using oblique rotation (Oblimin with Kaiser Normalization). Prior to performance of PCA, the suitability of the data for this statistical procedure was assessed. Inspection of the correlation matrix, as well as a Kaiser-Meyer-Olkin value of .803 and the result of the Bartlett's test of sphericity ($p<.001$), indicated suitability (23). To assess whether the resulting two components were differentially associated with mortality, we created subscales of the BDI-1A, namely a cognitive-affective and a somatic

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subscale. To this end, we assigned the 21 single items of the BDI-1A to either the cognitive-affective or the somatic subscale, based on the loadings from the pattern matrix, and calculated sum scores for the subscales, comparable to the total score. As a measure of internal consistency, we calculated Cronbach's alpha for these two subscales.

In parallel with the abovementioned, we calculated uni- and multivariate Cox proportional hazard models with the resulting two subscales of the BDI-1A. In the multivariate Cox proportional hazard model, we considered the two subscales of the BDI-1A simultaneously. The subscales of the BDI-1A were treated as continuous variables because no cut-offs have been established.

Level of significance was set to $p \leq .050$ in all analyses.

Statistical analyses were performed with IBM SPSS Statistics software (IBM Corporation, Armonk, NY, USA).

Results

Sample characteristics

At time of inclusion, mean age was 53.5 years, 20.6% were female, and 38.3% had been transplanted for non-ischemic cardiomyopathy. Of 141 participants, 36 (25.5%) had a BDI-1A total score of 10 or higher, indicative of clinically significant depression. Of these 36 participants, 24 had a BDI-1A total score between 10 and <19 (i.e., indicative of mild depression), and 12 had a BDI-1A total score of 19 or higher (i.e., indicative of moderate or severe depression). More details concerning sociodemographic and clinical characteristics are shown in Table 1. During follow-up, 100 (70.9%) of the 141 participants died. Cancer (30.0%), CAV (17.0%), and infection (12.0%) were the most frequently registered causes of death, while sudden death (7.0%), renal dysfunction (5.0%), acute rejection (4.0%), and myocardial infarction (1.0%) were

less frequently registered. Other miscellaneous causes of death were listed for 21.0%. Cause of death was unknown for 3.0%. No participant received left ventricular assist device as rescue therapy in our cohort.

Survival analyses

Figure 1 illustrates the course of survival for participants with and without clinically significant depression (i.e., BDI-1A total score ≥10 or <10). Log-rank test indicated increased mortality for those with clinically significant depression at inclusion compared to those without (χ^2: 12.079; df: 1; p=.001).

Results from the univariate Cox proportional hazard models are shown in Table 2. In these analyses, clinically significant depression (i.e., BDI-1A total score ≥10) was a significant predictor of mortality. Clinically significant depression remained an independent predictor of mortality in the multivariate analysis. For more details, including HR and 95% CI values, see Table 3.

Treating BDI-1A total score as continuous variable resulted in comparable findings. The BDI-1A total score was significantly associated with increased mortality in the univariate Cox proportional hazard model (HR: 1.032; 95% CI: 1.006–1.058; p=.016). It also remained an independent predictor of mortality in the multivariate analysis (HR: 1.032; 95% CI: 1.002–1.064; p=0.039).

Cognitive-affective and somatic symptom dimensions of depression and their association with mortality

The two-component solution of the PCA explained 40.6% of the variance. The components were interrelated (r=.362). After Oblimin rotation, items such as self-dislike, sense of failure, self-

punishment, sadness, and self-accusation loaded highest on component 1, while items such as fatigability, insomnia, loss of libido, and work difficulty loaded highest on component 2. Component 1 was labelled the cognitive-affective and component 2 was labelled the somatic symptom dimension of depression. Based on the pattern matrix (see Table S1 in the Supplemental Digital Content, which depicts the pattern and structure matrix for the PCA with Oblimin rotation of the two-component solution of the BDI-1A items), cognitive-affective and somatic subscales of the BDI-1A were established for the subsequent survival analyses, as outlined earlier. The cognitive-affective subscale consisted of the BDI-1A items 1, 2, 3, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 19, and 20, while the somatic subscale consisted of the BDI-1A items 4, 15, 16, 17, 18, and 21. Cronbach's alpha for the cognitive-affective subscale was .850, while it was .700 for the somatic subscale.

In univariate Cox proportional hazard models, the somatic subscale of the BDI-1A was significantly associated with increased mortality (HR: 1.191; 95% CI: 1.109–1.280; p<.001), while the cognitive-affective subscale of the BDI-1A was not significantly associated with mortality (HR: 1.017; 95% CI: .979–1.056; p=0.40). Neither the cognitive-affective nor the somatic subscale of the BDI-1A was independently associated with increased mortality in the multivariate analysis. More details, including HR and 95% CI values, are shown in Table 4.

Discussion

In the present study, we aimed to extend existing knowledge about the prognostic impact of depression after HTx on mortality. Clinically significant depression assessed at a median of 5.0 years after HTx, and defined as a score above threshold on a self-report scale of depressive symptoms (i.e., BDI-1A total score ≥10), was associated with increased mortality during

extended follow-up (i.e., up to 18.6 years), even after adjustment for relevant sociodemographic and clinical variables.

Subsequent exploratory analyses suggested that a cognitive-affective and a somatic symptom dimension of depression might exist in our sample of HTx recipients. While the somatic symptom dimension was associated with mortality in univariate analysis, neither the cognitive-affective nor the somatic symptom dimension was independently associated with mortality in multivariate analysis.

Our results confirm earlier reports on the association of depression with increased mortality (4-6) after HTx. At the same time, our results extend previous limited knowledge about depression's long-term effects on mortality. Only one earlier report examined the relationship between depression and survival during extended follow-up (i.e., mean follow-up: 7.8 years) (7). Among 107 HTx recipients, assessed with regard to depression by a clinician one to five years after HTx, depression was not associated with mortality, while age at HTx, cancer, and low adherence were (7). The discrepancy in findings might be due to inclusion of different covariates, differences in analytical techniques, and/or different methods for assessing depression. Our results are however, in line with results from a meta-analysis, considering studies with primarily shorter follow-up intervals (4).

Our results also suggest that a dose-response relationship between self-reported depressive symptoms after HTx and mortality might exist. Earlier reports on HTx samples were inconclusive in this regard (6, 24). However, existence of a dose-response relationship would be in accordance with data on patients with CAD (25, 26).

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We are not aware of any earlier report concerning different symptom dimensions of depression in HTx recipients. Thus, it is difficult to relate our exploratory results to truly comparable data, having in mind, that HTx recipients differ substantially from all other patients with heart disease (e.g., use of necessary immunosuppressive medication). However, our finding that a cognitive-affective and a somatic symptom dimension of depression might exist is consistent with data on patients with heart disease (9). However, a differential prognostic impact on mortality, as reported for samples of patients with heart disease (9), could not be demonstrated.

The following aspects need consideration in the interpretation of our main result. First, we defined clinically significant depression based on a score above threshold on a self-report scale of depressive symptoms (i.e., BDI-1A total score ≥10). While BDI-1A is an accepted measure and has been widely used in research on depression in somatic disease samples (included heart disease samples) (27), the methodological limitations of BDI-1A's use as measure of clinically significant depression have been discussed in the literature, including the possible inflation of scale scores due to somatic symptoms of the underlying somatic disease (28). In other words, without concurrent clinical diagnostic data, we cannot determine to which extent different factors, such as fatigue, psychiatric comorbidities (e.g., anxiety disorder), and/or somatic symptoms due to underlying somatic disease or somatic comorbidities might have influenced on our participants' self-report of depressive symptoms. Second, the participants were included at a median of 5.0 years after HTx. Thus, the results of our study are not necessarily generalizable to other cohorts of HTx recipients, especially those studied earlier after HTx. Third, numerous factors are associated with mortality after HTx, making it difficult to account for all potentially relevant confounding factors in the same study. Due to the extended follow-up period, we

focused on HTx specific factors, included HTx specific morbidities. However, there are other variables, which we ideally should have accounted for, such as socioeconomic status and a global measure of comorbidity (such as the Charlson comorbidity index). Fourth, depression is a complex syndrome. Several factors, that might be involved in the aetiology of depression or might be a result of depression (and hence mediators of any linkage between depression and mortality), were not assessed in our study. These include biological markers of changes in the hypothalamic-pituitary-adrenal axis (e.g., cortisol) and inflammation (e.g., C-reactive protein), as well as behavioural factors (e.g., physical inactivity, poor adherence to the medical regimen) (4, 8, 29, 30). Especially, the interplay between depressive symptoms/depression and physical function requires further exploration because both impaired self-reported physical health and peak oxygen uptake (an objective marker of cardiopulmonary fitness) have been associated with increased mortality (17). A better understanding of this interplay also would be of substantial interest regarding the hypothesis that persistent/recurrent depression may exert its negative prognostic impact via behavioural pathways (8).

Our study has several additional limitations. First, while we know that no participant was receiving treatment for depression at time of inclusion (5), we have no information about the longitudinal course of the included participants' depressive symptoms and/or whether they received treatment for depression at a later time point. It might seem surprising that no participant was receiving treatment for depression at time of inclusion (i.e., 1998-2000). However, at that time, depression screening was not done routinely in conjunction with annual follow-up assessments and a psychiatrist was only involved upon request. Thus, against the background of the widely accepted notion, that depressed patients not always are recognized as depressed by

their treating non-psychiatric physicians (31), depressed participants might have remained undetected and untreated. Moreover, repeated longitudinal assessment of depressive symptoms and information about treatment for depression after inclusion would have been of interest because persistent/recurrent depression might be associated with less favourable prognosis than brief episodes of depression (8, 32, 33). Second, the included participants' self-report of depressive symptoms was gathered at different time points after their HTx (i.e., time between HTx and inclusion/self-report of depressive symptoms varied considerably). However, to account for this limitation time between HTx and inclusion was included as covariate in the multivariate analyses. It is also noteworthy, that the correlation of time between HTx and inclusion and BDI-1A total score was small and not statistically significant (r=.103; p=.23). Third, several limitations pertain to the subsequent exploratory analyses. Even if Cronbach's alpha for the BDI-1A cognitive-affective and somatic subscales indicates good to acceptable internal consistency, detailed inspection of the pattern matrix resulting from the two-component solution of the PCA indicates that assignment of some of the items to one of the two subscales is not clear-cut (see Table S1 in the Supplemental Digital Content). However, the pattern in which the single items of the BDI-1A loaded highest on either component 1 (labelled the cognitive-affective symptom dimension of depression) or component 2 (labelled the somatic symptom dimension of depression) was broadly consistent with the results from a meta-analysis on studies in patients with heart disease (9). Thus, even though the two-component solution of the PCA presented here is broadly consistent with results from a meta-analysis on studies in patients with heart disease (9), it does not represent an ideal solution and must be replicated in other samples of HTx recipients before firm conclusions can be drawn. Another limitation concerning the PCA is the relatively small sample size, compromising the generalizability of the results. However, the sample size (n=141) is above the minimum recommended by some authors (i.e., at least 5 cases

per analysed item) (23). Furthermore, elevation of scale scores due to symptoms of underlying somatic disease (28) have to be discussed in this context as well. If scores on the resulting somatic subscale of the BDI-1A were elevated due to somatic symptoms, originating from somatic comorbidity in our HTx recipients, lack of adjustment for a global measure of comorbidity in our survival analyses would be problematic. The fact that the somatic subscale of the BDI-1A was associated with increased mortality only in univariate analysis, might support this view. On the other hand, lack of power to detect such an effect in the multivariate analysis must be considered as well. Again, concurrent clinical diagnostic data, including description of clinical subtypes of depression, would have been useful for interpreting the results of our exploratory analyses.

In conclusion, our findings both confirm and extend earlier reports, indicating that clinically significant depression after HTx, defined as score above threshold on a self-report scale of depressive symptoms, is associated with increased mortality during extended follow-up, even after adjustment for relevant sociodemographic and clinical variables. Furthermore, our findings suggest that different symptom dimensions of depression may exist. Their clinical utility and prognostic validity remains, however, unsettled and should be studied further in order to increase our understanding of the complex interplay between depression and prognosis after HTx. Increased understanding of this interplay could pave the way for better (i.e., more specific) strategies for clinical interventions.

Adequately powered studies are needed to assess if successful treatment for depression (by means of both psychotropic medications and/or psychotherapeutic interventions as appropriate) improves survival among HTx recipients. HTx recipients who screen positive for possible

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clinically significant depression during routine follow-up should in any case be referred to specialized diagnostics and treatment because depression negatively affects quality of life and function in daily life.

Authors' contributions

All authors contributed to the interpretation of data and revised the manuscript critically. All authors approved the final and submitted version. The specific author contributions were as follows: B.S. Bürker: updated the database, analysed the data, and drafted the manuscript. L. Gullestad: participated in designing the main study and supported the update of the database. O.E. Havik: participated in designing the main study. A. Relbo Authen and I. Grov: participated in collecting data for the main study and supported the update of the database.

Conflicts of interest

E. Gude has given lectures for Novartis and Heartware. A.E. Fiane is consultant for Heartware. All other authors declare no conflicts of interest.

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Supplemental Digital Content

Table S1. Pattern and structure matrix for principal component analysis with Oblimin rotation of the two-component solution of the BDI-1A items (Bürker Table S1.pdf)

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Table 1. Sociodemographic and clinical characteristics (n=141)

Recipient age[a] (years), mean (SD)	53.5	(12.5)
Recipient sex, female/male (% female)	29/112	(20.6)
Time between HTx and inclusion (years), mean (SD)	5.6	(3.9)
Reason for HTx, n (%)		
Non-ischemic cardiomyopathy	54	(38.3)
Ischemic cardiomyopathy	73	(51.8)
Other	14	(9.9)
Donor age (years), mean (SD) [n=138]	30.9	(11.5)
Cold ischemic time (min), mean (SD) [n=138]	136	(65)
eGFR[a,b] (ml/min/1.73 m^2), mean (SD) [n=137]	60.7	(17.6)
CAV[a], n (%)	33	(23.4)
Smoking status[a], yes/no (% yes)	31/110	(22.0)
BMI[a] (kg/m^2), mean (SD) [n=140]	26.2	(4.2)
BDI-1A total score[a,c], mean (SD)	7.4	(6.7)

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BDI-1A = Beck Depression Inventory – version 1A; BMI = body mass index; CAV = cardiac allograft vasculopathy; eGFR = estimated glomerular filtration rate; HTx = heart transplantation; SD = standard deviation.

[a]At time of inclusion. [b]50.4% had an eGFR <60 ml/min/1.73 m^2. [c]25.5% had a BDI-1A total score ≥10.

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Table 2. Univariate Cox proportional hazard models (n=141)

	Reference category (categorical variables)	**HR**	**95% CI**		**p**
Depression[a,b]	No depression	2.088	1.366	3.192	.001
Recipient age[a] (years)		1.074	1.049	1.099	<.001
Recipient sex	Female	1.108	.672	1.826	.70
Reason for HTx	Non-ischemic cardiomyopathy				<.001
Ischemic cardiomyopathy		2.793	1.766	4.417	<.001
Other		1.930	.954	3.903	.067
Donor age (years) [n=138]		1.001	.983	1.018	.94
Cold ischemic time (min) [n=138]		1.001	.998	1.004	.55
Renal dysfunction[a,c] [n=137]	No renal dysfunction	2.529	1.673	3.824	<.001
CAV[a]	No CAV	3.357	2.154	5.233	<.001
Smoking status[a,d]	No smoking	1.413	.892	2.237	.14
BMI[a] (kg/m^2) [n=140]		1.095	1.051	1.141	<.001

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Time between HTx and inclusion (years)	1.071	1.023	1.120	.003

BDI-1A = Beck Depression Inventory – version 1A; BMI = body mass index; CAV = cardiac allograft vasculopathy; eGFR = estimated glomerular filtration rate; HR = hazard ratio; HTx = heart transplantation; 95% CI = 95% confidence interval.

[a]At time of inclusion. [b]Depression defined as BDI-1A total score ≥10. [c]Renal dysfunction defined as eGFR <60 ml/min/1.73 m^2.

[d]Yes or no.

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Table 3. Multivariate Cox proportional hazard model – depression (n=136)

	Reference category (categorical variables)	**HR**	**95% CI**		**p**
Depression[a,b]	No depression	1.982	1.220	3.217	.006
Recipient age[a] (years)		1.057	1.026	1.088	<.001
Recipient sex	Female	.914	.492	1.700	.78
Reason for HTx	Non-ischemic cardiomyopathy				.019
Ischemic cardiomyopathy		2.061	1.198	3.546	.009
Other		2.518	1.069	5.782	.030
Donor age (years)		1.020	.997	1.043	.097
Cold ischemic time (min)		1.000	.996	1.003	.87
Renal dysfunction[a,c]	No renal dysfunction	2.036	1.279	3.241	.003
CAV[a]	No CAV	2.832	1.510	5.310	.001
Smoking status[a,d]	No smoking	1.040	.556	1.946	.90
BMI[a] (kg/m^2)		1.069	1.017	1.124	.008
Time between HTx and inclusion (years)		1.064	.993	1.139	.078

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BMI = body mass index; CAV = cardiac allograft vasculopathy; eGFR = estimated glomerular filtration rate; HR = hazard ratio; HTx = heart transplantation; 95% CI = 95% confidence interval.

[a]At time of inclusion. [b]Depression defined as Beck Depression Inventory – version 1A total score ≥10. [c]Renal dysfunction defined as eGFR <60 ml/min/1.73 m^2. [d]Yes or no.

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Table 4. Multivariate Cox proportional hazard model – cognitive-affective and somatic symptom dimension of depression (n=136)

	Reference category (categorical variables)	**HR**	**95% CI**		**p**
BDI-1A cognitive-affective subscale (resulting from PCA)[a]		1.007	.953	1.063	.081
BDI-1A somatic subscale (resulting from PCA)[a]		1.094	.983	1.218	.10
Recipient age[a] (years)		1.055	1.024	1.086	<.001
Recipient sex	Female	.911	.488	1.702	.77
Reason for HTx	Non-ischemic cardiomyopathy				.029
Ischemic cardiomyopathy		1.937	1.116	3.362	.019
Other		2.527	1.101	5.799	.029
Donor age (years)		1.022	.999	1.045	.066
Cold ischemic time (min)		1.000	.997	1.004	.81
Renal dysfunction[a,b]	No renal dysfunction	1.926	1.198	3.095	.007

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CAV[a]	No CAV	2.453	1.311	4.592	.005
Smoking status[a,c]	No smoking	1.138	.612	2.118	.683
BMI[a] (kg/m^2)		1.078	1.027	1.133	.003
Time between HTx and inclusion (years)		1.067	.996	1.142	.064

BDI-1A = Beck Depression Inventory – version 1A; BMI = body mass index; CAV = cardiac allograft vasculopathy; eGFR = estimated glomerular filtration rate; HR = hazard ratio; HTx = heart transplantation; PCA = principal component analysis; 95% CI = 95% confidence interval.

[a]At time of inclusion. [b]Renal dysfunction defined as eGFR <60 ml/min/1.73 m^2. [c]Yes or no.

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Figure 1.

Figure 1. Survival curves – Kaplan-Meier method

Depression, defined as BDI-1A total score ≥10.

BDI-1A = Beck Depression Inventory – version 1A.

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