CHAPTER

2

PREVALENCE OF PSYCHOLOGICAL PROBLEMS AND ASSOCIATED TRANSPLANT-RELATED VARIABLES AT DIFFERENT TIME PERIODS AFTER LIVER TRANSPLANTATION

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ABSTRACT

After liver transplantation, recipients often experience psychological problems that are influenced by demographic, personal, and transplant-related variables. However, because previous studies have mostly reported on psychological problems and their influencing factors in the first years after transplantation, less is known about their prevalence and influence in the long run. The aims of this study were to examine point-prevalence rates of symptoms of anxiety, depression, and posttraumatic stress (PTS) at different time periods after transplantation and to examine transplant-related variables associated with these problems. A cross-sectional survey was performed among 373 liver transplant recipients who received transplants between 1979 and 2009 at our center. Five clinically relevant time periods were identified: 0.5 to <2 years, 2 to <5 years, 5 to <10 years, 10 to <15 years, and ≥15 years after transplantation. The response rate was 75% (n = 281). Overall, 33.4% of the respondents experienced clinically relevant symptom levels of anxiety (28.7%), depression (16.5%), or PTS (10.0%). Symptoms of anxiety and depression were more prevalent in the first 2 years and in the long term after transplantation. PTS symptoms were more prevalent in the first 5 years after transplantation. However, the prevalence rates did not differ significantly between time periods. Viral hepatitis and the number of side-effects of the immunosuppressive (IS) medication were found to be associated with all psychological problems. Alcoholic liver disease was associated with anxiety and depression in the short term after transplantation. In conclusion, a significant subset of transplant recipients experience psychological problems, both shortly after transplantation and in the long run. These problems are often associated with side-effects of the IS medication. Therefore, the monitoring of psychological problems, the offering of psychological counseling, and the management of the medication's side-effects should be part of the routine care of transplant recipients.

INTRODUCTION

Although health-related quality of life improves after transplantation, it never reaches the level of the general population.[1-3] More specifically, a meta-analysis has shown that quality of life after liver transplantation significantly improves in the domains of physical and social functioning but not in the domain of psychological functioning.[4] This may be due to the fact that transplant recipients require psychological adaptation in order to integrate this experience into their lives. In fact, transplant recipients trade a chronic and potentially life-ending disease for a chronic situation that includes a lifelong medication regimen and adherence to strict guidelines. It is not unlikely that this adaptation process causes psychological distress in a significant subset of transplant recipients.[5-7]
Psychological problems are common in liver transplant recipients. High prevalence rates of psychological problems have been found in the first two years after the transplantation.[8-10] Studies describing on psychological problems up to 10 years after transplantation have shown that these problems become less prevalent, with rates ranging from approximately 20 to 25% for symptoms of anxiety[11-14] and from approximately 15% to 20% for depressive symptoms.[11,14-16] Prevalence rates ranging from 2% to 30%[1,17-19] have been described for symptoms of posttraumatic stress (PTS).
Because psychological problems after transplantation are associated with adverse outcomes such as morbidity, mortality,[20] and impaired quality of life,[7] it is important to identify at an early stage the transplant recipients who are at risk of psychological problems. Knowledge about the risk factors of anxiety, depression, and PTS after liver transplantation plays a pivotal role in this identification process. In the literature, a variety of risk factors of psychological problems have been described, including demographic, personal, and transplant-related variables. Transplant-related variables include pre-transplant factors as well as factors related to the hospitalization phase after the transplant surgery, and the post-transplant period. Pre-transplant risk factors that have been described include type of primary liver disease,[8,21-24] severity of disease,[9,19] and waiting time.[1,25] With regard to the hospitalization period, (the number of) medical problems,[1,19] the length of intensive care treatment,[1,26] and the length of hospitalization[21] have been reported as risk factors. In the post-transplant period comorbidities,[8] transplant-related medical problems,[9,27,28] the use of high doses of corticosteroid medications,[24] severe drug side-effects,[29] and the time since transplantation[11,24,29] have been described as risk factors.
However, little is known about the prevalence of psychological problems such as anxiety, depression, and PTS in the long term after transplantation because most studies have focused on the first 5 years after liver transplantation. Also, in these studies, no distinction between time periods after transplantation has been made. Besides this, data on the relationship between transplant-related variables and psychological problems are often discordant, and knowledge about the influence of transplant-related variables on these problems in the long run is lacking.
Therefore, the aims of this study were to examine the point-prevalence rates of symptoms of anxiety, depression, and PTS during a period ranging from 6 months to more than 30 years after liver transplantation; to identify transplant-related variables associ-

ated with symptoms of anxiety, depression, and PTS, and to examine whether the identified transplant-related variables differ between groups according to the time since transplantation.

PATIENTS AND METHODS

In this cross-sectional study, which is part of the Psychological Aspects of Transplantation"-study, all liver transplant recipients who received post-transplant care at the University Medical Center Groningen in April 2010 were invited to participate. Inclusion criteria were as follows: transplanted between 1979 and October 2009 at our center, transplanted at an adult age, still alive, and still receiving post-transplant care at our center. Exclusion criteria were as follows: not being able to fill out a Dutch questionnaire (because of language, physical impairments, or cognitive impairments), being enlisted for re-transplantation, or being lost to follow-up. Eligible recipients received an information letter together with a questionnaire and an informed consent form regarding permission to obtain data from the recipient's medical record. The questionnaires were coded to ensure confidentiality and respondent anonymity. After 4 weeks a reminder was sent and another two weeks were allowed for completion. The study met the criteria for an exemption from institutional review board approval (METc2010.039).

On the basis of time since transplantation, respondents were categorized into 5 groups representing clinically relevant time periods: 0.5 to <2 years (short-term), 2 to <5 years (intermediate short-term), 5 to <10 years (intermediate term), 10 to <15 years (intermediate long-term), and ≥15 years (long-term) after transplantation. This categorization is based on the clinical experience of expert transplant professionals on the general course of physical and psychological recovery after the transplantation surgery and the subsequent development of new medical problems. Transplant recipients in the short-term group, for instance, are fully focused on recovering from the transplant surgery and adjusting to life after transplantation. Recipients in the intermediate short-term group experience further recovery and eventually reach their own maximum level of physical, psychological, and social functioning. Recipients in the intermediate group find themselves in a rather stable situation. They realize that their functioning will not improve anymore and have resigned themselves to this situation. However, the first signs of long-term complications related to the transplantation will appear. In the intermediate long-term group these complications become even more apparent. The long-term group consists of strong survivors, but their overall health is often deteriorating as long-term complications become more prevalent. Also recipients often start wondering about the longevity of their transplanted organ.

Measures

To assess symptoms of depression, the validated Dutch version of the Center for Epidemiological Studies Depression scale (CES-D) was used.[30] The CES-D consists of 20 items, scored on a 4-point self-report scale [from 0 (seldom or never) to 4 (most of the time/always)]. Higher scores indicate more symptoms of depression. A cutoff score of ≥16

was used to identify clinically relevant cases.[31] Cronbach's alpha of the CES-D in the present study was 0.86.

The State Trait Anxiety Inventory short form (STAI-6), developed by Marteau and Bekker,[32] was used to measure symptoms of anxiety. The STAI-6 consists of 6 items rated on a 4-point intensity scale [from 1 (not at all) to 4 (very much)]. The sum score on the STAI-6 is extrapolated to the scores on the original STAI, resulting in a total sum score between 20 and 80. Higher scores indicate more symptoms of anxiety. A cutoff score of ≥40 is used to identify clinically relevant cases.[33] The convergent validity of the STAI-6 with the full form of the STAI showed a correlation of 0.95.[34] Cronbach's alpha of the STAI-6 in the present study was 0.81.

To measure symptoms of PTS, the Self-Rating Inventory for Posttraumatic Stress Disorder (SRIP) was used;[35] this is a Dutch screening instrument that registers symptoms of PTS. The 22 items, corresponding to the *Diagnostic and Statistical Manual of Mental Disorders* (4th edition) criteria, are rated on a 4-point self-report scale [from 1 (not at all) to 4 (extremely)]. Higher scores indicate more symptoms of PTS. A cutoff score of ≥39 is used to identify clinically relevant cases.[36] Cronbach's alpha of the SRIP in the present study was 0.89.

The Dutch version of the Modified Transplant Symptom Occurrence and Symptom Distress Scale (MTSOSD-59R) was used to assess the perceived occurrence of 59 symptoms associated with side-effects of immunosuppressive (IS) medications (cyclosporine, corticosteroids, azathioprine, tacrolimus, mycophenolate mofetil, sirolimus, and belatacept). Each item is scored on a 5-point self-report scale [from 0 (never) to 4 (always)]. Validation of the MTSOSD-59R showed excellent construct and discriminant validity.[37,38] For the present study, data from the MTSOSD-59R were dichotomized to distinguish between side-effects occurring less often (a score 0, 1 or 2) or often (a score of 3 or 4). In the analyses, only the number of IS side-effects that occur often was taken into account: all IS side-effects reported as often occurring (a score 3 or 4) were counted. Cronbach's alpha of the MTSOSD-59R could be retrieved because of the nature of the instrument.

To measure stressful events besides the transplantation that may have influenced a person's life, the Trauma and Life Events Self-report Inventory (TLESI) was used. The TLESI is a Dutch inventory consisting of a list of 11 stressful events (eg, illness or death of family member and losing a job) on which people can indicate which events happened in the past 5 years or longer ago if it still have an impact on their lives. Respondents had the possibility of adding stressful life events not mentioned in the questionnaire. The TLESI has shown stability over time (test-retest reliability .75 to .89).[39] The number of stressful life events was computed via the counting of all indicated stressful life events for each respondent.

Demographic variables were collected by self-report and included: age, sex, marital status, level of education, and employment status.

Transplant-related variables were retrieved from the hospital's liver transplant database, which contains medical data on liver transplant recipients from our center. Additional information, mostly pertaining to medical complications in the year before the survey, was retrieved from medical records.

Transplant-related variables included in the study were as follows: primary liver disease, onset of disease (chronic/acute), re-transplantation (no/yes), time on waiting list for transplantation (months), Model for End-stage Liver Disease (MELD) score at the time of transplantation, Karnofsky score at the time of transplantation, age at transplantation, length of stay on the intensive care unit (ICU), length of hospital stay after the transplantation, number of complications in the clinical phase, number of transplant-related medical problems in the year before the survey (eg, recurrence liver disease and rejection), number of non-transplant-related medical problems in the year before the survey (eg, hypertension and infections), number of side-effects of the IS medication, and type of IS medication at the time of the study.

Statistical analysis

Analyses were performed using IBM SPSS statistics 20 (SPSS, Inc., Chicago, IL). Descriptive statistics were used to calculate mean scores and prevalence rates. For continuous data, differences between groups were examined using the Students *t* test for normally distributed variables and with the Mann-Whitney U-test (2 groups) or the Kruskal-Wallis test (more than 2 groups) for non-normally distributed variables. The X^2 test was used to examine differences between categorical variables. Because the scores on the STAI6, CES-D, and SRIP were skewed, data were transformed to their natural logarithm. Bivariate correlation analysis (Pearson's *r*) was used to identify transplant-related variables that were significantly related to symptoms of anxiety, depression, or PTS in the total study population and within each group according to time since transplantation.

A generalized linear model (GLM) analysis was used to examine whether the significant associations of transplant-related variables with the psychological problems differed significantly between the time groups in 2 steps. In the first step, GLM analyses per independent transplant-related variable were performed to examine the main effect of the variable on the psychological problems. In the second step, the interaction effects between time groups and the significantly associated transplant-related variables were added. The short-term group (0.5 to <2years) was used as the reference category. Finally, all independent variables with a significant main effect or significant interaction effect (including the main effect of the variable) were entered into an overall GLM analysis. In this final analysis, potential confounding variables, such as age at the time of the study, sex, marital status (living with a partner/living alone), employment status (actively working/not actively working), and the number of life events were taken into account. The variable *length of hospital stay* was centered by 9 and the variable *age at the time of the study* was centered by 25 before they were entered into the GLM analysis. The *P* value was set at 0.05 for all analyses.

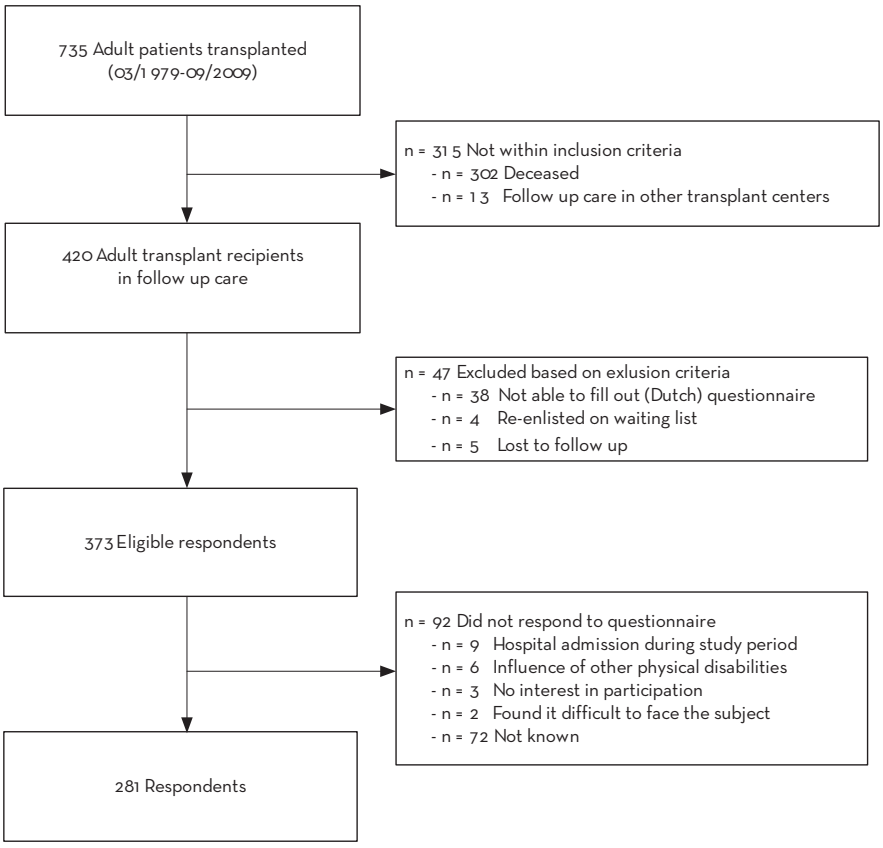

Figure 1. Flow diagram inclusion, exclusion and nonresponses of the study

RESULTS

Study population

Of the 735 adult patients undergoing transplantation between 1979 and October 2009, 420 recipients were still alive and received follow-up care at our center (Figure 1). On the basis of the exclusion criteria, 47 recipients were excluded from participation. Of the 373 eligible liver transplant recipients, 281 completed the questionnaire, this meant a response rate of 75%. The data for 2 recipients (0.7%) regarding psychological problems were insufficient, and they were, therefore, excluded from the analysis. No differences between respondents and non-respondents were found with respect to sex, number of transplants, time since transplantation, or primary diagnosis (data not shown). However, respondents were older than non-respondents both at the time of

Table 1. Demographic and transplant-related characteristics of all respondents and of the groups according to time since transplantation

	All (n = 279)	Short-Term Group (0.5 to <2 years; n = 32)	Intermediate Short-Term Group (2 to <5 Years; n = 42)	Intermediate Group (5 to <10 years; n = 74)	Intermediate Long-Term Group (10 to <15 years; n = 65)	Long-term Group (≥15 years; n = 66)	Differences Between Groups (*P* value)
Demographic variables							
Sex (%)							
Male	52.0	62.5	59.5	54.1	60.0	31.8	**0.01**[*]
Female	48.0	37.5	40.5	45.9	40.0	68.2	
Age at time study (years; mean, range)	56.4 (25-79)	54.8 (29-69)	56.0 (32-71)	56.5 (25-75)	54.7 (31-77)	58.2 (35-79)	0.67[†]
Marital status (%)							
Living with partner	76.0	68.8	78.6	79.7	76.9	72.7	0.73[*]
Living alone	24.0	31.2	21.4	20.3	23.1	27.3	
Level of education (%)							
Primary	30.8	31.3	47.6	25.0	18.8	37.9	**0.01**[*]
Secondary	40.2	53.1	23.8	34.7	53.1	37.9	
University	29.0	15.6	28.6	40.3	28.1	24.2	
Employment status (%)							
Actively working	31.9	43.8	23.8	28.4	33.8	33.3	0.42[*]
Not actively working	68.1	56.3	76.2	71.6	66.1	66.7	
Number of life events (mean, range)	1.59 (0-6)	1.50 (0-4)	1.60 (0-5)	1.54 (0-6)	1.49 (0-6)	1.79 (0-5)	0.64[†]
Transplant-related variables							
Age at Transplantation (years; mean, range)	46.3 (18-69)	53.6 (28-67)	52.7 (30-69)	49.0 (18-68)	42.4 (18-65)	39.5 (19-60)	**<0.01**[†]
Primary diagnoses (%)							
Biliary cirrhosis	35	19	36	38	26	47	**0.03**[*]
Cirrhosis of unknown etiology	19	19	19	14	23	23	0.61[*]
Metabolic disorders	11	13	12	11	11	11	0.99[*]
Viral hepatitis	10	9	10	10	17	3	-
Alcoholic liver disease	10	16	17	8	11	5	0.22[*]
Acute liver failure	5	6	5	8	5	2	-
Miscellaneous	12	19	2	12	8	11	-

Time on waiting-list (in months) (in months; mean, range)	6.6 (0-45)	8.0 (0-45)	10.8 (0-33)	9.3 (0-35)	3.3 (0-16)	3.3 (0-27)	**0.01**†
N° of Transplants (%)							
1	87	91	98	85	86	80	0.24*
2 or more	13	9	2	15	14	20	
MELD score at time of transplantation (mean, range)	17.9 (6-40)	19.2 (6-40)	16.6 (6-40)	NA	NA	NA	0.14†
Karnofsky score at time of transplantation (mean, range)	59.5 (10-100)	59.1 (20-90)	58.3 (20-90)	62.2 (10-100)	63.0 (10-90)	53.9 (10-100)	0.23†
Length of hospital stay after transplantation (days; mean, range)	33.0 (9-111)	22.4 (14-47)	23.2 (9-47)	31.4 (12-71)	34.6 (11-90)	44.3 (11-111)	**<0.01**†
Length of stay on ICU after transplantation (days; mean, range)	6.8 (0-76)	4.5 (1-21)	7.2 (1-76)	6.3 (0-50)	7.2 (1-52)	8.1 (1-73)	**0.01**†
Number of complications in clinical phase (mean, range)	5.3 (0-17)	5.6 (1-12)	5.4 (0-15)	5.5 (0-14)	5.5 (0-17)	4.7 (0-12)	0.61†
Number of medical problems in past year (mean, range)	3.2 (0-15)	4.4 (0-15)	3.7 (0-9)	3.4 (0-12)	2.5 (0-6)	2.6 (0-12)	**<0.01**†
Transplant-related	0.3 (0-2)	0.3 (0-2)	0.3 (0-2)	0.4 (0-2)	0.2 (0-2)	0.2 (0-2)	0.10†
Not transplant-related	2.9 (0-14)	4.1 (0-14)	3.4 (0-9)	3.0 (0-10)	2.3 (0-5)	2.4 (0-12)	**0.01**†
IS medication (%)							
Corticosteroids	74	66	62	78	62	92	**<0.01***
Cyclosporine	23	16	26	22	26	23	0.80*
Tacrolimus	42	81	64	45	36	12	**<0.01***
Sirolimus	2	3	2	4	0	2	-
Azathioprine	46	3	31	50	42	77	**<0.01***
Mycophenolate mofetil	17	53	12	15	12	8	**<0.01***
Number of side-effects of IS medication (mean, range)	4.2 (0-29)	3.5 (0-11)	4.3 (0-27)	3.6 (0-21)	4.3 (0-18)	5.0 (0-29)	0.53†

NOTE: bolded values are significant

* X^2 test.

† Kruskal-Wallis test.

‡ Students *t* test.

the survey (56.4 years and 52.3 years, respectively; $P = 0.04$) and at the time of transplant (46.4 years and 42.2 years, respectively; $P = 0.02$).
Table 1 describes demographic and transplant-related characteristics of respondents, both for all respondents and for each time period. In particular, the long-term group differed significantly from other groups with respect to sex, age at transplantation, primary disease, length of hospital stay, and use of IS medication (Table 1). These differences may reflect the developments in organ transplantation in general, such as advances in medical and surgical procedures, and, more specifically, in the area of IS medication (eg, the introduction of cyclosporine and tacrolimus as therapeutic agents) over the past decades.

Prevalence rates of psychological problems at different time periods

Overall, 33.4% of the respondents experienced 1 or more clinically relevant symptom levels of anxiety, depression, or PTS (Table 2). Correlations between the psychological problems were strong (r = 0.58-0.73, $P < 0.01$). The highest percentage (46.9%) of respondents with clinically relevant symptom levels of all the psychological problems included in this study was found in the short-term group, whereas respondents in the intermediate group had the lowest percentage (25.7%).
However, the time groups did not differ significantly either with regard to mean levels of symptoms of anxiety, depression, or PTS, or with respect to point-prevalence rates of respondents with clinically high levels of anxiety, depression, or PTS (Table 2). Both anxiety and depression showed the highest prevalence rates in the short-term and long-term group, whereas PTS was more prevalent in the short-term and intermediate short-term group.

Relationship of transplant-related variables to psychological problems

In the total study population, only a few transplant-related variables showed significant bivariate associations with psychological problems (Table 3). Viral hepatitis and the number of side-effects from the IS medication were significantly associated with all of the psychological problems. In addition, the length of hospital stay and the number of transplant-related medical problems in the past year were significantly associated with symptoms of depression. The number of both transplant-related and transplant-unrelated medical problems in the past year were significantly associated with symptoms of PTS. However, bivariate correlation analyses of transplant-related variables with symptoms of anxiety, depression, and PTS per time group revealed additional significant correlations within the groups (Table 3).

Relationship of transplant-related variables to symptoms of anxiety

Bivariate correlation analyses showed that the number of side-effects from the IS medication was significantly associated with symptoms of anxiety within all time groups. Alcoholic liver disease ($r = 0.41$, $P = 0.02$) was associated with symptoms of anxiety in the short-term group. Viral hepatitis ($r = 0.30$, $P = 0.01$) was associated with symptoms of anxiety in the intermediate group. The number of complications in the clinical phase ($r = -0.32$, $P = 0.04$), the use of cyclosporine ($r = 0.31$, $P = 0.048$), and the use of tacroli-

Table 2: Prevalence and mean scores and SDs of clinically relevant levels of symptoms of anxiety, depression, and PTS of all respondents and in the groups according to time since transplantation

	All (n = 279)	Short-Term Group (0.5 to <2 years; n = 32)	Intermediate Short-Term Group (2 to <5 Years; n = 42)	Intermediate Group (5 to <10 years; n = 74)	Intermediate Long-Term Group (10 to <15 years; n = 65)	Long-term Group (≥15 years; n = 66)	Differences Between Groups (*P* value)
Psychological problems							
Respondents with clinically relevant symptom levels (%)	33.4	46.9	28.6	25.7	35.4	36.4	0.25*
Type of psychological health problems (%)							
Anxiety	13.3	12.5	9.5	12.2	18.5	12.1	
Depression	2.2	0	0	1.4	4.6	3.0	
Posttraumatic stress	2.5	3.1	4.8	4.1	1.5	0	
Anxiety + Depression	7.5	15.6	4.8	4.1	4.6	12.1	
Anxiety + PTS	1.1	3.1	2.4	0	0	1.5	
Depression + PTS	0.4	0	0	0	1.5	0	
Anxiety + Depression + PTS	6.5	12.5	7.1	4.1	4.6	7.6	
Anxiety							
Prevalence (%)	28.7	46.9	23.8	20.3	27.7	33.3	0.06*
Mean (SD)	33.9 (10.5)	35.5 (10.8)	33.7 (10.4)	31.5 (9.8)	34.1 (8.9)	35.7 (12.1)	0.16†
Depression							
Prevalence (%)	16.5	28.1	11.9	9.5	15.4	22.7	0.08*
Mean (SD)	8.5 (9.1)	10.7 (9.1)	7.3 (7.0)	6.4 (7.5)	9.1 (8.7)	10.1 (11.5)	0.07†
Posttraumatic stress							
Prevalence (%)	10.0	15.6	14.3	8.1	7.7	9.1	0.61*
Mean (SD)	29.1 (7.3)	30.3 (7.9)	30.0 (7.8)	28.7 (7.1)	28.1 (6.3)	29.2 (7.7)	0.68†

* X^2test.

† Kruskal-Wallis test.

Table 3. Bivariate correlations of transplant-related variables with symptoms of anxiety, depression, and PTS of all respondents and in the 5 groups according to the time since transplantation, significant main effects, and significant interaction effects between transplant-related variables and time groups

	Bivariate correlation (Pearson's r)							
	All (n = 279)	**Short-Term Group (0.5 to <2 years; n = 32)**	**Intermediate Short-Term Group (2 to <5 Years; n = 42)**	**Intermediate Group (5 to <10 years; n = 74)**	**Intermediate Long-Term Group (10 to <15 years; n = 65)**	**Long-term Group (≥15 years; n = 66)**	**GLM Main effect: B (*P* value)**	**GLM Interaction effect B (*P* value) Reference category = 0.5 to <2 years**
Symptoms of anxiety								
Viral hepatitis	**0.12***	-0.03	0.08	**0.30***	0.09	0.15	B = 0.13 (0.03)	NS
Alcoholic liver disease	0.03	**0.41***	(a) -0.11	(b) -0.16	0.08	0.06	NS	(a) B = -0.53 (0.02) (b) B = -0.44 (0.01)
Number of complications in clinical phase	-0.10	0.23	(a) **-0.32***	-0.09	-0.01	-0.15	NS	(a) B = -0.06 (0.02)
Number of transplant-related medical problems in past year	0.06	0.09	-0.06	-0.07	**0.34**†	0.18	NS	NS
Number of side-effects from IS medication	**0.33**†	**0.37***	**0.54**†	**0.28***	**0.27***	**0.27***	B = 0.02 (<0.01)	NS
Use of prednisolone	0.06	0.24	0.26	0.10	0.22	(d) **-0.26***	NS	(d) B = -0.48 (0.01)
Use of cyclosporine	0.12	-0.17	**0.31***	0.03	0.16	0.18	NS	NS
Use of tacrolimus	-0.03	0.16	**-0.33***	0.14	-0.14	<0.01	NS	NS
Symptoms of depression								
Viral hepatitis	**0.16**†	0.06	0.13	**0.33**†	0.18	0.03	B = 0.64 (<0.01)	NS
Alcoholic liver disease	0.04	**0.35***	-0.02	(b) -0.15	0.06	0.01	NS	(b) B = -1.59 (0.03)
Acute liver failure	-0.01	**-0.39***	0.10	< 0.01	(c) 0.13	0.05	NS	(c) B = 2.41 (0.02)
Cryptogenic cirrhoses	-0.07	-0.02	-0.09	-0.01	0.23	**-0.27***	NS	NS
Length of hospital stay	**0.17**†	0.18	-0.01	0.11	**0.30***	0.22	B = 0.01 (<0.01)	NS

Number of transplant-related medical problems past year	**0.16**†	0.16	0.04	0.11	**0.46**†	0.14	B = 0.42 (<0.01)	NS
Number of side-effects from IS medication	**0.42**†	**0.45***	**0.59**†	**0.33**†	**0.48**†	**0.35**†	B = 0.10 (<0.01)	NS
Use of tacrolimus	-0.05	0.10	**-0.32***	0.03	-0.11	0.02	NS	NS
PTS symptoms								
Viral hepatitis	**0.18**†	0.05	0.22	**0.39**†	0.05	**0.28***	B = 0.06 (<0.01)	NS
Length of hospital stay	0.09	0.36*	0.01	0.12	0.33†	(d) **<0.01**	B = 0.01 (0.03)	(d) B = -0.01 (0.03)
Number of transplant-related medical problems in past year	**0.18**†	**0.48**†	0.14	(b) **0.08**	**0.38**†	(d) <0.01	B = 0.04 (<0.01)	(b) B = -0.09 (0.03) (d) B = -0.10 (0.02)
Number of non-transplant-related medical problems in past year	**0.15***	0.09	0.08	-0.04	0.21	**0.36**†	B = 0.01 (0.02)	NS
Number of side-effects from IS medication	**0.40**†	**0.43***	**0.49**†	**0.31**†	**0.60**†	**0.31***	B = 0.01 (0.01)	NS
Use of prednisolone	0.06	0.17	0.14	-0.08	**0.28***	(d) **-0.27***	NS	(d) B = -0.14 (0.01)
Use of cyclosporine	0.10	0.04	0.20	-0.02	0.06	**0.26***	NS	NS
Use of tacrolimus	-0.06	0.03	-0.24	0.07	**-0.26***	-0.08	NS	NS

NOTE: (a) indicates the interaction effect of the "2 to <5 years" group with the reference category of 0.5 to <2 years; (b) indicates the interaction effect of the "5 to <10 years" group with the reference category of 0.5 to <2 years; (c) indicates the interaction effect of the "10 to <15 years" group with the reference category of 0.5 to <2 years; (d) indicates the interaction effect of the "≥15 years" group with the reference category of 0.5 to <2 years. Bolded values are significant.
*Significant at *P* <0.05 level (2-tailed).
†Significant at *P* <0.01 level (2-tailed).

mus (r = -0.33, P = 0.04) where associated with symptoms of anxiety in the intermediate short-term group. The number of transplant-related medical problems in the past year were associated with symptoms of anxiety in the intermediate long-term group (r = 0.34, P = 0.01). The use of prednisolone (r = -0.26, P = 0.03) was associated with symptoms of anxiety in the long-term group. With respect to potential confounding variables the number of life events (r = 0.26, P <0.01) and marital status (r = 0.16, P = 0.01) were significantly associated with symptoms of anxiety.
The separate GLM analyses, which included the significantly associated transplant-related variables with symptoms of anxiety, showed a main effect of the following variables: viral hepatitis, number of side-effects from the IS medication, and use of cyclosporine. Significant interaction effects with the time groups were found for 3 variables: alcoholic liver disease, number of complications in the clinical phase, and use of prednisolone (Table 3).
The overall GLM analysis of all variables with significant main or interaction effect with symptoms of anxiety, showed that when we controlled for confounding variables, viral hepatitis, and the number of side-effects from the IS medication had a main effect on the symptoms of anxiety (Table 4). Significant interaction effects were found for alcoholic liver disease and the number of complications in the clinical phase. Regarding alcoholic liver disease the intermediate short-term group (B = -0.44, P = 0.01), and the intermediate group (B = -0.55, P <0.01) differed significantly from the short-term group. As for the number of complications in the clinical phase the intermediate short-term group (B = -0.05, P = 0.02) differed significantly from the short-term group.

Relationship of transplant-related variables to symptoms of depression

With respect to depressive symptoms, the bivariate correlation analyses showed that the number of side-effects from the IS medication was significantly associated within all time groups (Table 3). Alcoholic liver disease (r = 0.35, P = 0.048) and acute liver failure (r = -0.39, P = 0.03) were significantly associated with symptoms of depression in the short-term group. Viral hepatitis (r = 0.33, P <0.01) was significantly associated with symptoms of depression in the intermediate group, as was cryptogenic cirrhosis in the long-term group (r = -0.27, P = 0.03). The use of tacrolimus (r = -0.32, P = 0.04) was associated with symptoms of depression in the intermediate short-term group. The number of transplant-related medical problems in the past year (r = 0.46, P <0.01) and the length of hospital stay (r = 0.30, P = 0.02) were associated with symptoms of depression in the intermediate long-term group. As for potential confounding variables, the number of life events (r = 0.37, P <0.01) and marital status (r = 0.25, P <0.01) were significantly associated with symptoms of depression.
The separate GLM analyses, which included the transplant-related variables significantly associated with symptoms of depression, showed a main effect of the following variables: viral hepatitis, length of hospital stay, number of transplant-related medical problems in the past year, and number of side-effects from the IS medication. Significant interaction effects were found for 2 variables: alcoholic liver disease and acute liver failure (Table 3).
The overall GLM analysis of all variables with significant main effects or interaction ef-

Table 4. Unstandardized regression coefficients of GLM analyses of transplant-related variables with main effects or interaction effects per psychological problem with controlling for confounding variables

		Parameter Estimates 95% Wald Confidence Interval		Significance
Variable	B	Lower	Upper	(*P* Value)
Symptoms of Anxiety				
Intercept	1.99	1.74	2.23	**<0.01**
Main effects				
Alcoholic liver disease	0.43	0.18	0.68	**<0.01**
Viral hepatitis	0.16	0.05	0.27	**<0.01**
Number of complications clinical phase	0.02	-0.01	0.06	0.19
Number of side-effects from IS medication	0.02	0.01	0.02	**<0.01**
Number of life events	0.05	0.02	0.08	**<0.01**
Interaction effects*				
Alcoholic liver disease				
Intermediate short-term group (2 to <5 years)	-0.44	-0.76	-0.11	**0.01**
Intermediate group (5 to <10 years)	-0.55	-0.89	-0.22	**<0.01**
Number of complications in clinical phase				
Intermediate short-term group (2 to <5 years)	-0.05	-0.09	-0.01	**0.02**
Symptoms of Depression				
Intercept	1.01	0.58	1.55	**<0.01**
Main effects				
Alcoholic liver disease	1.40	0.54	2.25	**<0.01**
Viral hepatitis	0.72	0.34	1.11	**<0.01**
Length of hospital stay	0.01	0.002	0.02	**0.01**
Number of transplant-related medical problems in past year	0.23	0.01	0.46	**0.04**
Number of side-effects from IS medication	0.08	0.06	0.10	**<0.01**
Number of life events	0.25	0.15	0.34	**<0.01**
Interaction effects*				
Alcoholic liver disease				
Intermediate group (5 to <10 years)	-1.43	-2.55	-0.298	**0.01**
PTS symptoms				
Intercept	1.36	1.29	1.43	**<0.01**
Main effects				
Viral hepatitis	0.06	0.03	0.10	**0.01**
Length of hospital stay	0.004	0.00	0.01	**0.03**
Number of transplant-related medical problems in past year	0.07	0.01	0.12	**0.02**
Number of side-effects from IS medication	0.01	0.004	0.01	**<0.01**
Number of life events	0.01	0.004	0.02	**<0.01**
Interaction effects*				
Number of transplant-related medical problems in past year				
Long-term group (≥15 years)	-0.09	-0.17	-0.02	**0.02**
Length of hospital stay				
Long-term group (≥15 years)	-0.004	-0.01	0.00	**0.04**

NOTE: Only variables with significant main effects or interaction effects in the overall GLM analyses are shown. Bolded values are significant. * The reference category is 0.5 to <2 years.

fects with symptoms of depression showed that when we controlled for confounding variables, viral hepatitis, the length of hospital stay, the number of transplant-related medical problems in the past year, and the number of side-effects from the IS medication had a main effect on the symptoms of depression (Table 4). A significant interaction effect was found only for alcoholic liver disease, which showed significant differences between the intermediate group (B = -1.43, *P* <0.01) and the short-term group.

Relationship of transplant-related variables to PTS symptoms

Also, with respect to symptoms of PTS, the bivariate correlation analysis showed that the number of side-effects from the IS medication were significantly associated with symptoms of PTS in all time groups (Table 3). Viral hepatitis was associated with symptoms of PTS in the intermediate and long-term groups (*r* = 0.39, *P* = 0.01 and *r* = 0.28, *P* = 0.03, respectively). The length of the hospital stay (*r* = 0.36, *P* = 0.04) and the number of transplant-related medical problems in the past year (*r* = 0.48, *P* = 0.01) were associated with symptoms of PTS in the short-term group. In the intermediate long-term group, the length of hospital stay (*r* = 0.33, *P* <0.01), the number of transplant-related medical problems in the past year (*r* = 0.38, *P* <0.01), the use of prednisolone (*r* = 0.28, *P* = 0.03), and the use of tacrolimus (*r* = -0.26, *P* = 0.03), were associated with PTS symptoms. However, the number of non-transplant-related medical problems in the past year (*r* = 0.36, *P* = 0.01), the use of prednisolone (*r* = -0.27, *P* = 0.03), and the use of cyclosporine (*r* = 0.26, *P* = 0.04), were associated with PTS symptoms in the long-term group. As for potential confounding variables, the number of life events (*r* = 0.27, *P* <0.01) and marital status (*r* = 0.17, *P* = 0.01) were significantly associated with symptoms of PTS.

The separate GLM analyses, which included the transplant-related variables significantly associated with symptoms of PTS, showed a main effect of the following variables: viral hepatitis, length of hospital stay, number of transplant-related medical problems in the past year, number of non-transplant-related medical problems in the past year, and the number of side-effects from the IS medication. Significant interaction effects were found for 3 variables: length of hospital stay, number of transplant-related medical problems in the past year, and use of prednisolone (Table 3).

The overall GLM analysis of all variables with main effects or interaction effects with symptoms of PTS showed that when we controlled for confounding variables, viral hepatitis and the number of side-effects from the IS medication had a main effect on the symptoms of PTS. Significant interaction effects were found for the number of transplant-related medical problems in the past year and the length of hospital stay. For both variables, differences in significance were found between the long-term group and the short-term group (transplant-related medical problems in the past year: B = -0.09, *P* = 0.02; length of hospital stay: B = -0.004, *P* = 0.04) (Table 4).

DISCUSSION

The aims of our study were to examine point-prevalence rates of symptoms of anxiety, depression, and PTS among liver transplant recipients at different time periods after transplantation, to identify transplant-related variables associated with these psychological problems, and to examine whether the associated transplant-related variables differed between groups according to time since transplantation. Our study showed that a substantial subset of transplant recipients experienced psychological problems, both shortly after liver transplantation and in the long run. Overall, 33.4% of the liver transplant recipients in our study showed high symptom levels of psychological problems. More specifically, 28.7% had high symptom levels of anxiety, 16.5% high symptom levels of depression, and 10.0% high symptom levels of PTS. Although point-prevalence rates between the time groups did not differ significantly, these differences were considered clinically relevant. Symptoms of anxiety and depression were more prevalent in the first 2 years and in the long-term (≥15 years) after transplantation. Symptoms of PTS were more prevalent in the first 5 years after transplantation. The lower prevalence rates in symptom levels of PTS in the following years suggest that recipients learned to cope with the traumatic aspects of their transplantation.

The prevalence rates of symptoms of anxiety and depression in our sample are in line with prevalence rates described by other studies: higher prevalence rates in the first years after transplantation,[8-10] and stabilization at a lower level in the following years.[11,14-16] In the long run (>10 years) after liver transplantation, slightly higher but not statistically significant prevalence rates of symptoms of anxiety and depression were found.

Regarding transplant-related variables associated with psychological problems, we found a main effect of viral hepatitis and the number of side-effects from the IS medication for all of the psychological problems. The length of hospital stay and the number of transplant-related medical problems in the past year were found to have a main effect on the symptoms of depression. Interaction effects were found for alcoholic liver disease regarding anxiety and depression and for the number of complications in the clinical phase regarding anxiety; they were also found for PTS for the length of hospital stay, and the number of transplant-related medical problems in the past year.

With respect to viral hepatitis, this is in line with previous studies. In particular, the recurrence of hepatitis C is often associated with anxiety [28,40] and depression.[28,41-43] We found that viral hepatitis was also associated with symptoms of PTS. However, regarding alcoholic liver disease, often no influence on anxiety or depression was found in other studies.[44,45] This might be due to that in these studies, no distinction was made regarding time periods since transplantation because we found that the association of alcoholic liver disease differed significantly between groups: there was a lower influence of alcoholic liver disease in the intermediate group compared to the short-term group. Beforehand, we expected that, in line with other studies,[1,26] the duration of the stay in the ICU would be associated with psychological problems, but this finding was not supported by our data. We found that the length of the hospital stay showed a main effect on symptoms of depression and PTS. However, this variable differed significantly

between time groups probably because of the developments in the field of liver transplantation over time. Therefore, the relevance of this finding remains unclear.
In line with previous studies,[9,19,21] transplant-related medical problems had a main effect on the symptoms of depression and PTS. It would be interesting to explore in future studies which specific medical problems (eg, nonanastomotic biliary strictures, rejection, disease recurrence) have the most influence on the development of psychological problems. Regarding PTS, a negative interaction effect was found with the long-term group, and this indicated that transplant-related medical problems were of lower influence in this group. Although we did not find a significant main effect of non-transplant-related medical problems, these problems may become of more importance in the long term because they may become more severe (eg, cardio-vascular problems, cancer). However, we were able to consider the number of medical problems only in the past year, and we did not account for the severity of these problems. This should be further examined in future studies.
In particular, the number of side-effects from the IS medication was found to be of importance, and it was associated with symptoms of anxiety, depression and PTS in all time periods. This indicates that side-effects from IS medications are an ongoing burden for transplant recipients. As for specific IS medications, no main effects or interaction effects were found. However, the differences between groups regarding the use of IS medications may have influenced these results.
Except for the number of life events other than transplantation, we found no influence on psychological problems of other well-known confounding variables such as age, sex, marital status and employment.

The strengths of this study are the adequate overall sample size (n = 281) and the high response rate (75%). Except for age at the time of the survey and at the time of transplantation, the sample was representative of the target population. Although we found no associations between age at time of study or age at time of transplantation with psychological problems in our study, this could have biased our results because younger age is considered a risk factor for psychological problems.[21] Selection bias may also have occurred due to selective survival of psychologically healthy recipients, given the association between psychological problems and mortality found in other studies.[20]
A limitation of our study is that the sample sizes, especially in the short-term groups, were small. This may have hampered our attempt to detect significant differences between groups. The groups also differed with respect to some baseline characteristics (eg, sex and age) and transplant-related variables (eg, primary disease and length of hospital stay) mainly because of developments in the area of transplantation. Because of these limitations, the interpretation of the results of our study need to be handled carefully and generalizability is limited. Because of the cross-sectional design of our study, conclusions on inferences about the development of psychological problems or about the predictive value of transplant-related variables on psychological problems could not be drawn. Therefore, a prospective study is needed to examine how psychological problems develop over time and the predictive value of transplant-related variables associated with these problems that were found in this study.

In summary, a significant subset (33%) of liver transplant recipients experience psychological problems after transplantation, especially in the first 2 years and in the long run (>10 years after transplantation). Transplant-related variables associated with psychological problems were mainly viral hepatitis, alcoholic liver disease, the number of transplant-related medical problems in the past year, and the length of hospital stay. In particular, the number of side-effects from of IS medication seems to play an ongoing role with respect to psychological problems after transplantation. This may reflect the ongoing burden that the IS medication regimen places on transplant recipients. The point-prevalence rates of psychological problems warrants routine screening to identify these problems. In addition, psychological counseling after transplantation is important, not only shortly after transplantation but also in the long run. Finally, side-effects from the IS medication should be monitored, and actions should be undertaken to diminish the impact on the psychological problems of transplant recipients.

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