Transplant International

Transplant International ISSN 0934-0874

ORIGINAL ARTICLE

Composite risk scores and depression as predictors of competing waiting-list outcomes: the Waiting for a New Heart Study

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Keywords
competing risks, depression, heart failure, mortality, risk scores, waiting-list.

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Received: 13 January 2010
Revision requested: 22 February 2010
Accepted: 10 June 2010
Published online: 13 July 2010

doi:10.1111/j.1432-2277.2010.01133.x

Summary

We evaluated two composite risk scores, (Heart Failure Survival Score, HFSS; German Transplant Society Score, GTSS), and depression as predictors of mortality and competing waiting-list outcomes [high-urgency transplantation (HU-HTx), elective transplantation, delisting because of clinical improvement] in 318 heart transplant (HTx) candidates (18% women; aged 53 ± 11 years) from 17 hospitals and newly registered with Eurotransplant. Demographic variables and depression (Hospital Anxiety and Depression Scale, HADS) were assessed using questionnaires. Variables to compute HFSS and GTSS, age, medications, and outcomes were provided by Eurotransplant. At 12 months, 33 patients died, 83 received urgent HTx, 30 elective HTx, and 17 were delisted because of improvement. Applying cause-specific Cox regressions, only the HFSS was significantly associated with 1-year mortality [HR = 0.64 (95% CI = 0.43–0.95), $P = 0.029$]. The GTSS was the strongest predictor of HU-HTx [HR = 1.02 (95% CI = 1.01–1.02), $P < 0.001$]. Low depression scores contributed significantly to clinical improvement, even after adjusting for age and risk scores [HADS: HR = 0.12 (95% CI = 0.02–0.89), $P = 0.039$]. These findings confirm the usefulness of composite risk scores for the prediction of mortality and HU-HTx, validating both scores for their intended use. The finding that depression was an independent predictor of the waiting-list outcome clinical improvement suggests that considering patients' psychological attributes in addition to their medical characteristics is advisable.

Introduction

Heart transplantation (HTx) provides a treatment option for end-stage heart failure patients with already optimized medical therapy. As a consequence of the persistent scarcity of donor organs, time to HTx is prolonged, and mortality during the first 12 months of waiting time is about 16% [1]. Therefore, the number of patients receiving a

transplant in high-urgency status has increased [1]. As patients who are successfully transplanted avoid death during waiting time, these outcomes have to be considered as competing events. In addition, risk factors could have different effects on the competing events [2]. Hence, the cumulative event proportions of one outcome may also be ''indirectly'' affected via an effect on a competing outcome [3]. Therefore, prediction of waiting-list mortality, high-urgency transplantation (HU-HTx), and other outcomes might benefit from competing risks analyses.

To identify HTx candidates with the highest mortality risk, composite risk scores have been suggested [4], i.e. the Heart Failure Survival Score (HFSS) [5] and the German Transplant Society Score (GTSS) [6]. Yet, to our knowledge, these risk scores are not routinely used in donor organ allocation. The Heart Failure Survival Score was developed and validated with cohorts of ambulatory heart failure patients undergoing evaluation for HTx [5]. The HFSS consists of seven noninvasively measured prognostic variables. Studies indicate acceptable prognostic performance of the HFSS, even in the era of widespread beta-blocker use [4,7,8]. The German Transplant Society Score [6] was developed with a cohort of German HTx candidates in 1997 to predict the necessity for HU-HTx. While demonstrating good discrimination of risk groups, particularly in patients with high-urgency status [6], the GTSS has been criticized for being too physician-dependent [4] as it includes variables such as ''current stay'' (home, ward, intensive care unit), need for intravenous inotropes, and mechanical circulatory support.

There is initial evidence that the HFSS and the GTSS are associated with mortality and HTx in different ways: for high-urgency patients, the HFSS predicted HTx, but not 1-month mortality, whereas the GTSS did not predict either of these events. For elective patients, 1-year mortality and HTx could be explained by the GTSS, while the HFSS failed to predict these events [1]. Therefore, a competing risks analysis to evaluate the prognostic validity of these risk scores could illuminate the associations between the HFSS and the GTSS and different outcomes in HTx candidates.

In addition to medical risk scores, psychosocial risk factors, such as depression, may contribute to a better risk stratification of HTx candidates. There is evidence that depressive symptoms are common in both heart failure patients and HTx candidates [9,10]. While depression adversely affects prognosis in heart failure patients [11–13], far less is known about the prognostic relevance of depression in HTx candidates [4,9]. A first German study suggests that depressive symptoms before HTx predict mortality after HTx in patients with ischemic heart failure, but not during waiting time [14]. Due to the small sample size and insufficient adjustment for disease severity, this study requires replication.

Therefore, the aim of the present investigation was twofold: first, to evaluate the association of the HFSS and GTSS with waiting-list outcomes in newly listed HTx candidates employing a competing risk analysis [15], and second, to analyze the contribution of depression to waiting-list outcomes.

Materials and methods

Procedures

The Waiting for a New Heart Study is a 2-year prospective multi-center observational study of patients newly listed for HTx. The study procedure has been described elsewhere [10]. Briefly, patients were enrolled consecutively in seventeen German-speaking hospitals (one in Austria) between April 2005 and December 2006. Eligible patients, who gave written informed consent, were mailed the questionnaires assessing depression and demographic data by the coordination center at the University of Mainz and were asked to return them within 10 days. The study was approved by local ethic committees before starting recruitment and carried out in accordance with the 2000 Declaration of Helsinki. This report presents results from the 1-year follow-up.

Participants

Patients were eligible for the study if their evaluation for transplantation resulted in being registered on the Eurotransplant HTx waiting-list, if they were 18 years or older at time of listing, were able to speak German fluently, had not received a donor heart before, and did not need a combined heart–lung transplantation. All underlying causes of heart failure were accepted. In 17 hospitals, 479 patients met initial eligibility criteria. Further screening by local physicians resulted in 380 study candidates, thereby excluding patients whose condition was too poor to answer questionnaires or an interview, or who could not be reached (for more details, see [10]). Of these, 340 consented. The questionnaires were returned by 318 patients (response rate = 93.5%). The 161 nonparticipants (99 subsequently excluded patients, 40 decliners, 22 dropouts) and the 318 participants were similar with regard to gender and age; however, nonparticipants seemed to have on average a worse NYHA class than participating patients [$\chi^2(2) = 32.6$, $P < 0.001$], with 51.1% vs. 24.5% categorized as NYHA class IV [10].

Variables at time of wait-listing

Medical variables at time of registration on the waiting-list, medications, and devices were provided by Eurotransplant and collaborating centers. We calculated both

the HFSS and the GTSS. The HFSS includes mean arterial blood pressure, heart rate at rest, left ventricular ejection fraction (LVEF), serum sodium, presence of intraventricular conduction delay (QRS-interval ≥0.12 s), etiology of heart failure (ischemic versus dilated), and maximum oxygen uptake (VO_2 max). A *lower* score indicates a higher mortality risk and patients can be grouped into risk scores based on cut-off values [5]. The GTSS was derived from data of all patients newly registered on the German HTx waiting-list 1997, and was validated in all new patients of the following year using death while waiting as outcome measure [6]. The model includes LVEF, cardiac index, patient location (home, ward, intensive care unit), use of catecholamines, mechanical circulatory support, and dialysis. A *higher* score indicates a worse health status [6]. Computational algorithms and risk categories for both scores are displayed in Table 1. Missing data in medical parameters ranged from 0.9% (blood pressure, heart rate) to 24.8% in VO_2 max.

Depression was assessed using the German version of the Hospital Anxiety and Depression Scale (HADS) [16]. This scale has been validated extensively [17]. As this study focuses on depression, anxiety was not considered in the analyses. Descriptive information about anxiety is provided elsewhere [10]. Depression is measured using seven items (e.g. ''I look forward with enjoyment to things'', ''I feel cheerful'' – both reverse scored; ''I feel as if I am slowed down''). Responses range from 0 to 3 and are added (maximum score = 21). Greater scores are indicative of depression. In addition, we dichotomized depression scores yielding the variable depression status (not depressed versus depressed), based on the cut-off score of 9 [16]. Internal consistency for depression was Cronbach's $\alpha = 0.81$ in the norm sample of 6200 patients (90% cardiology patients) [16] and $\alpha = 0.77$ in our sample.

Outcome events

Changes in waiting-list status with date of change during the 12 months of follow-up were provided by Eurotransplant. We defined events of interest as (i) death attributable to all causes, (ii) high-urgency HTx (HU-HTx; transplantation while in high-urgency status), (iii) elective HTx (transplantation while not in high-urgency status), (iv) delisting because of clinical improvement (HTx no longer indicated), and (v) delisting because of clinical deterioration (HTx no longer indicated). High urgency status is applied to patients in intensive care units who fulfill one of the following criteria: (i) Cardiac index <2.2 l/min/m^2 or SVO_2 <55% while on inotropic therapy for at least 48 h and beginning secondary organ failure, (ii) life-threatening assist device complications, and (iii) additional special cases i.e. acute retransplantation or age <16 years. High urgency status is evaluated by an Eurotransplant audit group and lasts 7 days (Eurotransplant, Leiden, The Netherlands, see also http://www.eurotransplant.org). To prolong HU status for another 7 days, reevaluation is necessary and might be declined if the criteria are no longer met. Hence, we did not use HU status as endpoint, but chose the endpoint HU-HTx instead, which considers HU status directly before HTx.

Table 1. Calculation of the Heart Failure Survival Score and German Transplant Society Score.

Score	Algorithm
HFSS	
Absolute sum of all seven values weighted by their regression coefficients	
Ischemic cardiomyopathy (yes = 1, other = 0)	x +0.6931
Resting heart rate (BPM)	x +0.0216
LVEF (%)	x –0.0464
Mean arterial blood pressure (mmHg)	x –0.0255
QRS >0.12 s (yes = 1, other = 0)	x +0.6083
VO_2 max (ml/m/kg)	x –0.0546
Serum sodium (mmol/l)	x –0.0479
GTSS	
Algorithm depending on ''current stay'' and use of inotropes and mechanical circulatory support	
Home	{0 – 0.055 × [(cardiac index/0.022) + (LVEF/0.25) – 186.12]} × 100
Ward, no inotropes	{0.79 – 0.055 × [(cardiac index/0.022) + (LVEF/0.25) – 186.12]} × 100
Ward, inotropes	{0.87 – 0.055 × [(cardiac index/0.022) + (LVEF/0.25) – 186.12]} × 100
ICU, no VAD, no dialysis/hemofiltration	{0.89 – 0.055 × [(cardiac index/0.022) + (LVEF/0.25) – 186.12]} × 100
ICU, VAD or dialysis or hemofiltration	{1.96 – 0.055 x [(cardiac index/0.022) + (LVEF/0.25) – 186.12]} × 100

HTSS risk categories: low risk ≥8.10, medium risk = 7.2–8.09, high risk ≤7.19.

GTSS risk categories: low risk <82, medium risk = 82–118, high risk >118.

HFSS, Heart Failure Survival Score; GTSS, German Transplant Society Score; BPM, beats per minute; LVEF, left ventricular ejection fraction; VO_2 max, peak oxygen uptake; ICU, intensive care unit; VAD, ventricular assist device.

Statistical analysis

To deal with missing data (if <30%) in medical parameters, the semiparametric multiple imputation procedure of van Buuren and Oudshoorn was employed [18,19]. According to the ''missing at random'' assumption [20], imputation models were built based on variables that were correlated with the missing variable in the complete data set and with missingness (Pearson correlation ≥0.15) [19]. For detailed information see Spaderna *et al.* [21]. Multiple imputation was computed using the package MICE 1.16 for R 2.7.2 [22]. Analyses were conducted across the 10 imputed data sets and the results were pooled using R 2.7.2 and the packages MICE, mitools, cmprsk, survival, and Zelig.

For descriptive purposes, medical characteristics are reported for original and imputed data. All analyses were rerun on the original data set (nonimputed variables).

We employed a competing risks analysis with outcomes death, HU-HTx, elective HTx, delisting because of improvement and delisting because of deterioration, i.e., we analyzed time until first outcome and outcome type. We plotted cumulative incidence functions for all outcome types, i.e., the proportion of patients having experienced an outcome over the course of time. Risk factors were investigated in cause-specific Cox models. Due to the small number of delistings because of deterioration ($n = 9$), we did not fit a Cox model for this outcome. Patients delisted because of deterioration or lost to follow-up were censored at their time of delisting. One hundred and forty-two patients were administratively censored by the end of 12 months.

As only 3% of our sample fell into the GTSS high risk category, both GTSS and HFSS were analyzed as continuous scores in all Cox regression models. Because of low event rates, the number of covariates had to be restricted. As demographic characteristics did not show significant effects in univariate analysis, they (with the exception of age) were not included in the multivariate analyses. Three multivariate models were then computed: Model 1 contained HFSS, age, and depression status; in Model 2, the GTSS was substituted for the HFSS; Model 3 examined all five variables simultaneously. In case of a significant association of depression status with outcome, cumulative incidences were compared between the high- and low-depression groups [23]. All Cox analyses were repeated using continuous depression scores.

Proportional hazard assumptions for all variables included in univariate and multivariate models were checked by inspection of the Schoenfeld's residuals for all 10 data sets. To detect associations between risk factors, Pearson correlations for all variables were computed. Results were considered statistically significant if $P < 0.05$.

Results

Patient characteristics are shown in Table 2. Patients' mean age was 53 ± 11 years (range 18–75 years), and 18% were women. About 39% of the participants reported depressive symptoms indicative of clinical depression. Almost all patients were on beta-blocker-therapy (86.8%), angiotensin-converting enzyme-inhibitors (75.9%), and diuretics (89.1%). Antidepressant medication was assessed in three hospitals only ($n = 189$), and 8.5% of these patients received antidepressants. The GTSS varied between −133.63 and +143.63 with *higher* values denoting worse health status. A majority of patients (75.4%) had low mortality risk, according to the GTSS (values <82), and only 3.4% fell into the high risk group (values >118). The HFSS varied between 5.71 and 11.20, with *lower* values denoting worse health status. Risk stratification based on this score showed that only 36% of the study sample had low mortality risk (values ≥8.10) and 22% were in the high risk group (values ≤7.19). The GTSS and the HFSS correlated −0.50 ($P < 0.001$). Depression was not associated with the GTSS ($r = 0.076$, $P = 0.203$) or the HFSS ($r = -0.01$, $P = 0.926$).

At 12 months, 33 candidates had died (four while in HU status), 83 had received HU-HTx, 30 patients elective HTx, and 17 patients were delisted due to clinical improvement. Four patients were lost to follow-up (three patients declined their consent for HTx, for one patient, the reason for delisting was not documented) (Fig. 1). Figure 2 displays the survival function and cumulative incidence functions for these competing events over the course of the waiting time, thereby considering that the probability of an event at a certain time depends on the probability that the other events have not occurred prior to that time [24].

In univariate analyses, death was only associated with a lower baseline HFSS, denoting greater disease severity (Table 3) with HR = 0.64 (95% CI = 0.43–0.95), $P = 0.025$. Greater disease severity, as indicated by both the HFSS (HR = 0.75, 95% CI = 0.59–0.95; $P = 0.022$) and the GTSS (HR = 1.02, 95% CI = 1.01–2.02; $P < 0.001$) had a significant impact on HU-HTx. Clinical improvement was associated with less disease severity according to the GTSS (HR = 0.99, 95% CI = 0.98–1.00, $P = 0.009$), and with not being depressed (HR = 0.11, 95% CI = 0.01–0.65, $P = 0.029$). None of these variables was associated with elective HTx in univariate analyses.

In the first two multivariate models, including either GTSS or HFSS, and age and depression, only the HFSS had an impact on mortality (models 1 and 2, Table 3). With all variables in the model (model 3, Table 3), the contribution of HFSS to death dropped to $P = 0.065$. This reduction might in part be as a result of the correlation of

Table 2. Baseline demographic, medical, and psychosocial characteristics of HTx candidates.

	Total sample						
	Original data			Imputed data (n = 318)			
	n	M/n	(SD)/(%)	M	(SD)/(%)	Min_M/Min_n	Max_M/Max_n
Demographic characteristics	318						
Age (M/SD)		53.1	(11.1)				
Women (*n*/%)		58	(18.2)				
Married (*n*/%)		212	(66.7)				
Living with others (*n*/%)		264	(83.0)				
Education 9 years or less (*n*/%)		119	(37.4)				
BMI (M/SD)		25.9	(4.0)				
Psychosocial variables	318						
Depression (0–21; M/SD)		7.7	(3.9)				
Depression scores ≥9 (*n*/%)		123	(38.7)				
Medical characteristics							
Diagnosis (*n*/%)	318						
Ischemic		122	(38.4)				
Idiopathic dilated cardiomyopathy		160	(50.3)				
Other		36	(11.3)				
Current stay (*n*/%)	285						
Home		179	(62.8)	n.a.	(59.7)	185	192
Ward		96	(33.7)	n.a.	(36.2)	110	116
Intensive care unit		10	(3.5)	n.a.	(4.1)	10	16
VO_2max (ml/min/kg)	239	11.1	(3.0)	10.9	(3.1)	10.7	11.0
Cardiac Index (l/min/m^2)	289	2.1	(0.6)	2.1	(0.6)	2.0	2.1
LVEF (%)	312	23.7	(10.6)	23.7	(10.6)	23.5	23.9
Heart rate (beats/min)	316	77.3	(16.6)	77.6	(16.6)	77.5	77.6
BP systolic (mmHg)	316	105.1	(16.2)	105.1	(16.2)	105.0	105.2
BP diastolic (mmHg)	316	63.9	(12.1)	63.9	(12.1)	63.8	64.0
Mean arterial blood pressure (mmHg)	316	77.6	(11.9)	77.6	(11.9)	77.5	77.7
HFSS (M/SD)	224	7.9	(1.0)	7.9	(0.9)	7.8	7.9
Low risk (≥8.1; *n*/%)		81	(36.2)	n.a.	(36.0)	108	118
Medium risk (7.2–8.09; *n*/%)		94	(41.9)	n.a.	(41.9)	128	142
High risk (≤7.19; *n*/%)		49	(21.9)	n.a.	(22.1)	67	74
GTSS (M/SD)	262	28.2	(51.0)	32.2	(52.9)	31.0	33.3
Low risk (<82; *n*/%)		208	(79.4)	n.a.	(75.4)	236	243
Medium risk (82–118; *n*/%)		51	(19.5)	n.a.	(21.2)	65	70
High risk (>118; *n*/%)		3	(1.1)	n.a.	(3.4)	9	12
NYHA (*n*/%)	316						
II, II–III, III		125	(39.6)	n.a.	(39.7)	125	127
III–IV		114	(36.1)	n.a.	(36.1)	114	116
IV		77	(24.4)	n.a.	(24.2)	77	78
Comorbidities, devices (*n*/%)							
Diabetes mellitus	279	75	(26.9)	n.a.	(26.4)	80	88
Previous heart surgery	290	95	(32.8)	n.a.	(33.7)	102	109
Dialysis/Hemofiltration	292	5	(1.7)	n.a.	(1.6)	5	6
QRS > 0.12 s	301	161	(53.5)	n.a.	(54.1)	170	173
VAD	314	7	(2.2)	n.a.	(2.2)	7	8
Medication (*n*/%)							
Catecholamines	309	49	(15.9)	n.a.	(15.9)	49	52
Beta-blockers	313	272	(86.9)	n.a.	(86.8)	275	277
ACE inhibitors	312	237	(76.0)	n.a.	(75.9)	240	243
Aldosterone antagonists	312	208	(66.7)	n.a.	(66.6)	210	213
Diuretics	312	279	(89.4)	n.a.	(89.1)	282	285
Digitalis	313	154	(49.2)	n.a.	(40.0)	155	158

Imputed categorical data are presented with percentages plus minimum and maximum absolute numbers observed in the 10 imputed data sets. Continuous values are presented with means and standard deviations plus minimum and maximum means obtained in the 10 imputed data sets.

HTx, heart transplantation; BMI, body mass index; VO_2 max, peak oxygen consumption; LVEF, left ventricular ejection fraction; BP, blood pressure; GTSS, German Transplant Society Score; n.a., not applicable; HFSS, Heart Failure Survival Score; NYHA, New York Heart Association; ACE, angiotensin-converting enzyme.

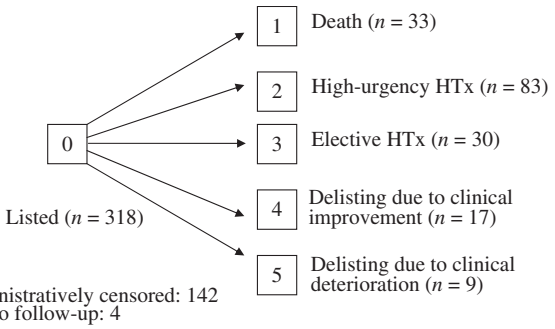

Figure 1 Competing endpoints during 12-month follow-up. As the number of delistings due to deterioration was relatively small, we did not investigate the impact of potential risk factors on this outcome.

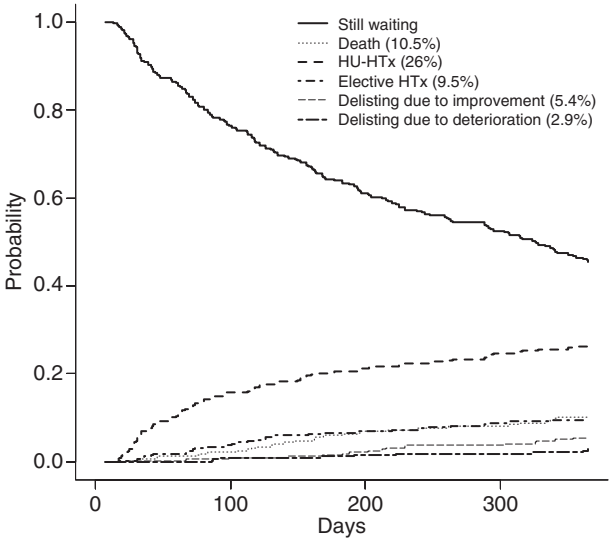

Figure 2 Cumulative incidence functions for the competing events death, high-urgency HTx, elective HTx, delisting due to improvement, and delisting due to deterioration.

the HFSS with the GTSS. Regarding HU-HTx, both variables were significantly associated with HU-HTx in models 1 and 2 (Table 3). When both the HFSS and the GTSS were considered together (model 3), the GTSS remained highly significant, whereas the HFSS completely lost its impact on this outcome (model 3, Table 3). Inspection of Schoenfeld's residuals indicated that the GTSS did not meet the proportional hazard assumption for HU-HTx. As a consequence, the impact of the GTSS on HU-HTx reflects a time-averaged effect [25].

In the multivariate model for improvement including the GTSS (model 1), the hazard ratio for improvement decreased by 1% with each unit increase in GTSS (HR = 0.99, 95% CI = 0.98–1.00; $P = 0.027$) and by 88% if depression scores were ≥9 (HR = 0.12, 95% CI = 0.92–0.90, $P = 0.029$). The effect of depression remained significant when the HFSS (model 2) or both composite risk scores were included in the model (model 3, Table 3). The results for depression are further illustrated in Fig. 3. Cumulative incidence for improvement was 8.3% for patients with low-depression scores and 0.8% for patients with depression scores above the clinical cut-off ($P < 0.01$). Analyses using the continuous depression scores yielded a similar pattern of findings. Analyses using only patients with complete medical data (not imputed) showed comparable results. However, because of the reduced sample size (model 1: $n = 262$, model 2: $n = 224$, model 3: $n = 194$), the HFSS failed to reach significance in predicting mortality in the multivariate models; the same was true for the GTSS in predicting clinical improvement in model 3. Continuous depression scores were still significantly associated with clinical improvement after controlling for age, HFSS, and GTSS ($P = 0.019$ in model 2; $P = 0.021$ in model 3).

Discussion

This prospective study indicates that adopting a competing risks approach provides a useful strategy to evaluate medical and psychological patient characteristics as predictors of mutually exclusive waiting-list outcomes. The HFSS was particularly relevant for death, whereas the GTSS was more important for the prediction of HU-HTx. Depression reduced the chance for improvement, even when controlled for disease severity. These results show that a competing risks analysis contributes additional information about prognostic variables in HTx candidates not detectable with standard survival analysis using the single endpoint death during waiting time or transplant-free survival.

Stratification of patients into low, moderate, and high-risk groups based on HFSS and GTSS cut-offs yielded quite different distributions, with 22% vs. 3.4% patients classified as ''high risk''. HFSS and GTSS only shared 25% of common variance. Hence, these scores appear to reflect different aspects of disease severity. It should be noted that patients with characteristics indicative of a GTSS high risk-categorization (e.g. stay in intensive care unit, need for mechanical circulatory or inotropic support), were probably under-represented in our sample, as patients considered ''medically unfit'' by their physician were excluded. However, the proportion of high risk patients as defined by the HFSS was similar, if not higher, than that in other studies [7,8,26]. Elevated depression scores were prevalent in 39% of patients, a finding commonly reported in heart failure patients [9,27]. Interestingly, depression was uncorrelated with disease severity as measured by the HFSS and GTSS.

Table 3. Univariate and multivariate predictors of the competing events death, high-urgency transplantation (HU-HTx), elective HTx and delisting due to improvement 12 months after listing.

	Death		High-urgency HTx		Elective HTx		Improvement	
	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Univariate predictors								
GTSS	1.01 (1.00–1.01)	0.160	1.02 (1.01–1.02)	0.000	1.00 (1.00–1.01)	0.479	0.99 (0.98–1.00)	0.009
HFSS	0.64 (0.43–0.95)	0.025	0.75 (0.59–0.96)	0.022	0.94 (0.63–1.39)	0.743	1.55 (0.95–2.53)	0.083
Age	1.00 (0.97–1.04)	0.884	0.99 (0.97–1.00)	0.118	1.01 (0.97–1.04)	0.699	0.96 (0.92–1.00)	0.075
Depression ≥9	1.39 (0.70–2.76)	0.345	1.32 (0.85–2.03)	0.211	0.96 (0.46–2.02)	0.920	0.11 (0.01–0.65)	0.029
Multivariate models								
Model 1								
GTSS	1.01 (1.00–1.01)	0.176	1.02 (1.01–1.02)	0.000	1.00 (1.00–1.01)	0.472	0.99 (0.98–1.00)	0.027
Age	1.00 (0.97–1.04)	0.902	0.99 (0.97–1.00)	0.114	1.01 (0.97–1.04)	0.688	0.97 (0.93–1.02)	0.227
Depression ≥9	1.35 (0.68–2.68)	0.398	1.16 (0.75–1.81)	0.498	0.94 (0.44–1.97)	0.860	0.12 (0.02–0.90)	0.039
Model 2								
HFSS	0.64 (0.43–0.95)	0.029	0.72 (0.56–0.93)	0.011	0.94 (0.63–1.41)	0.781	1.53 (0.89–2.63)	0.127
Age	1.00 (0.96–1.03)	0.790	0.98 (0.96–1.00)	0.036	1.01 (0.97–1.04)	0.726	0.97 (0.93–1.01)	0.151
Depression ≥9	1.32 (0.66–2.63)	0.430	1.30 (0.84–2.01)	0.231	0.95 (0.45–2.00)	0.890	0.11 (0.01–0.84)	0.033
Model 3								
GTSS	1.00 (0.99–1.01)	0.555	1.02 (1.01–1.02)	0.000	1.00 (1.00–1.01)	0.508	0.99 (0.98–1.00)	0.093
HFSS	0.67 (0.43–1.03)	0.065	1.01 (0.74–1.36)	0.997	1.01 (0.64–1.61)	0.957	1.14 (0.60–2.17)	0.678
Age	1.00 (0.96–1.03)	0.830	0.99 (0.97–1.00)	0.133	1.01 (0.97–1.05)	0.685	0.97 (0.93–1.02)	0.225
Depression ≥9	1.31(0.66–2.62)	0.439	1.16 (0.75–1.80)	0.499	0.93 (0.44–1.97)	0.859	0.12 (0.02–0.89)	0.039

HTx, heart transplantation; HR, hazard ratio; CI, confidence interval; GTSS, German Transplant Society Score; HFSS, Heart Failure Survival Score.

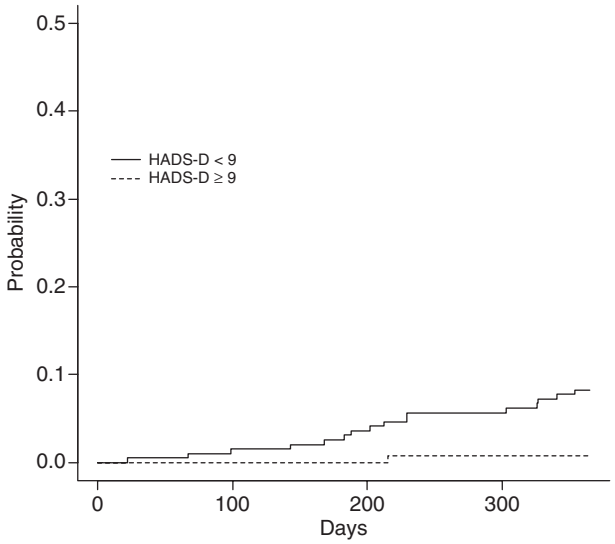

Figure 3 Unadjusted cumulative incidence function of delisting due to improvement stratified by low depression and high depression.

During the first 12 months of waiting time, cumulative incidence was the highest for HU-HTx (26%). For death on the waiting-list, it was considerably lower (10.5%). The corresponding percentage for death on the waiting list reported by Eurotransplant for Germany between 1998 and 2001 was 19% [1]. The lower death rate in our study might be a result of recent improvements in medical therapy. It is also conceivable that more patients received HU-HTx compared with preceding years, a trend that has been reported previously [1]. Interestingly, the GTSS appeared to be a better predictor for HU-HTx than the HFSS when both scores were considered simultaneously. The GTSS has been criticized to be influenced too much by physicians' behavior rather than by the patient's characteristics [4], e.g. when deciding whether a patient should be referred to ward or intensive care unit, or whether a patient should receive mechanical circulatory support or/and intravenous medication. These characteristics might also be part of the decision to update waiting-list status to HU, thereby increasing the ''risk'' of HU-HTx.

The HFSS predicted the event ''death on the waiting-list'', extending its validity to a sample that included both ambulatory and inpatients. The GTSS did not predict 1-year mortality, a finding that contrasts with other studies [1,6]. This result might be because severely ill patients as measured by the GTSS were more likely to be excluded from our study, resulting in a somewhat reduced range of GTSS values. Developed on an ambulatory cohort, the HFSS might be more suitable to than the GTSS differentiate mortality risk among patients with less than decompensated heart failure. Moreover, the competing risks approach employed in this study considered HU-HTx as an event competing against death. In other words, patients who received HU-HTx avoided death on the

waiting-list. As the GTSS effectively predicted HU-HTx, it is not to be expected that this score also predicts death. Accessory analyses of the waiting-list outflow in our study revealed that only four patients died while in HU-status.

Depression was not associated with 1-year mortality or HU-/elective HTx. This finding is in concordance with the results reported by Zipfel *et al.* [14]. However, depression predicted time till the combined endpoint death/transplantation in another study with outpatients [28]. Also, in studies of heart failure patients with less severe disease, depression constitutes an independent risk factor for mortality [12,27,29,30]. Hence, it is conceivable that in end-stage heart failure, with about 1/3 of the sample being inpatients, mortality risk is better explained by disease severity (as measured with the HFSS) than by depression.

Our study is the first to show that low depression at baseline has an impact on improvement in health status of HTx candidates during the first 12 months on the waiting-list, independent of age and disease severity. Although the phenomenon of clinical improvement among HTx candidates has been recognized [14,26], predictors for this outcome have not yet been studied. Only one retrospective study based on a small sample reported that patients who improved were similar to patients delisted because of deterioration regarding indicators of disease severity and medications [31]. Our prospective study shows that improvement is more likely to occur when patients are less severely ill at baseline, and above all, have no signs of clinical depression. These results give further evidence for the important role of depression during the course of heart transplantation [32].

Clearly, more information on the role of depression during the course of heart transplantation is needed. The mechanisms by which depression may assert its influence on disease progression also remain unclear. It has been suggested that depression might contribute to a worsening health status in heart failure by means of a dysregulated hypothalamic pituitary adrenal axis and autonomic nervous system, enhancing inflammation, and impairing adherence to health behaviors [33,34]. Therefore, psychosocial interventions aimed at improving mental health and reducing depression might also be helpful for stabilizing HTx candidates.

Several limitations of this study should be noted. First, our findings may not be generalized to all patients registered for HTx with Eurotransplant, as patients who could not be included in our study were more likely to have severe heart failure as documented by NYHA class. Second, the study relied on self-reports for depression. However, depression in our study was defined as scores ≥9 on the HADS, which are considered indicative of clinical depression [17]. Nevertheless, clinical interview assessment would have been desirable to confirm a diagnosis of depression in those with scores in the clinically relevant range. Unfortunately, use of antidepressants was not systematically assessed and could not be considered as an additional covariate. However, the role of antidepressant medication for prognosis in heart failure remains controversial [35,36]. Third, covariates had to be restricted to a minimum due to low event rates in this competing risks setting. With an extended follow-up, statistical power will be enhanced to control for additional covariates (e.g. creatinine), and to take into account the additive or multiplicative effects of depression with other psychosocial risk factors, e.g. social isolation [37]. Fourth, it may be argued that HU status has to be regarded as an additional endpoint in HTx candidates. As HU status is highly time-dependent and typically varies during waiting time within patients, we focused on HU-HTx as an endpoint, as suggested by Cortese and Andersen [38].

In conclusion, our findings confirm the validity of the HFSS as a predictor of 1-year mortality, while the GTSS was more relevant for the prediction of HU-HTx. Depression, although not associated with mortality, should receive further attention, as it appears to affect prognosis by reducing the chance of clinical improvement. Overall, these findings suggest that expanding the search for risk factors to multiple levels (i.e., physiological, psychological, social), and considering outcomes as competing events (rather combining clinically different outcomes into one endpoint) will hold much promise for the prognosis of HTx candidates.

Authorship

HS and GW designed the study and, together with DZ, wrote the manuscript. DZ analyzed the data, and, together with HS, FMW, UM, HR, MCD, SM, IK and JMAS, participated in data collection and (with JB) contributed to the writing of the manuscript. JB provided advice on data analysis.

Funding

This work was supported by grants from the Alexander-von-Humboldt Foundation (GW); Eurotransplant International Foundation; German Academic Exchange Service (GW); German Research Foundation (SP 945/1-1, SP 945/1-3 to HS, and MA 155/75-1 to GW); and the Johannes Gutenberg-University Mainz (HS).

Acknowledgements

We thank Dr. Judith Kahn, and Dr. Björn Sill for their helpful comments on an earlier version of this manu-

script. We are indebted to Annette Dangmann, Markus Homberg, and Katharina Schury for their assistance in data collection and preparation of the manuscript. We also thank the collaborating HTx-hospitals: Med. Klinik I/Kardiologie, Pneumologie, Angiologie Universitätsklinikum Aachen: Prof. Dr. Kelm, Dr. Koch; Herz-Zentrum Bad Krozingen: Prof. Dr. Neumann, Dr. Zeh; Herz- und Diabeteszentrum Nordrhein-Westfalen Bad Oeynhausen: Prof. Dr. Körfer, Dr. Schulze Schleithoff, Dr. Tenderich; Herzzentrum Dresden: Prof. Dr. Strasser, Dr. Thoms; Herzchirurgische Klinik der Universitätsklinik Erlangen: Prof. Dr. Weyand, Dr. Tandler; Med. Klinik III/Kardiologie Klinikum der Universität Frankfurt: Prof. Dr. Zeiher, Dr. Seeger; Klinik für Thorax-, Herz-, und Gefäßchirurgie des Klinikums Fulda: Dr. Dörge, Dr. Weipert; Abt. Kardiologie, Universitätsklinikum Gießen und Marburg, Standort Gießen, Dr. Heidt, Dr. Stadlbauer; Klinik für Chirurgie der Medizinischen Universität Graz/University of Graz: Prof. Dr. Tscheliessnigg, Dr. Kahn; Universitätsklinik und Poliklinik für Herz- und Thoraxchirurgie Halle-Wittenberg: Prof. Dr. Silber, Dr. Friedrich, Dr. Hofmann; Universitäres Herzzentrum Hamburg GmbH: Prof. Dr. Dr. Reichenspurner, Dr. Meffert, Dr. Wagner; Klinik für Herz-, Thorax- und Gefäßchirurgie des Universitätsklinikums Jena: Prof. Dr. Gummert, Dr. Malessa, Frau Tigges-Limmer; Klinik und Poliklinik für Herz- und Thoraxchirurgie der Universität zu Köln: Prof. Dr. Wahlers, Dr. Müller-Ehmsen; Klinik für Herzchirurgie des Herzzentrums Leipzig GmbH: Prof. Dr. Mohr, Dr. Doll; II. Medizinische Klinik und Poliklinik Universitätsmedizin Mainz: Prof. Dr. Münzel, Dr. Koniordos; Herzchirurgische Klinik der Universität München: Prof. Dr. Reichart, Dr. Kaczmarek; Klinik und Poliklinik für Herz-, Thorax- und herznahe Gefäßchirurgie der Universität Regensburg: Prof. Dr. Schmid, Dr. Rupprecht, Prof. Dr. Birnbaum.

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