Trajectories of Anxiety and Depression After Liver Transplantation as Related to Outcomes During 2-Year Follow-Up: A Prospective Cohort Study

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ABSTRACT

Objective: The aims of the study were to examine whether distinct trajectories of anxious and depressive symptoms are present among liver transplant recipients from before transplantation to 2 years afterward, to identify associated demographic, clinical, and individual characteristics, and to examine the influence of distinct trajectories on outcomes.

Methods: A prospective, multicenter cohort study was performed among 153 liver transplant recipients. Data were retrieved using questionnaires administered before transplantation and at 3, 6, 12, and 24 months after transplantation. Clinical data were retrieved by medical record review. Latent class growth analysis was used to identify distinct trajectories. χ^2 test, analyses of variance, and multinomial logistic regression were used to identify associated variables and the impact of the distinct trajectories on outcomes.

Results: Three distinct trajectories for symptoms of anxiety (State-Trait Anxiety Inventory-short form) as well as depression (Center for Epidemiological Studies Depression Scale) were identified: "no symptoms," "resolved symptoms," and "persistent symptoms." The trajectories of persistent anxiety and depression comprised, respectively, 23% and 29% of the transplant recipients. Several clinical and individual variables were associated with the trajectories of persistent anxiety and/or depression: experiencing more adverse effects of the immunosuppressive medication, lower level of personal control, more use of emotion-focused coping, less disclosure about the transplant, and more stressful life events. The trajectories of persistent symptoms were associated with worse outcomes regarding medication adherence and health-related quality of life, but not with mortality.

Conclusions: A significant subset of transplant recipients showed persistent symptoms of anxiety and depression from before to 2 years after transplantation. These results emphasize the importance of psychosocial care in the transplant population.

Key words: adherence, psychological functioning, quality of life, transplant candidates, transplant recipients.

INTRODUCTION

Among liver transplant candidates, symptom levels of 19% to 55% have been described for anxiety and 17% to 62% for depression (1–4), whereas among liver transplant recipients (LTRs), prevalence rates of 6% to 35% regarding symptoms of anxiety (5,6) and of 3% to 58% regarding depressive symptoms (5–9) have been described. These prevalence rates show the burden of psychological problems in the liver transplant population, problems that may also interfere with medical treatment and may influence outcomes after transplantation.

Studies reporting on the course of anxiety and depression over time have shown a general pattern of significant decrease in symptoms levels between pre- and posttransplant as well as a stable situation thereafter (2,7,10). However, these studies all describe the course of symptoms of anxiety and depression based on mean symptom levels or prevalence rates for the whole study population. Given the individual variation in symptom levels, distinct trajectories of anxiety and depression may be present within this general pattern. Because of the aggregation and averaging of data, these individual patterns may go unnoticed. Consequently, subgroups of patients with unfavorable courses of anxiety or depression might be missed and may not receive adequate support. Exploring whether distinct trajectories are present in LTRs and examining their influence on outcomes after transplantation may help gain a better understanding of anxiety and depression in this patient population. Moreover, examining variables associated with distinct trajectories may provide insight into variables related to the persistence or development of psychological problems after

CES-D = Center for Epidemiological Studies Depression scale, **CISS-SF** = Coping Inventory for Stressful Situations-short form, **HRQoL** = health-related quality of life, **ISM** = immunosuppressive medication, **LCGA** = latent class growth analysis, **LTRs** = liver transplant recipients, **MELD** = model for end-stage liver disease, **MLR** = multinomial logistic regression, **MTSOSD-59R** = Modified Transplant Symptom Occurrence and Symptom Distress Scale, **HR** = hazard ratio, **STAI-6** = State-Trait Anxiety Inventory-short form, **TxEQ** = Transplant Effects Questionnaire

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transplantation and may provide direction for interventions aimed at improving psychological functioning.

To date, only two studies have reported on distinct trajectories of anxiety and depression in transplant recipients over time. Based on cutoff scores, Miller et al. (11) reported on trajectories of resolved, unresolved, and no anxiety or depression, measured before and at 6 months after liver transplantation. Mental health status before transplantation was identified as a risk factor, and LTRs with unresolved anxiety or depression were found to show lower scores on several domains of quality of life. Using statistical modeling techniques, DiMartini et al. (12) identified three trajectories of depression from 3 to 12 months after transplantation in recipients transplanted for alcoholic liver disease: constantly high, increasing, and constantly low symptom levels. Younger age, no partner, history of depression or substance use, hepatitis C virus, and fewer years of heavy drinking were identified as risk factors. Recipients within the trajectories of increasing or persistent depression were more than twice as likely to die (all causes).

So far, studies on the course of anxiety and depression in transplant recipients with measurement points before and at several time points after transplantation are lacking. Therefore, this study aims to the following: (1) to examine whether distinct trajectories of anxious and depressive symptoms are present in LTRs from before transplantation to 2 years afterward; (2) to gain insight into demographic, clinical, and individual characteristics associated with the distinct trajectories; and (3) to examine the influence of the distinct trajectories on medication adherence, health-related quality of life, and mortality after transplantation.

METHODS

A prospective, multicenter cohort study was performed among LTRs at three transplant centers in the Netherlands. All consecutive transplant candidates who were on the waiting list between October 2009 and April 2013 were asked to participate. Inclusion criteria were 18 years or older and those receiving medical treatment in one of the three transplant centers. Exclusion criteria were those unable to fill out a questionnaire because of physical, mental, or cognitive functioning or because of a language barrier. In addition, recipients receiving a retransplant within the study period were excluded. Transplant recipients who could not be included in the study before transplantation (e.g., in cases of acute liver failure) were invited to participate in the study, starting at 3 months after transplantation.

Eligible patients received a letter explaining the purpose and procedure of the study, together with an informed-consent form, which also granted permission to obtain data from the medical record. After written informed consent, the participants received a baseline questionnaire. Measures of psychological functioning were repeated every 6 months after inclusion in the study until the transplantation was conducted. In this study, the data from the latest measurement point before the transplant surgery were used to describe symptoms of anxiety and depression before transplantation. After transplantation, the participants filled out a questionnaire at 3, 6, 12, and 24 months. The time needed to fill out the various questionnaires was 60 to 90 minutes. The study ended in October 2015. The institutional review board of the University Medical Center Groningen approved the study, and a positive recommendation of local feasibility was obtained from the other transplant centers (METc2009.190).

Research Instruments

Outcome Variables

Symptoms of anxiety and depression were measured at all measurement points.

Symptoms of anxiety were measured using the short form of the State-Trait Anxiety Inventory (STAI-6) (13). The STAI-6 consists of six items rated on a four-point intensity scale (1 = not at all; 4 = very much), resulting in a total sum score between 6 and 24. Higher scores indicate more symptoms of anxiety. Based on a transformation of the original cutoff of 40 or greater for the general population found in the 20-item scale (14), a cutoff score of 12 or greater is used to identify clinically relevant cases. The Dutch version of the STAI-6 has shown good internal consistency scores (Cronbach $\alpha = .83$) (13). In this study, α values varied from .84 to .87.

Symptoms of depression were assessed using the Dutch version of the Center for Epidemiological Studies Depression Scale (CES-D)(15). The CES-D consists of 20 items, scored on a four-point self-report scale (0 = seldom or never; 4 = most of the time or always). Higher scores indicate more symptoms of depression. A cutoff score of 16 or greater is used to identify clinically relevant cases (16). The Dutch version of the CES-D has shown good internal consistency scores with α values between .79 and .92 (15). In this study, α values varied from .92 to .93.

Associated Variables

In studies measuring psychological problems on a group level, a variety of demographic variables, such as sex, age, and marital status (6,8,9), clinical variables, such as primary liver disease, medical complications, and adverse effects of the immunosuppressive medication (ISM) (8,9,17,18), along with individual variables, such as previous psychiatric disorders, coping style, and health beliefs (10,18,19), have been found to be associated with symptoms of anxiety and depression. Because little is known about factors associated with trajectories of anxiety and depression, we relied on these studies to identify variables possibly associated with distinct trajectories.

Regarding d*emographic variables*, sex, age at transplantation, marital status (partner yes/no), and educational level (primary, secondary, university) were considered. These data were retrieved by self-report in the baseline questionnaire or medical record review (age at transplantation).

Regarding c*linical variables*, several variables that may be influential in the first 2 years after transplantation were considered. The presence of *transplant-related medical complications* in the first 2 years after the transplantation was retrieved by medical record review and comprised the following complications: biliary complications (yes/no), rejection (yes/no), vascular complications (yes/no), graft failure (yes/no), and disease recurrence (yes/no).

The *number of days readmitted to the hospital* was recorded, starting from the day of hospital discharge after the transplant surgery up until 2 years after transplantation. Hospital admissions that were part of the protocolled follow-up care after transplantation were not taken into account.

Perceived adverse effects of the ISM were measured at 24 months after transplantation by using the Modified Transplant Symptom Occurrence and Symptom Distress Scale (MTSOSD-59R) (20). This questionnaire assesses the occurrence of symptoms associated with ISM adverse effects. Each item is scored on a five-point scale (0 = never; 4 = always). Validation of the MTSOSD-59R showed excellent construct and discriminant validity (20). In this study, data of the MTSOSD-59R were dichotomized to distinguish between adverse effects occurring less often (score 0 to 2) and often (score 3 or 4). In the analyses, the number of ISM adverse effects occurring often was taken into account by counting all ISM adverse effects with a score of 3 or 4.

Regarding *individual variables,* three variables were considered, measured at 24 months after the transplantation.

Personal control was measured using the Pearlin-Schooler Mastery Scale (21). The mastery scale measures the degree to which individuals feel they can control things that happen to them and consists of seven items rated on a five-point Likert scale (1 = totally disagree; 5 = totally agree). Higher scores indicate a higher level of personal control. The mastery scale is used in a variety of healthy and ill populations and has shown good reliability and validity (21). In this study, α value was .80.

Coping style was measured using the short form of the Coping Inventory for Stressful Situations (CISS-SF) (22). The CISS-SF measures the following three dimensions of coping: task-oriented coping, in which an individual generally takes an active problem solving approach; emotion-oriented coping, in which an individual habitually engages in maladaptive behaviors such as ruminating as response to stress; and avoidance coping, in which an individual typically uses behaviors aimed at avoiding the stressful situation. The CISS-SF consists of 21 items, rated on a five-point Likert scale (1 = not at all; 5 = very much). Higher scores on a subscale indicate more use of the specific coping style. In this study, α value was .84 for the task-oriented coping scale, .86 for the emotion-oriented coping scale, and .80 for the avoidance coping scale.

The emotional response to the receipt of a transplanted organ was measured by using the following three subscales of the Transplant Effects Questionnaire (TxEQ): worries about the transplant, feelings of guilt toward the donor, and disclosure about having had a transplant (23). Items are scored on a five-point Likert scale (1 = strongly disagree; 5 = strongly agree). On the subscales "worry" and "guilt," a higher score indicates a problematic response, whereas on the "disclosure" subscale, a lower score indicates a problematic response (24). The Dutch version of the TxEQ showed acceptable internal consistency scores (.66-.79) and an adequate fit with the original TxEQ (24). In this study, α values of the subscales were as follows: worry .78; guilt .65; and disclosure .79.

Because life events other than the transplantation may exert an influence on the psychological functioning of transplant recipients, *the total number of other life events* during the first 2 years after the transplantation was taken into account as a confounding variable. These data were retrieved by questionnaire at 12 and 24 months after transplantation using the Trauma and Life Event Self-report Inventory (25). The Trauma and Life Event Self-report Inventory consists of a list of 11 stressful events (e.g., death of a loved one) on which a person can indicate which events happened in the past 5 years. We adjusted this to "past year" to establish that the life events were present during the first or second year after the transplant. Additional life events that influence a person's life could be added. The total number of different life events during the first 2 years after the transplantation were taken into account.

Transplant Outcomes

Anxiety and depression have been associated with worse outcomes regarding quality of life, adherence, and survival in LTRs (8–11,18,26) and were, therefore, taken into account as transplant outcomes in this study, measured at 24 months after transplantation.

Medication adherence was measured using the adherence subscale of the TxEQ (23,24), which measures behavioral (e.g., "Sometimes I forget to take my antirejection medicines") as well as emotional (e.g., "Sometimes I think I do not need my antirejection medicines") aspects of adherence to the ISM regimen. Items are scored on a five-point Likert scale (1 = strongly disagree; 5 = strongly agree). Higher scores indicate better adherence. The TxEQ-adherence subscale was found to have adequate internal consistency (α = .78-.79) and test-retest reliability (23,24). In this study, α value was .76.

Health-related quality of life (HRQoL) was measured using the World Health Organization Quality of Life-BREF questionnaire, the abbreviated version of the WHOQOL-100 questionnaire (27). This questionnaire consists of 24 items covering the following four domains of HRQoL: physical capacity, psychological functioning, social relationships, and environment; and two items regarding general quality of life and health. All items are rated on a five-point Likert scale. For each subscale, a higher mean score indicates better quality of life. In this study, α values for the subscales were, respectively, .87, .87, .65, and .85.

Mortality was assessed by medical record review and was defined as follows: death of all causes within the first 2 years after transplantation (yes/no).

Statistical Analyses

Descriptive statistics were used to calculate mean scores and prevalence rates. Regarding differences between respondents with and without a baseline measurement, continuous data were examined with the Student's *t* test or the Mann-Whitney *U* test and categorical data were examined with the χ^2 test or Fisher exact test where appropriate.

To identify distinct trajectories of anxiety and depression, latent class growth analysis (LCGA) with robust maximum likelihood estimation was used using Mplus 7.1. (Muthen & Muthen, Los Angeles, CA). The LCGA can identify unobserved differences in growth trajectories over time (28). MPlus uses full information maximum likelihood for missing data, currently a highly recommended approach (29). Based on the continuous scores on the STAI-6 and CES-D, the best model was selected, using several criteria: (1) the Bayesian Information Criterion and the Akaike Information Criterion were used to measure the relative fit of the model, with lower values indicating a better fit; (2) the significance of the Bootstrapped Likelihood Ratio Test and the Vuong-Lo-Mendel Rubin Likelihood Ratio Test, which indicate whether a K-class model is superior to a K-1-class model, was used to compare the identified models; (3) entropy was used to examine latent class separation, with higher entropy (>0.6) indicating better separation; and (4) an extra class of substantial size (>5%) should be conceptually meaningful and represent a trajectory differing from trajectories with fewer classes (30). Based on the LCGA, each respondent was assigned to one class, representing the personal trajectory of anxiety and depression, which was used in subsequent analyses in IBM SPSS 22.0 (IBM SPSS, Inc, Chicago, IL).

To identify demographic, clinical, and individual variables that differed significantly between the distinct trajectories, χ^2 tests and analyses of variance were used. After checking for collinearity, multinomial logistic regression analysis was used to examine the independent effect of variables differing significantly on the distinct trajectories using odds ratios.

The association of the identified trajectories of anxiety and depression with outcomes was examined using χ^2 tests or analyses of variances. Effect sizes were calculated using Cohen's *d*. With respect to associated and outcome variables, data were not imputed. The *p* value was set at .05, two-sided, for all analyses.

RESULTS

Study Sample

Figure 1 provides an overview of the study inclusion, the available data, and reasons for missing data. Demographic and clinical characteristics of the study sample are shown in Table 1. Because of the number of missing data at baseline (37/153, 24%), differences between respondents with and without a baseline measurement were examined. No differences were found regarding demographic variables. However, respondents without a baseline measurement were on the waiting list for a significantly shorter period, had a higher model for end-stage liver disease score at transplantation, and differed significantly regarding primary liver disease; the proportion of respondents transplanted for acute liver failure was higher in this group ($p < .05$).

Trajectories of Symptoms of Anxiety and Depression

The parameter estimates of the LCGA analysis showed that the three-class model was the best model for both symptoms of anxiety and depression (Table 2). Regarding symptoms of depression, the four-class model seemed to be the best model, but the Vuong-Lo-Mendel Rubin Likelihood Ratio was not significant and the additional class was not meaningful conceptually.

The distinct trajectories of symptoms of anxiety and depression are depicted in, respectively, Figure 2 and Figure 3. LTRs in trajectory 1 (no symptoms) did not show clinically relevant symptom levels at any measurement point. LTRs in trajectory 2 (resolved

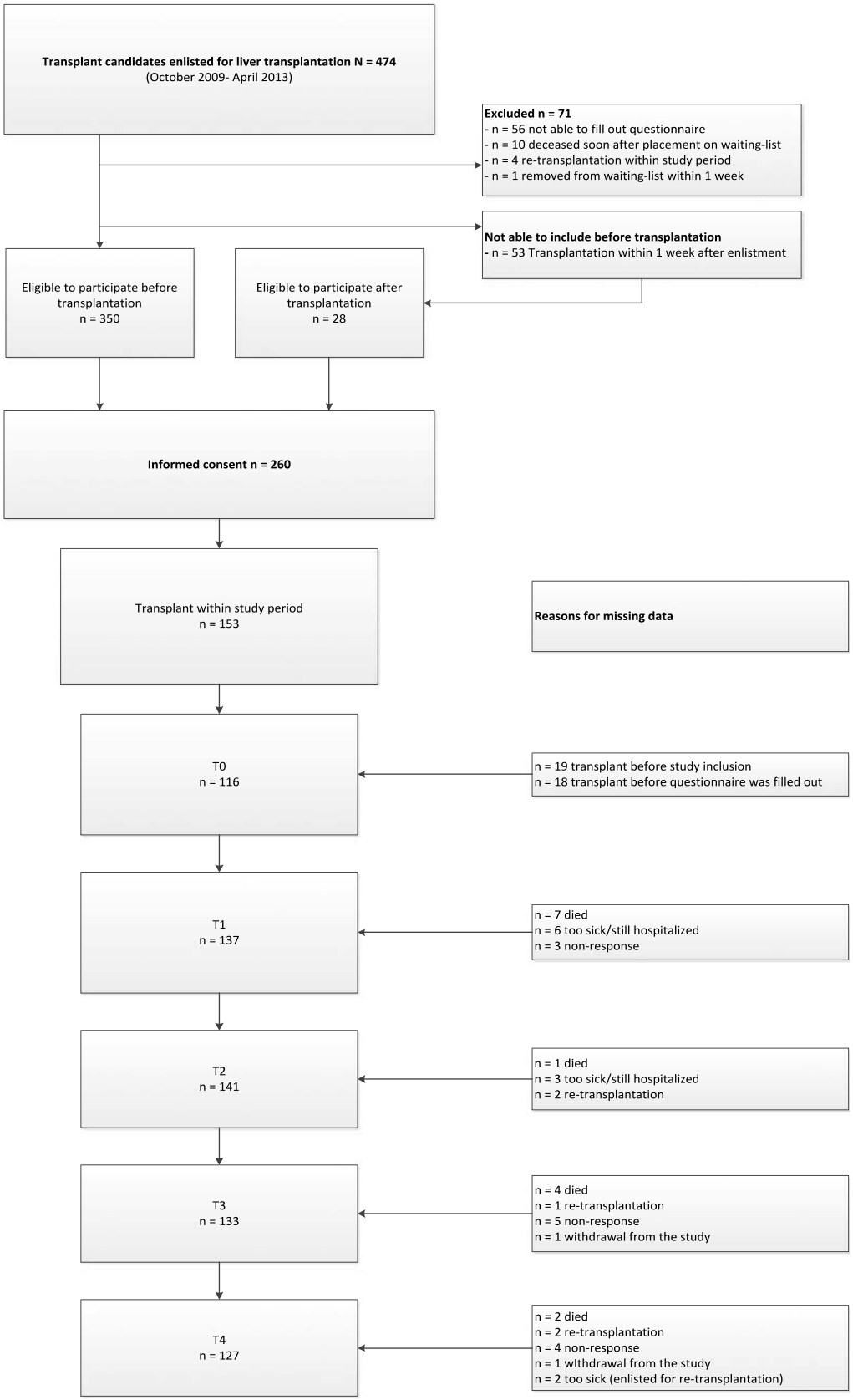

FIGURE 1. Overview of study inclusion and data.

TABLE 1. Demographic and Clinical Characteristics of the Total Study Sample and of Respondents With and Without a Baseline Measurement

	All (N = 153)	Respondents With Baseline Measurement (n = 116)	Respondents Without Baseline Measurement (n = 37)	p
n (%)[a]				
Sex: male	103 (67.3)	76 (65.5)	27 (73.0)	.40
Marital status: partner	117 (76.5)	90 (77.6)	27 (73.0)	.57
Educational level:				
Primary	28 (18.5)	21 (18.3)	7 (19.4)	.85
Secondary	69 (45.7)	54 (47.0)	15 (41.7)	
University	54 (35.8)	40 (34.8)	14 (38.9)	
Nationality: Dutch	142 (92.9)	109 (94.0)	33 (89.2)	.33
Employment status:				
Working	35 (23.0)	33 (28.4)	4 (10.8)	.087
Sick leave/work disability	82 (53.9)	58 (50.0)	22 (59.5)	
Others	35 (23.0)	25 (21.6)	11 (29.7)	
Primary disease:				
Biliary cirrhosis	54 (35.3)	42 (35.2)	12 (32.4)	**.019**
Metabolic liver disease	19 (12.4)	16 (13.8)	3 (8.1)	
Cryptogenic liver cirrhosis	12 (7.8)	9 (7.8)	3 (8.1)	
Viral hepatitis	17 (11.1)	15 (12.9)	2 (5.4)	
Alcoholic liver disease	36 (23.5)	26 (22.4)	10 (27.0)	
Acute liver failure	4 (2.6)	0	4 (10.8)	
Miscellaneous	11 (7.2)	8 (6.9)	3 (8.1)	
Hepatocellular carcinoma	32 (20.3)	25 (21.6)	6 (16.2)	.48
Retransplantation	15 (9.8)	11(9.5)	4 (10.8)	.81
ISM at discharge (n = 149)				
Corticosteroids	140 (94.0)	104 (92.9)	36 (97.3)	.45
Calcineurin inhibitor	140 (94.0)	104 (92.9)	36 (97.3)	.33
Mofetil	71 (47.7)	50 (44.6)	21 (56.8)	.20
Others	11 (7.4)	8 (7.2)	3 (8.1)	>.99
Use of psychiatric drugs				
Antidepressants	10 (6.5)	8 (6.9)	2 (5.4)	>.99
Benzodiapines	12 (7.8)	10 (8.6)	2 (5.4)	.73
Others	7 (4.6)	5 (4.3)	2 (5.4)	.68
Mortality	14 (9.2)	13 (11.2)	1 (2.7)	.12
M (SD)[b]				
Age at transplantation, y	51.0 (11.8)	50.8 (11.4)	51.5 (13.1)	.78
Time on waiting list, d	343 (542)	405 (418)	149 (505)	**<.001**
MELD score at transplantation	17.7 (8.0)	16.2 (7.4)	22.5 (10.9)	**.002**
Duration of hospital stay after transplant surgery, d	32.9 (33.5)	34.1 (37.2)	29.1 (17.7)	.43
Duration of ICU stay after transplant surgery, d	9.6 (21.6)	10.6 (24.3)	6.2 (7.9)	.27

ICU = intensive care unit.

[a] χ^2 test.

[b] Student's t test (normally distributed data) or Mann-Whitney U test (nonnormally distrusted data).

MELD, model for end-stage liver disease.

symptoms) showed symptom levels around the cutoff score before but not after transplantation. LTRs in trajectory 3 (persistent symptoms) showed clinically relevant symptom levels at all measurement points. The trajectories regarding symptoms of anxiety comprised, respectively, 38.6%, 38.6%, and 22.9% of the LTRs. Those involving depressive symptoms comprised, respectively, 22.9%, 47.7%, and 29.4%.

Within all trajectories, a significant decrease ($p < .001$) in symptom levels was found between the measurement points before and at 3 months after transplantation.

The percentage of LTRs with or without a pretransplant measurement differed significantly within the trajectories of anxiety ($p = .016$) and depression ($p = .007$). Additional analyses revealed that the percentage of LTRs without a pretransplant measurement

TABLE 2. Parameter Estimates for Model Selection of the Trajectories of Anxiety and Depression

						Size, %				
	BIC	AIC	Entropy	VLMR, *df*	BLRT, *df*	1	2	3	4	5
Symptoms of anxiety										
2 class	3302.11	3238.47	0.85	285.83*	285.83*	72.8	27.2	—	—	
3 class	**3283.08**	**3186.10**	**0.77**	**74.37***	**74.37***	**38.6**	**38.6**	**22.8**	—	
4 class	3298.42	3168.11	0.80	33.10	33.10	37.3	25.5	13.7	23.5	
Symptoms of depression										
2 class	4469.15	4405.51	0.88	469.09*	469.09*	52.9	47.1	—	—	—
3 class	**4332.73**	**4235.76**	**0.88**	**191.75***	**191.75***	**22.9**	**47.7**	**29.4**	—	—
4 class	4192.69	4162.38	0.89	95.74	95.38*	9.8	23.5	37.9	28.8	—
5 class	4309.40	4145.76	0.85	38.62	38.62**	10.5	26.1	18.9	26.1	18.3

BIC = Bayesian Information Criterion; AIC = Akaike Information Criterion; VLMR = Vuong-Lo-Mendel Rubin Likelihood Ratio Test; BLRT = Bootstrapped Likelihood Ratio Test.

*Significant at $p = .01$ level.

**Significant at $p = .05$ level.

was significantly lower ($p < .05$) in the trajectories of resolved symptoms (anxiety: 19% versus 45%; depression 30% versus 53%) and significantly higher ($p < .05$) in the trajectories of no symptoms (anxiety: 54% versus 34%; depression: 41% versus 17%). In the trajectories of persistent symptoms, no significant differences were found between these groups. Of all LTRs, 18.3% ($n = 28$) showed persistent symptoms of both anxiety and depression.

Variables Associated With Trajectories of Anxiety and Depression

As shown in Table 3, regarding demographic variables, no significant differences between trajectories of anxiety and depression were found. With respect to clinical variables, the number of ISM adverse effects, biliary complications, and the number of days readmitted to the hospital differed significantly between trajectories of anxiety and/or depression. Regarding individual variables, personal control, emotion-oriented coping, task-oriented coping, the emotional response to the receipt of a transplanted organ, and the number of other life events differed significantly between the trajectories of anxiety and/or depression.

Multivariate analysis, in which the trajectories of persistent symptoms were used as the reference category, showed that the number of ISM adverse effects, the level of personal control, emotion-oriented coping, and the number of other life events were independently associated with the distinct trajectories of anxiety and/or depression (Table 4). Personal control was positively associated with the trajectories of anxiety and depression indicating that LTRs within the trajectories of no or resolved symptoms were more likely to have a higher level of personal control than those in the trajectories of persistent symptoms. The number of ISM adverse effects was negatively associated with the distinct trajectories of both anxiety and depression. However, the odds ratios were only significant between the trajectories of persistent and no symptoms, indicating that LTRs in the trajectories of no anxiety and depression were less likely to report severe ISM adverse effects compared with LTRs with persistent symptoms. Furthermore, the use of emotion-oriented coping and the number of other

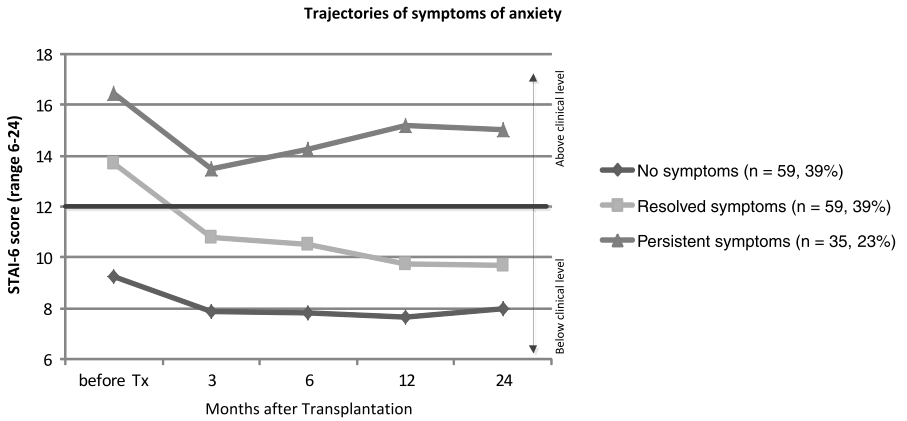

FIGURE 2. Trajectories of symptoms of anxiety from before transplantation to 24 months after transplantation. Note: the bold line depicts the cutoff of ≥12 of the clinical relevant symptoms level.

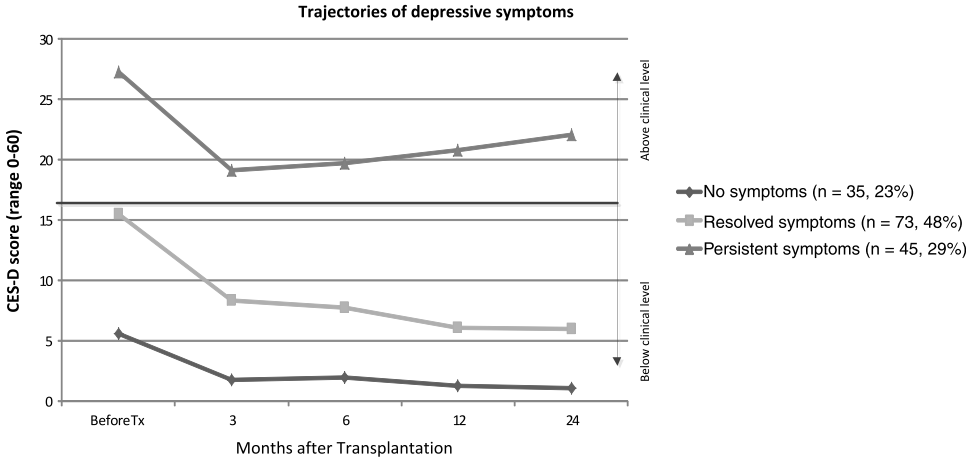

FIGURE 3. Trajectories of symptoms of depression from before transplantation to 24 months after transplantation. Note: the bold line depicts the cutoff of ≥16 of the clinical relevant symptom level.

life events were negatively associated, and disclosure about the transplant was positively associated with the trajectories of depression. LTRs in the trajectory of resolved depression were less likely to use emotion-oriented coping and were more likely to disclose that they had received a transplant compared with LTRs with persistent symptoms. LTRs in the trajectory of no depression were less likely to have experienced other life events compared with LTRs with persistent symptoms.

Influence of Distinct Trajectories on Transplant Outcomes

LTRs within the distinct trajectories of anxiety and depression differed significantly regarding medication adherence ($p = .016$ and $p = .007$, respectively). LTRs in the trajectories of no symptoms showed the M (SD) highest adherence scores of 4.6 (0.5) and 4.7 (0.5), respectively, compared with 4.4 (0.6) in both the trajectories of resolved symptoms, and respectively 4.0 (0.9) and 4.1 (0.9) in the trajectories of persistent symptoms. These differences indicated large effects sizes (Cohen's $d = .82$) between the trajectories of no and persistent symptoms of both anxiety and depression, and small to medium effects sizes (Cohen's $d = .39–.54$) between the other trajectories.

Regarding HRQoL, LTRs within the distinct trajectories differed significantly ($p < .001$) on all domains. LTRs in the trajectories of no symptoms showed the highest scores on all domains, whereas LTRs in the trajectories of persistent symptoms showed the lowest scores. Effect sizes regarding HRQoL were large (Cohen's $d > .80$) on almost all domains, only regarding the social domain the effect sizes were small to negligible (Cohen's $d = .17–.39$).

With respect to mortality, no significant differences were found between the distinct trajectories of anxiety ($p > .99$) or depression ($p = .78$). Additional analysis using Cox hazard ratio (HR) regression analysis showed that neither having symptoms levels above the cutoff point of anxiety (≥12) or depression (≥16) before transplantation (respectively, HR = .99, 95% CI = 0.72–1.38; HR = .99, 95% CI = 0.71–1.37) nor at 3 months after transplantation (respectively, HR = 1.00, 95% CI = 0.71–1.41; HR = 1.00; 95% CI = 0.69–1.46) were associated with mortality within the first 2 years after transplantation.

DISCUSSION

Three distinct trajectories of symptoms of both anxiety and depression in adult LTRs were identified as follows: a trajectory of "no symptoms," "resolved symptoms," and "persistent symptoms." Of all recipients, 23% showed persistent symptoms of anxiety and 29% persistent symptoms of depression from before to 2 years after transplantation, with a negative effect on medication adherence and HRQoL. The trajectories of persistent symptoms were associated with several clinical and individual variables: ISM adverse effects, coping style, personal control, disclosure about the transplant, and other life events.

Our findings are in line with the study of Miller et al. (14), who also found trajectories of no, resolved, and unresolved symptoms of anxiety and depression. In contrast to DiMartini et al. (15), no trajectory resembling an increase in symptom levels after transplantation was found. This might be due to the sample size, but differences in study sample and design might also have been responsible for this. DiMartini et al. (15) only included LTRs transplanted for alcoholic liver disease and did not comprise a pretransplant measurement. In our study, the study sample was composed of LTRs with various primary liver diseases and a pretransplant measurement was included.

All trajectories showed a significant decrease in symptom level between the measurements before and at 3 months after transplantation, implying a beneficial effect of the transplantation on psychological functioning for all LTRs. Despite this beneficial effect, LTRs with high symptom levels of either anxiety or depression before transplantation seem to benefit less and to be more at risk for maintaining high symptom levels after transplantation. Although we did not find that LTRs in the trajectories of persistent symptoms had a higher mortality rate in the first 2 years after the transplantation, these recipients did report a significantly lower level of HRQoL and lower medication adherence. These results show the burden of psychological problems in LTRs, and indicate that recipients with persistent symptoms present a vulnerable group.

In contrast to studies examining associated variables of anxiety and depression on a group level (6,8,9,31), we found no associations between demographic variables and the distinct trajectories of anxiety and depression. However, these findings are in line with

TABLE 3. Differences in Demographic, Clinical, and Individual Variables Between the Distinct Trajectories of Anxiety and Depression in Liver Transplant Recipients

	Trajectory of No Anxiety (*n* = 59)	Trajectory of Resolved Anxiety (*n* = 59)	Trajectory of Persistent Anxiety (*n* = 35)	*p*	Trajectory of No Depression (*n* = 35)	Trajectory of Resolved Depression (*n* = 73)	Trajectory of Persistent Depression (*n* = 45)	*p*
n (%)[a]								
Sex: male[c]	42 (71.2)	38 (64.4)	23 (65.7)	.72	24 (68.6)	51 (69.9)	28 (62.2)	.68
Marital status: partner[c]	43 (74.1)	49 (83.1)	25 (71.4)	.35	26 (76.5)	60 (82.8)	31 (68.9)	.25
Educational level[c]								
Low	9 (15.3)	9 (15.5)	10 (29.4)	.41	4 (11.4)	15 (20.5)	9 (20.9)	.21
Middle	30 (50.8)	26 (44.8)	13 (38.2)		18 (51.4)	37 (50.7)	14 (32.6)	
High	20 (33.9)	23 (39.7)	11 (32.4)		13 (37.1)	21 (28.8)	20 (46.5)	
Medical complications								
Biliary complications	18 (30.5)	34 (57.6)	14 (40.0)	**.031**	12 (34.3)	36 (49.3)	18 (40.0)	.30
Vascular complications	18 (30.5)	19 (32.2)	12 (34.3)	.93	12 (34.3)	18 (24.7)	19 (42.2)	.13
Rejection	9 (15.3)	14 (23.7)	10 (28.6)	.28	6 (17.1)	14 (19.2)	13 (28.9)	.35
Graft failure	7 (11.9)	10 (16.9)	5 (14.3)	.73	2 (5.7)	11 (15.1)	9 (20.0)	.19
Disease recurrence	5 (8.5)	7 (11.9)	3 (8.6)	.79	1 (2.9)	11 (15.1)	3 (6.7)	.095
M (SD)[b]								
Age at transplantation, y	53.4 (11.0)	49.8 (12.0)	48.9 (12.3)	.12	52.4 (12.0)	52.1 (11.4)	48.0 (12.0)	.13
No. ISM adverse effects[e]	2.0 (3.7)	3.9 (4.1)	6.3 (6.0)	**.001**	0.8 (1.0)	3.5 (4.3)	6.4 (5.7)	**<.001**
No. days rehospitalization[d]	13.4 (20.0)	20.6 (24.6)	28.2 (33.3)	**.028**	10.7 (17.8)	21.4 (25.5)	23.8 (34.1)	.066
Personal control[e]	28.4 (3.9)	25.2 (4.4)	20.2 (4.4)	**<.001**	28.6 (3.7)	26.5 (4.5)	20.7 (4.2)	**<.001**
Coping style[e]								
Task-oriented coping	26.2 (5.0)	25.3 (3.9)	22.7 (5.4)	**.011**	26.2 (4.3)	25.2 (4.8)	23.9 (5.3)	.14
Emotion-oriented coping	14.2 (4.7)	16.4 (5.5)	21.9 (6.5)	**<.001**	14.0 (4.1)	15.2 (4.5)	21.6 (7.3)	**<.001**
Avoidance coping	15.4 (5.6)	17.5 (4.7)	15.8 (4.2)	.081	15.8 (5.4)	16.4 (4.8)	16.5 (5.2)	.81
Emotional response to the receipt of a transplanted organ[e]								
Worry about transplant	2.5 (0.8)	2.8 (0.6)	3.2 (0.7)	**.001**	2.4 (0.8)	2.7 (0.7)	3.3 (0.7)	**<.001**
Guilt toward donor	1.6 (0.5)	1.7 (0.5)	2.0 (0.7)	**.001**	1.7 (0.5)	1.7 (0.5)	2.0 (0.7)	**.018**
Disclosure transplantation	4.6 (0.5)	4.4 (0.7)	3.9 (0.8)	**<.001**	4.6 (0.5)	4.6 (0.5)	4.0 (0.9)	**<.001**
No. life events[d]	1.4 (1.4)	2.5 (2.2)	2.4 (2.1)	**.009**	1.3 (1.2)	2.0 (1.8)	2.8 (2.5)	**.006**

ISM = immunosuppressive medication.

[a] χ^2 test.

[b] Analyses of variance.

[c] Measured at baseline.

[d] Measured throughout the first 2 years after transplantation.

[e] Measured at 24 months after transplantation.

other studies examining variables associated with trajectories of anxiety and depression in other patient groups, in which also no relations were found with demographic variables (32,33).

Regarding clinical variables, none of the transplant-related medical complications examined were associated with the distinct trajectories. This seems to indicate that these medical complications do not contribute to the persistence of symptoms of anxiety and depression. Another explanation of this finding may be that a longer period might be needed to observe distress in LTRs as a consequence of medical complications, because they may not be aware of the possible negative influence of these complications on outcomes at the long term.

The finding that LTRs in the trajectories of persistent symptoms reported more severe ISM adverse effects is in line with an earlier study among LTRs (17). However, it remains unclear whether experiencing more adverse effects leads to persistent symptoms of anxiety and/or depression or vice versa. Although management of ISM adverse effects is warranted, little is known about the treatability of these adverse effects and effective management strategies are lacking (34).

TABLE 4. Odds Ratios and 95% CI of Variables Associated With Trajectories of Persistent Symptoms of Anxiety Compared With No Anxiety and Resolved Anxiety and of Trajectories of Persistent Symptoms of Depression Compared With No Depression and Resolved Depression

	Persistent Anxiety Versus No Anxiety			Persistent Anxiety Versus Resolved Anxiety		
		95% CI			95% CI	
Variable	Odds Ratio	Lower	Upper	Odds Ratio	Lower	Upper
Biliary complications[a]	1.58	0.16	15.76	5.44	0.69	42.67
No. ISM adverse effects[b]	**0.82**	**0.68**	**0.98**	0.92	0.81	1.06
No. days rehospitalization[a]	0.97	0.93	1.02	0.98	0.95	1.01
Personal control[b]	**1.44**	**1.17**	**1.76**	**1.22**	**1.02**	**1.46**
Task-oriented coping[b]	1.18	0.99	1.40	1.11	0.95	1.30
Emotional coping[b]	0.87	0.75	1.00	0.90	0.80	1.02
Worry about the transplant[b]	1.20	0.35	4.06	1.27	0.43	3.73
Guilt toward donor[b]	0.47	0.11	2.04	0.54	0.14	2.02
Disclosure about transplantation[b]	1.92	0.61	6.04	1.80	0.73	4.44
No. life events[a]	0.75	0.52	01.09	0.98	0.82	1.16
	Persistent Depression Versus No Depression			Persistent Depression Versus Resolved Depression		
		95% CI			95% CI	
	Odds Ratio	Lower	Upper	Odds Ratio	Lower	Upper
No. ISM adverse effects[b]	**0.56**	**0.38**	**0.82**	0.91	0.79	1.05
Personal control[b]	**1.42**	**1.17**	**1.72**	**1.28**	**1.11**	**1.49**
Emotional coping[b]	0.89	0.76	1.04	**0.88**	**0.79**	**0.99**
Worry about the transplant[b]	0.42	0.12	1.50	1.16	0.43	3.11
Guilt toward donor[b]	0.55	0.14	2.14	0.64	0.22	1.85
Disclosure about transplantation[b]	1.29	0.41	4.03	**2.78**	**1.10**	**7.01**
No. life events[a]	**0.54**	**0.34**	**0.85**	0.76	0.56	1.05

Bold variables significantly associated with the distinct trajectories of anxiety or depression in MLR.

ISM = immunosuppressive medication.

[a] Measured throughout the first 2 years after transplantation.

[b] Measured at 24 months after transplantation.

Regarding individual variables, we found that LTRs in the trajectories of persistent symptoms had a lower level of personal control, made more use of emotion-oriented coping, and disclosed less often about having had a transplant. These results indicate that individual characteristics play an important role in the persistence of symptoms of anxiety and depression. Therefore, interventions aimed at empowering transplant recipients by strengthening coping skills or personal control may help improve their psychological functioning. However, a recent systematic review revealed that evidence regarding effective psychosocial interventions in transplant recipients is limited. So far, only a few studies showed that psychosocial interventions may well be effective in reducing distress in transplant recipients (35). Therefore, psychosocial interventions for transplant recipients need to be developed and examined for their effectiveness. Psychosocial interventions that have shown to be effective in other chronic illness patient groups (36,37) can be used to develop interventions tailored to the needs of the transplant population.

Overall, the results of our study emphasize the importance of psychological evaluation and support in the care of LTRs. Individual factors associated with symptoms of anxiety and depression need to be assessed early in the transplant process, for example, with the "Stanford Integrated Psychosocial Assessment for Transplantation" (38), and a continuous follow-up of the psychological functioning of LTRs using patient-reported outcome measures, such as PROMIS (39) is warranted.

Based on the findings, interventions aimed at empowerment can be offered to enhance the psychological functioning of transplant candidates and recipients.

The strength of our study was its prospective, multicenter design, the adequate response rate (69%), and the reasonable sample size (N = 153). Although, data for pretransplant psychological functioning were missing in 24% of the respondents, respondents with and without a baseline measurement only differed regarding some transplant-related variables that could be expected beforehand. This indicates that the results of our study are valid for our study population.

Despite this, the generalizability of our results may be limited. The sample size was relatively small for LCGA; therefore, replication of our findings in larger samples is needed to be able to generalize our result to the liver transplant population as a whole. The generalizability of our results may also be composed by the relatively large number of respondents (17%) who were lost over time. Larger sample sizes may also be needed to be able to identify additional trajectories

(e.g., increasing symptoms) of anxiety and depression. In future studies, additional trajectories may also be revealed by considering symptoms of anxiety and depression together.

CONCLUSIONS

In this study, three distinct trajectories of symptoms of both anxiety and depression in adult LTRs were identified as follows: a trajectory of no symptoms, resolved symptoms, and persistent symptoms. A significant subset of LTRs showed persistent symptoms of anxiety (23%) or depression (29%) after transplantation, with a negative effect on medication adherence and HRQoL. The trajectories of persistent symptoms were mainly associated with individual variables such as coping, personal control, and disclosure about the transplant. The results of our study emphasize the importance of psychological evaluation and support in the care of transplant recipients.

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REFERENCES

1. López-Navas A, Ríos A, Riquelme A, Martínez-Alarcón L, Pons JA, Miras M, Sanmartín A, Febrero B, Ramírez P, Parrilla P. Psychological care: social and family support for patients awaiting a liver transplant. Transplant Proc 2011;43:701–4.
2. Russell RT, Feurer ID, Wisawatapnimit P, Salomon RM, Pinson CW. The effects of physical quality of life, time, and gender on change in symptoms of anxiety and depression after liver transplantation. J Gastrointest Surg 2008;12:138–44.
3. Rocca P, Cocuzza E, Rasetti R, Rocca G, Zanalda E, Bogetto F. Predictors of psychiatric disorders in liver transplantation candidates: logistic regression models. Liver Transpl 2003;9:721–6.
4. Guimaro MS, Lacerda SS, Karam CH, Ferraz-Neto BH, Andreoli PB. Psychosocial profile of patients on the liver transplant list. Transplant Proc 2008;40:782–4.
5. Chen PX, Yan LN, Wang WT. Health-related quality of life of 256 recipients after liver transplantation. World J Gastroenterol 2012;18:5114–21.
6. Pelgur H, Atak N, Kose K. Anxiety and depression levels of patients undergoing liver transplantation and their need for training. Transplant Proc 2009;41:1743–8.
7. O'Carroll RE, Couston M, Cossar J, Masterton G, Hayes PC. Psychological outcome and quality of life following liver transplantation: a prospective, national, single-center study. Liver Transpl 2003;9:712–20.
8. Rogal SS, Dew MA, Fontes P, DiMartini AF. Early treatment of depressive symptoms and long-term survival after liver transplantation. Am J Transplant 2013;13:928–35.
9. Corruble E, Barry C, Varescon I, Falissard B, Castaing D, Samuel D. Depressive symptoms predict long-term mortality after liver transplantation. J Psychosom Res 2011;71:32–7.
10. Stilley CS, Flynn WB, Sereika SM, Stimer ED, DiMartini AF, deVera ME. Pathways of psychosocial factors, stress, and health outcomes after liver transplantation. Clin Transplant 2012;26:216–22.
11. Miller LR, Paulson D, Eshelman A, Bugenski M, Brown KA, Moonka D, Abouljoud M. Mental health affects the quality of life and recovery after liver transplantation. Liver Transpl 2013;19:1272–8.
12. DiMartini A, Dew MA, Chaiffetz D, Fitzgerald MG, Devera ME, Fontes P. Early trajectories of depressive symptoms after liver transplantation for alcoholic liver disease predicts long-term survival. Am J Transplant 2011;11:1287–95.
13. Van der Bij AK, De Weerd S, Cikot RJ, Steegers EA, Braspenning JC. Validation of the Dutch short form of the state scale of the Spielberger State-Trait Anxiety Inventory: considerations for usage in screening outcomes. Community Genet 2003;6:84–7.
14. Spielberger CD, Gorsuch RL, Lushene R, Vagg PR, Jacobs GA. Manual for the State-Trait Anxiety Inventory (Self-Evaluation Questionnaire), Palo Alto, CA.: Consulting Psychologists Press; 1983.
15. Bouma J, Ranchor AV, Sanderman R, Van Sonderen E. Measurement of depressive symptoms with the CES-D. In: A manual, Groningen: Northern Center of Health Research; 1995.
16. Radloff LS. The CES-D Scale: a self-report depression scale for research in the general population. Appl Psychol Measur 1977;1:385–401.
17. Annema C, Roodbol PF, Stewart RE, Porte RJ, Ranchor AV. Prevalence of psychological problems and associated transplant-related variables at different time periods after liver transplantation. Liver Transpl 2015;21:524–38.
18. Santos Junior R, Miyazaki MC, Domingos NA, Valério NI, Silva RF, Silva RC. Patients undergoing liver transplantation: psychosocial characteristics, depressive symptoms, and quality of life. Transplant Proc 2008;40:802–4.
19. Caccamo L, Azara V, Doglia M, Sessini M, Rossi G, Gala C, Fassati LR. Longitudinal prospective measurement of the quality of life before and after liver transplantation among adults. Transplant Proc 2001;33:1880–1.
20. Moons P, De Geest S, Versteven K, Abraham I, Vlaminck H, Moens G, Waer M. Psychometric properties of the "Modified Transplant Symptom Occurrence and Symptom Distress Scale". J Nurs Meas 2001;9:115–34.
21. Pearlin LI, Schooler C. The structure of coping. J Health Soc Behav 1978;19:2–21.
22. Cohan SL, Jang KL, Stein MB. Confirmatory factor analysis of a short form of the Coping Inventory for Stressful Situations. J Clin Psychol 2006;62:273–83.
23. Ziegelmann JP, Griva K, Hankins M, Harrison M, Davenport A, Thompson D, Newman SP. The Transplant Effects Questionnaire (TxEQ): the development of a questionnaire for assessing the multidimensional outcome of organ transplantation - example of end stage renal disease (ESRD). Br J Health Psychol 2002;7:393–408.
24. Annema C, Roodbol PF, Stewart RE, Ranchor AV. Validation of the Dutch version of the Transplant Effects Questionnaire in liver transplant recipients. Res Nurs Health 2013;36:203–15.
25. Hovens JE, Bramsen I, van der Ploeg HM, Reuling IE. Test-retest reliability of the trauma and life events self-report inventory. Psychol Rep 2000;87:750–2.
26. Rodrigue JR, Nelson DR, Hanto DW, Reed AI, Curry MP. Patient-reported immunosuppression nonadherence 6 to 24 months after liver transplant: association with pretransplant psychosocial factors and perceptions of health status change. Prog Transplant 2013;23:319–28.
27. O'Carroll RE, Smith K, Couston M, Cossar JA, Hayes PC. A comparison of the WHOQOL-100 and the WHOQOL-BREF in detecting change in quality of life following liver transplantation. Qual Life Res 2000;9:121–4.
28. Nagin D. Analyzing developmental trajectories: a semiparametric, group-based approach. Psychol Methods 1999;4:139–57.
29. Enders CK. Applied Missing Data Analysis, New York: Guilford Press; 2010.
30. Nylund KL, Asparoutiov T, Muthen BO. Deciding on the number of classes in latent class analysis and growth mixture modeling: a Monte Carlo simulation study. Struct Equ Modeling 2007;14:535–69.
31. Newton SE. Relationship between depression and work outcomes following liver transplantation: the nursing perspective. Gastroenterol Nurs 2003;26:68–72.
32. Henselmans I, Helgeson VS, Seltman H, de Vries J, Sanderman R, Ranchor AV. Identification and prediction of distress trajectories in the first year after a breast cancer diagnosis. Health Psychol 2010;29:160–8.
33. van den Broek KC, Kupper N, van der Voort PH, Alings M, Denollet J, Nyklíček I. Trajectories of perceived emotional and physical distress in patients with an implantable cardioverter defibrillator. Int J Behav Med 2014;21:149–59.
34. Kugler C, Geyer S, Gottlieb J, Simon A, Haverich A, Dracup K. Symptom experience after solid organ transplantation. J Psychosom Res 2009;66:101–10.
35. Conway A, Schadewaldt V, Clark R, Ski C, Thompson DR, Kynoch K, Doering L. The effectiveness of non-pharmacological interventions in improving psychological outcomes for heart transplant recipients: a systematic review. Eur J Cardiovasc Nurs 2014;13:108–15.
36. Farver-Vestergaard I, Jacobsen D, Zachariae R. Efficacy of psychosocial interventions on psychological and physical health outcomes in chronic obstructive pulmonary disease: a systematic review and meta-analysis. Psychother Psychosom 2015;84:37–50.
37. Klainin-Yobas P, Ng SH, Stephen PDM, Lau Y. Efficacy of psychosocial interventions on psychological outcomes among people with cardiovascular diseases: a systematic review and meta-analysis. Patient Educ Couns 2016;99:512–21.
38. Maldonado JR, Dubois HC, David EE, Sher Y, Lolak S, Dyal J, Witten D. The Stanford Integrated Psychosocial Assessment for Transplantation (SIPAT): a new tool for the psychosocial evaluation of pre-transplant candidates. Psychosomatics 2012;53:123–32.
39. Fries JF, Bruce B, Cella D. The promise of PROMIS: using item response theory to improve assessment of patient-reported outcomes. Clin Exp Rheumatol 2005;23:S53–7.