What's on your mind?

Emotions and perceptions of liver transplant candidates and recipients

Coby Annema

Het ondergaan van een levertransplantatie is niet een enkele gebeurtenis maar een heel proces. Dit concrete proces omvat meerdere facetten. Wat dit proces doet met de emoties van een persoon is ongrijpbaarder en kent vele nuances. Tegelijkertijd grijpen deze processen op elkaar in en zijn ze onlosmakelijk met elkaar verbonden.

The study described in this thesis was performed within the University Medical Center Groningen, Groningen, the Erasmus Medical Center, Rotterdam, and the Leiden University Medical Center, Leiden, all in the Netherlands. Financial support for this study was kindly given by the University Medical Center Groningen.
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WHAT'S ON YOUR MIND?

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CHAPTER

1

GENERAL INTRODUCTION

For patients with end-stage liver disease, liver transplantation is the only treatment option. Orthotopic liver transplantation is a surgical procedure, in which the diseased liver is replaced by a donor liver. The first liver transplant was performed in the USA by Thomas E. Starzl in March 1963.[1] Since the start of the liver-transplant program in the Netherlands in 1979, over 3000 liver transplantations have been performed on more than 2500 patients (Eurotransplant, 2016). The main primary liver diseases before transplantation were viral hepatitis, cholestatic diseases, and hepatocellular carcinoma. At this point in time, liver transplantations are performed in three liver transplant centers in the Netherlands: the University Medical Center Groningen in Groningen (since 1979), the Erasmus Medical Center in Rotterdam (since 1986), and the Leiden University Medical Center in Leiden (since 1992). In the Netherlands, each year about 200 patients with end-stage liver disease are placed on the waiting list for a liver transplant, while about 145 patients receive a transplant.[2]

Due to improvements in medical and surgical procedures and immunosuppressive drugs, the clinical outcomes and survival of liver transplant patients have improved over the past decades. The European Liver Transplant Registry (www.ELTR.org) reports survival rates at 1, 5, and 10 years after liver transplantation of 84%, 73%, and 63% respectively, and graft survival rates at 1, 5, and 10 years of 79%, 66%, and 56% respectively.

Psychological consequences of liver transplantation

As a consequence of the improved survival after liver transplantation, other outcomes such as health-related quality of life and psychosocial consequences of transplantation have become increasingly important targets of evaluation.[3] Although health-related quality of life improves after liver transplantation, it does not restore to the level of the general population.[4-6] More specifically, meta-analyses have 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.[7,8]

This might be due to the stressful nature of the transplant experience both before and after the transplantation. Having to undergo a liver transplantation is a major event in a person's life. After being diagnosed with a life-threatening disease and learning about the need for a transplant, patients have to wait for a suitable donor. For transplant candidates the waiting-list period is a period of unpredictability and uncertainty. They do not know when a donor organ will become available or if this donor organ will arrive in time. Each year, approximately 10%-15% of transplant candidates die while they are on the organ transplant waiting list.[2] If a donor organ becomes available, patients have to undergo major surgery that may be accompanied by medical complications. In general, the transplantation itself is beneficial for the health of the transplant recipients, but they also have to adjust to a life with a life-long regimen of immunosuppressive drugs and adherence to strict guidelines, and may have to deal with serious, potentially life-ending, complications. In fact, transplant recipients trade a chronic disease for a chronic situation. Given these stressors, it is not unlikely that the transplant process will cause psychological distress in a subset of transplant candidates and recipients, such as clinically relevant symptoms of anxiety, depression, and/or posttraumatic stress.

Anxiety

Symptoms of anxiety, such as feeling tense, upset, or worried, can be a burden all by themselves but may also interfere with the daily functioning of transplant candidates and recipients. Prevalence rates of clinically relevant symptom levels of anxiety are described in 11%-52% of the adult liver transplant candidates,[9,10] and in 6%-33% of the adult liver transplant recipients.[11,12] Although several demographic variables, such as female gender, marital status, and employment status,[13-15] clinical variables, such as primary liver disease, time since transplantation, time on waiting list, and use of steroids,[13-17] and individual variables, such as self-perceived health status, coping style, and personality[18-20] have been associated with clinically relevant symptom levels of anxiety, these results are still inconclusive. The impact of anxiety on outcomes after transplantation is even less well studied. So far, a few studies have found that clinically relevant symptom levels of anxiety have a negative impact on outcomes after transplantation: impaired quality of life,[11,14,21,22] lower medication adherence,[23] and lower survival.[24]

Depression

Symptoms of depression, such as persistent feelings of sadness and worthlessness, and loss of interest in previously enjoyed activities, affect how people feel, think, and behave. Among adult liver transplant candidates prevalence rates of 17%-60% of clinically relevant symptom levels of depression have been described.[10,12] In adult liver transplant recipients, prevalence rates of 4%-58% have been described.[4,13] Variables associated with clinically relevant symptom levels of depression are basically the same as for symptoms of anxiety. Only with respect to clinical variables, medical complications after the transplant, such as graft failure, diseases recurrence, and rejection, have been mentioned more often as associated variables.[14-16,25] Regarding individual variables, depression before the transplant and low self-efficacy have been identified as influencing factors.[21,26] However, results regarding variables associated with depression in liver transplant candidates and recipients also remain inconclusive. With respect to outcomes, depressive symptoms have been related to impaired quality of life in transplant candidates and recipients,[11,14,15,25] and seem to have a negative impact on survival after transplantation.[24,27,28]

Posttraumatic stress

Showing high symptom levels of posttraumatic stress, such as intrusive memories, avoidance of reminders of the event, hopelessness, and hyper-arousal, can be seen as a failure to adapt to extreme stress and may lead to posttraumatic stress disorder (PTSD). PTSD is described as a trauma and stress-related disorder, triggered by exposure to actual or threatened death, serious injury or sexual violation, either experiencing it or witnessing it,[29] and is often accompanied by impairments in areas of functioning. Posttraumatic stress has been less well studied in adult liver transplant recipients. One study among liver transplant candidates revealed a prevalence rate of PTSD of 2%,[9] while PTSD after transplantation has been found in 2%-9% of the liver transplant recipients based on DSM-IV criteria,[30,31] and 23%-47%[4,12] based on clinically relevant symptom levels. Regarding associated variables, only demographic and clinical vari-

ables have been investigated, showing that a lower educational level, a higher Model for End-stage Liver Disease-score (MELD), medical complications, a shorter waiting period, a longer stay in the Intensive Care Unit, and an episode of acute rejection of the transplanted organ are associated with higher symptom levels of PTSD.[4,30] The impact of PTSD on outcomes after liver transplantation has not been studied so far.

The above mentioned studies show that psychological problems are common in liver transplant candidates and recipients. However, relatively little attention has been paid to the subjective experience and psychological processing of the transplant process.[32] The care for liver transplant candidates and recipients is usually provided by a multidisciplinary team of medical doctors, surgeons, nurse practitioners, staff nurses, social workers, and physiotherapists. Nursing care for transplant recipients mainly focuses on the ability to perform everyday tasks and a return to daily living. Counseling by a psychologist or psychiatrist is provided on an as-needed basis, for example in cases of alcohol-dependency or if psychiatric problems are suspected.
Despite the multidisciplinary approach, the focus of care for transplant patients is mainly on the somatic medical management of the patient both before and after transplantation.[33] In addition to this, studies on the psychosocial aspects of transplantation in Dutch liver transplant candidates and recipients have focused mainly on quality of life and non-adherence.[34-37] Therefore, little is known about psychological problems in Dutch liver transplant candidates and recipients. To be able to optimize the psychosocial care for liver transplant candidates and recipients, more insight into the psychological functioning of those patients is needed.

The Psychological Aspects of Transplantation-study

The aim of the Psychological Aspects of Transplantation-study (PATx) was to examine psychological problems among adult Dutch liver transplant candidates and recipients, both in the short term and long term after transplantation, by gaining insight into prevalence rates of symptoms of anxiety, depression, and posttraumatic stress, by examining demographic, clinical, and individual characteristics associated with these psychological problems, and by examining their association with outcomes after transplantation. For this purpose, the overall study comprised both a cross-sectional study and a prospective cohort study.
In the cross-sectional study, we examined the prevalence rates of anxiety, depression, and posttraumatic stress and their associated variables, from the short term (>6 months) after the transplantation to the long term (>15 years) after transplantation. All liver transplant recipients who received post-transplant care at the University Medical Center Groningen (UMCG) in April 2010 were invited to participate. Liver transplant recipients who were transplanted between 1979 and October 2009 at the UMCG, received their transplant at an adult age, and were still receiving post-transplant care at the UMCG were included. Transplant recipients who were unable to fill out a questionnaire (due to impairments in physical, mental or cognitive functioning, or due to a language barrier), who were enlisted for re-transplantation, or who were lost to follow-up care were excluded. Eligible recipients received an explanatory letter together with a

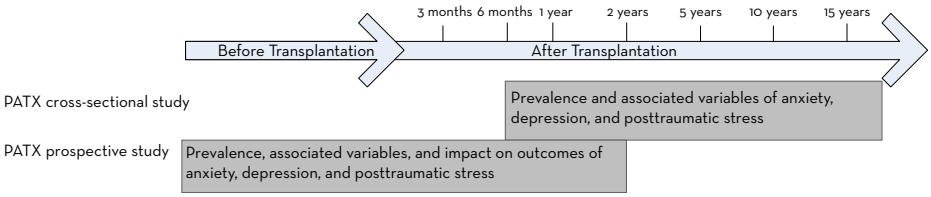

Figure 1. Overview PATx-study.

questionnaire and an informed consent form regarding permission to obtain data from the recipient's medical record.

The prospective cohort study was performed among transplant patients from all three liver transplant centers in the Netherlands: the University Medical Center Groningen (UMCG), the Erasmus Medical Center of Rotterdam (EMC), and the Leiden University Medical Center (LUMC). The study started in October 2009 in the UMCG, followed by the EMC in June 2011, and the LUMC in September 2011.

Transplant candidates who were on the waiting list at the start of the study, or were placed on the waiting list after the start of the study until April 2013, were asked to participate. Inclusion criteria for this study were: ≥18 years of age, and receiving medical treatment in one of the three transplant centers. Exclusion criteria were: unable to fill out a questionnaire due to physical, mental, or cognitive functioning, or due to a language barrier.

After written informed consent, respondents received a baseline questionnaire (T0). Measurements of psychological functioning were repeated every six months after inclusion in the study until transplantation or removal from the waiting list. After transplantation, respondents filled out a questionnaire at three (T1), six (T2), twelve (T3), and twenty-four (T4) months after transplantation. Transplant recipients who could not be included in the study before transplantation (eg, in case of acute liver failure or transplantation soon after placement on the waiting list) were invited to participate in the study, starting at 3 months after transplantation. Clinical data were retrieved by medical record review.

Power analysis, based on a difference in symptom levels of posttraumatic stress of at least 10%, and on inclusion of five associated variables, revealed that a sample size of n = 87 liver transplant recipients, who filled in a questionnaire at all five measurement-points, was needed to answer our various research questions.

Opinions of transplant candidates and recipients concerning topics related to the transplant process

Knowledge about the functioning of transplant candidates and recipients is important in order to provide appropriate care for this patient group. Moreover, it is important to know how patients think about topics related to the transplant process which might influence care or policies. In recent years, two topics of interest for transplant patients received increased attention: the principle of anonymity of organ donation and shared decision making regarding the acceptance of an organ offer.

The principle of anonymity of organ donation was questioned by the general public and by a subset of transplant recipients in reaction to a television documentary, in which transplant recipients were given the possibility of meeting the family of their donor. In the Netherlands, the anonymity of organ donors and recipients is protected by legislation to avoid possible undesirable and adverse consequences for both the donor family and the transplant recipient.[38-40] However, should the majority of transplant recipients favor a change in this policy, transplant healthcare professionals may play a role in advocating this change. To be able to make an informed decision as to advocate a change in the legislation regarding anonymity of organ donation, the opinion of Dutch liver transplant recipients about the principle of anonymity of organ donation and direct contact with the donor's family was investigated.

Shared decision making (SDM) between health care providers and patients concerning treatment options has received increased attention in the medical literature in recent years.[41-43] SDM refers to the process in which a healthcare provider communicates personalized information about the options, outcomes, probabilities, and the uncertainties of treatments available to the patient, and the patient communicates his or her values and the relative importance ascribed to the benefits and potential harms.[44] Although SDM has been examined and implemented in clinical settings,[45,46] little attention has been paid to SDM in the field of solid organ transplantation.[41,47] In the field of liver transplantation, SDM would involve a discussion of, the use of standard criteria donors (SCD) versus extended criteria donors (ECD), organ availability, and the timing of transplantation.[41] But also the acceptance of a specific donor offer could be discussed. SDM at time of donor offer would involve a discussion about the donor-related risks of the organ offered, and the willingness to accept a specific ECD organ, versus the risk of remaining on the waiting list, while hoping for a better donor. However, little is known about the willingness of transplant recipients to be involved in the decision making process regarding accepting a donor offer and about the information they would like to receive. Therefore, opinions regarding these topics were explored.

Because both of the abovementioned topics are related to the donor and to communication about the donation, a combined study regarding these topics was carried out.

The Communication about Donation-study

The aim of the "Communication about donation"-study was to gain insight into: 1) the opinion of Dutch liver transplant recipients about the principle of anonymity of organ donation and direct contact with the donor's family was investigated; and 2) the willingness of Dutch liver transplant candidates and recipients to be involved in the decision making process regarding accepting a donor offer and the information they would like to receive about donor-related risks.

This cross-sectional study was performed among liver transplant candidates and recipients receiving treatment at the UMCG in the fall of 2012. All liver transplant recipients transplanted at the UMCG between 2000 and 2010, who received their transplant at an adult age, and who were still receiving post-transplant care at the UMCG, were invited to participate. In addition, adult liver transplant candidates, who were actively listed for transplantation, were invited to participate in the part of the study regarding SDM.

Eligible transplant candidates and recipients received a letter explaining the purpose of the study, a questionnaire and a pre-addressed and stamped return envelope.

Aims and outline

In this thesis, several psychosocial aspects associated with the liver transplant process were investigated. On the one hand, psychological problems and associated variables of liver transplant candidates and recipients, both in the short- and long-term after transplantation, were examined. On the other hand, opinions of liver transplant candidates and recipients regarding two topics of interest to these patient groups were explored. In addition, a research instrument measuring the emotional response to the receipt of a transplanted organ was translated and validated for use with Dutch transplant recipients. The outline of this thesis is as follows:

Chapters 2 and 3 describe the results of the cross-sectional part of the "Psychological Aspects of Transplantation"-study. **Chapter 2** reports the prevalence rates of psychological problems and associated transplant-related variables among 281 transplant recipients at different time periods after liver transplantation. In **Chapter 3** the validation of the Dutch version of the Transplant Effects Questionnaire, a research instrument measuring the emotional response to the receipt of a transplanted organ, is presented.

Chapters 4 and 5 discuss the results of the "Communication about Donation"-study. In C**hapter 4**, the opinions of Dutch liver transplant recipients concerning the principle of the anonymity of organ donation and their wish for direct contact with the donor's family, are described. **Chapter 5** reports the views of liver transplant candidates and recipients with respect to their role in the decision making process of accepting an organ offer.

Chapters 6 to 8 involve the results of the prospective cohort study part of the "Psychological Aspects of Transplantation"-study. In **Chapter 6,** the trajectories of anxiety and depression of liver transplant candidates during the waiting-list period are described. Furthermore, associated clinical and individual variables are explored. **Chapter 7** reports prevalence rates, symptom occurrence, and the nature of re-experiencing symptoms of posttraumatic stress disorder before and during the first year after liver transplantation. In **Chapter 8,** the course of symptoms of anxiety and depression before and during the first two years after liver transplantation are described. In addition, the association of demographic, clinical, and individual variables with the distinct trajectories of anxiety and depression, and the influence of these trajectories on outcomes regarding health-related quality of life and medication adherence are described.

Chapter 9 provides a general discussion of the study results, their clinical implications, and addresses possible directions for future research.

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CHAPTER

2

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

Coby Annema, Petrie F. Roodbol, Roy E. Stewart, Robert J. Porte, Adelita V. Ranchor

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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.

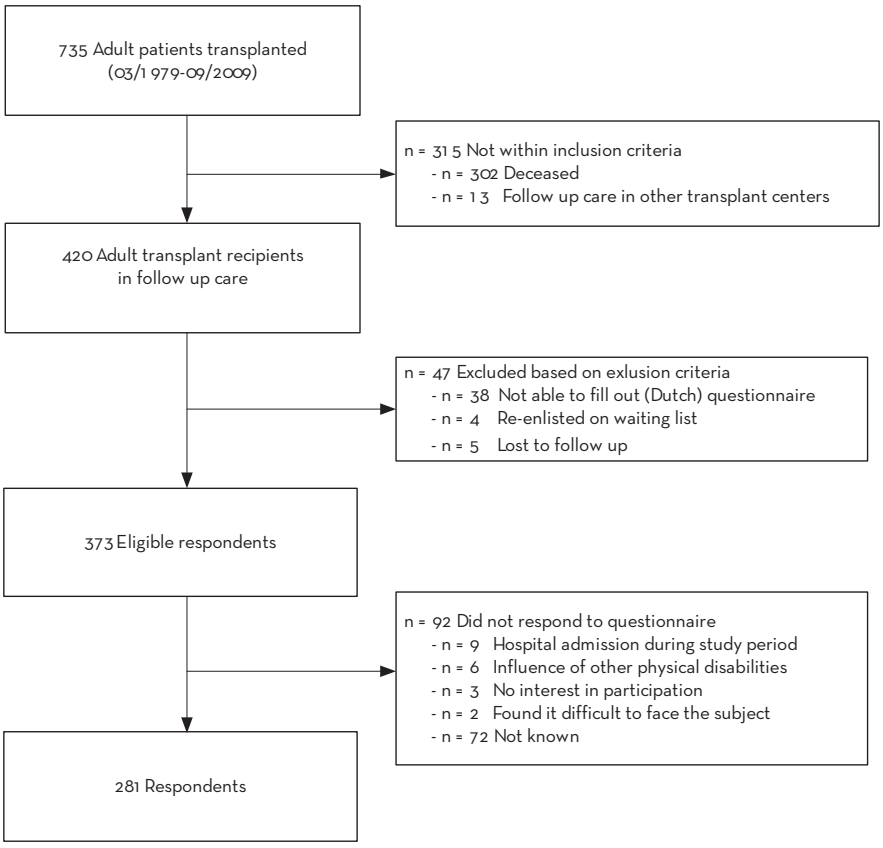

Figure 1. Flow diagram inclusion, exclusion and nonresponses of the study

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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CHAPTER 3

VALIDATION OF THE DUTCH VERSION OF THE TRANSPLANT EFFECTS QUESTIONNAIRE IN LIVER TRANSPLANT RECIPIENTS

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ABSTRACT

Little is known about the extent to which transplant recipients face emotional problems with the receipt of a transplanted organ. The Transplant Effects Questionnaire (TxEQ) enables the quantification of these problems. This study evaluates the psychometric properties of the Dutch translation of the TxEQ (TxEQ-NL) in a group of liver transplant recipients. Confirmatory factor analyses of the TxEQ-NL revealed an adequate fit with the original version. However, four items showed factor loadings <.40. Internal consistency was acceptable (.66-.79). The small correlations between the TxEQ-NL and generic measures of psychological functioning indicated that the constructs measured are related but distinguishable. Therefore, the TxEQ-NL adds a new dimension to the measurement of psychological functioning of transplant recipients.

INTRODUCTION

Liver transplantation has become the treatment of choice for end stage liver disease. Over the past decades, advances in medical and surgical technology, together with the availability of new immunosuppressive medications, have led to improved clinical outcomes, such as decreased morbidity, better survival rates, and prolonged life expectancy of liver transplant recipients. Nowadays, the 5- and 10-year survival rates of liver transplant recipients are 72% and 62% respectively (European Liver Transplant Registry, 2012).

Due to these improvements, other outcomes such as health-related quality of life and psychosocial consequences of transplantation become increasingly important targets of evaluation.[1] Information about different aspects of life relevant to organ transplant recipients, such as in-depth knowledge of physical, psychological, and social functioning, together with knowledge about health behaviour, may contribute to our understanding of how transplantation influences transplant recipients' lives. Consequently, it may improve the possibility to react appropriately to problems of the transplant recipient regarding these aspects.[2]

A point of interest with regard to psychological functioning is the emotional response of transplant recipients to the receipt of an organ. Qualitative studies in particular have shown that transplant recipients worry about their transplant,[3-5] have feelings of gratitude and guilt towards donors,[6-8] or find it hard to disclose about their transplants.[9] However, little is known about the extent to which these emotional problems occur, because these aspects are generally not covered by traditional research instruments.

To be able to quantify the emotional response to the receipt of a transplant organ, Ziegelmann et al.[10] developed the Transplant Effects Questionnaire (TxEQ). The original English version of the TxEQ (TxEQ-E) was developed on the basis of literature review, a focus group of transplant health care providers, and in-depth interviews with kidney transplant recipients. The TxEQ encompasses five topics important to transplant recipients: worries about the transplant, feelings of guilt towards the donor, disclosure about having a transplant, feelings and behaviour regarding medication adherence, and perceived responsibility to others. Although the TxEQ was initially developed as a research instrument, it has been indicated to be a useful screening tool for assessing problematic responses to the receipt of an organ.[10,11]

The TxEQ-E has been developed and tested in kidney transplant recipients, but given comparable results of the German version of the TxEQ (TxEQ-D) in a group of heart, lung, liver, and kidney transplant recipients, the TxEQ can be used in other organ transplant groups as well.[11] The TxEQ also has demonstrated its capacity for illustrating different emotional responses in transplant recipients.[10-12]

Psychometric testing of the TxEQ-E showed modest to good reliability scores with Cronbach's alpha between .72 and .86, and acceptable test-retest reliability (r = .60 – .80).[10] The TxEQ-D showed overall satisfactory reliability scores with Cronbach's alpha between .71 and .79.[11]

The Short Form Health Survey (SF-36) was used to test the construct validity of the TxEQ, and indicated that the subscales "Worry about the transplant" and "Feelings of

guilt towards the donor" were associated with lower scores on the mental health component of the SF-36. The overall small to moderate correlations (r =.12 - .30) indicate that the constructs of the TxEQ and the SF-36 can be distinguished from each other and can be seen as independent constructs.[11]

The TxEQ was translated into Dutch (TxEQ-NL) to be able to measure the emotional response to the receipt of an organ in Dutch transplant recipients. The aim of this study is to examine the psychometric properties of the TxEQ-NL by testing its factorial structure, internal consistency, and construct validity. To test the construct validity, the relationship between psychological functioning and the emotional and behavioural response to the receipt of an organ, as mentioned by Griva et al.[12] and Klaghofer et al.,[11] will be further examined. Therefore, the convergent validity (the degree to which a measure is correlated with other measures to which it is theoretically predicted to correlate with) and divergent validity (the degree to which a measure does not correlate with other measures that it theoretically should be independent of) between the subscales of the TxEQ-NL and measures of depression, anxiety, posttraumatic stress, and positive and negative affect will be examined. The relationship between the subscales of the TxEQ-NL and the concepts personality and coping -known to be related to psychological functioning- also were examined.

Expected convergent and divergent correlations

In general, few researchers have reported on the relationship between emotional responses and psychological functioning, personality style, or coping style of transplant recipients. However, worries about the transplant has been shown to lead to anxiety and depression.[3-5,13] Kidney transplant recipients who score high on the neurotic personality style were found to complain more about health issues.[14] This might indicate that they worry more about the transplants.

In a recent meta-analysis,[15] both shame (r = .43) and guilt (r = .28) were associated with depression. The recipients' feelings of guilt towards the donor after transplantation have also been related to poor organ integration and the development of psychiatric syndromes.[7,9,16] The recipients' use of avoidance, suppression, and denial coping have been described as defense mechanisms for dealing with feelings of sorrow, indebtedness, and guilt.[17]

Although several researchers have shown that disclosure after a traumatic experience has no effects on symptoms of anxiety, depression, or posttraumatic stress,[18,19] low disclosure among transplant recipients was found to be related to poor organ integration.[9] In colorectal cancer patients, an expressive disclosure group intervention was found to improve psychological functioning.[20]

Medication non-adherence has been associated with anxiety,[21] depression,[22-24] posttraumatic stress,[25,26] and negative affect[27] in transplant recipients. Additionally, personalities with low sense of conscientiousness[28] and the use of an active[29] or avoidance[30] coping style are associated with medication non-adherence.

Research on feelings of responsibility is scarce. Only Buldukoglu et al.[31] described that feelings of responsibility were related to worries about the transplant. This might indicate that feelings of responsibility are indirectly related to psychological functioning.

Table 1. Expected convergent and divergent correlations between TxEQ subscales and measures of psychological functioning, personality, and coping

TxEQ subscale	Worry about the transplant	Guilt towards the donor	Disclosure about the transplant	Adherence to immuno-suppressive medication	Responsibility towards others
Psychological functioning					
Depressive symptoms	+	+	-	-	o
Anxiety	+	+	-	-	o
Posttraumatic stress	+	+	-	-	o
Positive affect	o	o	o	o	o
Negative affect	+	+	-	-	o
Personality					
Conscientiousness	-	-	+	+	o
Neuroticism	+	+	o	-	+
Coping					
Avoidant	+	+	-	-	o
Task-oriented	o	o	o	+	+
Emotional	+	+	-	-	o

Note: + = expected positive correlation; - = expected negative correlation; o = null association expected

Table 1 summarizes the expected convergent and divergent correlations of the subscales of the TxEQ-NL with measures for psychological functioning, personality, and coping, based on the literature and general psychological knowledge. When no empirical support between concepts was found in the literature, expected correlations were based on theoretical psychological expectations of connections between these constructs. Overall, we expected to find small correlations (*r* between .10 and .30), with the correlations in support of convergent validity higher than correlations for divergent validity.

METHODS

Participants and procedure

Data were collected as part of a cross-sectional study on psychological consequences of transplantation among liver transplant recipients at the University Medical Center Groningen, the Netherlands, in April 2010. All liver transplant recipients transplanted at our center between 1979 and October 2009 who were transplanted at an adult age and who were still receiving post-transplant care at our center were invited to participate. Additional inclusion criteria were being able to fill in a Dutch questionnaire and

not being enlisted for re-transplantation. Of the 420 potentially eligible recipients, 373 met the inclusion criteria. They received an information letter, a questionnaire, and an informed consent form regarding permission to obtain data from the recipient's medical record. To ensure a frank response the questionnaires had code numbers and confidentiality was guaranteed. After 4 weeks, a reminder was sent to non-responders and another 2 weeks were allowed for completion. The study met the criteria for an exemption from institutional review board approval (METc2010.039).

Measures

The Transplant Effects Questionnaire and its translation

With permission from the authors, the TxEQ-E was translated into Dutch by three independent translators, and the items were subsequently compared and checked for use of natural language. After consensus was reached on a single Dutch translation for each item, the translated items were translated back into English by a native English speaker to check the accuracy of translation. Based on the back translation two items (8 and 14) were slightly changed to better fit the original English language statements. To test feasibility, the TxEQ-NL was pilot tested in a group (n = 9) of transplant recipients who took part in a prospective study on psychological consequences of liver transplantation. The pilot test did not reveal substantial problems that warranted changes.

The TxEQ consist of 23 items comprising five subscales: worry about the transplant (6 items), guilt towards the donor (5 items), disclosure about the transplant (3 items), adherence to immunosuppressive medication (5 items), and responsibility towards others (4 items). The items are scored on a 5-point Likert scale (1 = *strongly disagree* to 5 = *strongly agree*). To identify recipients with a problematic response a mean value of the items, ranging from 1 to 5, is computed for each subscale. A score >3.5 on the subscales "Worry" and "Guilt" and a score <2.5 on the subscales "Disclosure," "Adherence," and "Responsibility" indicates a problematic response.[32] Though these cutoff scores are mentioned in the literature there are no reports on their validity. As for the original version of the TxEQ, a total score is not computed.

Measures used to test the construct validity

Psychological functioning

Depressive symptoms. To assess depressive symptoms the Centre for Epidemiological Studies Depression scale (CES-D) was used.[33] The CES-D consists of 20 items, scored on a 4-point self-report scale (0 = *seldom or never* to 4 = *most of the time-always*). Higher scores indicate more depressive symptoms. Validation of the Dutch version of the CES-D showed good internal consistency scores, with Cronbach's alpha ranging from .79 to .92 depending on the study population. Test–retest reliability was .90 and convergent validity with the Beck Depression Inventory was .66.[34]

Symptoms of anxiety. In this study the short form of the STAI (STAI-6), developed by Marteau and Bekker,[35] was used to measure symptoms of anxiety. The STAI-6 consists of 6 items rated on a 4-point intensity scale (1 = *not at all* to 4 = *very much*). Higher scores indicate more symptoms of anxiety. Validation of the Dutch version of the STAI-

6 has shown good reliability (Cronbach's alpha = .83), and the convergent validity of the STAI-6 with the full form of the STAI showed a correlation of .95.[36]
Posttraumatic stress symptoms. To measure symptoms of posttraumatic stress the Self-rating Inventory for Posttraumatic stress disorder (SRIP) was used.[37] The SRIP is a Dutch screening instrument for posttraumatic stress disorder (PTSD) and registers symptoms of PTSD independently of the degree of traumatization. The 22 items, corresponding to the DSM-IV criteria, are rated on a 4-point self-report scale (1 = *not at all* to 4 = *extremely*). Higher scores indicate more symptoms of posttraumatic stress. The SRIP has good psychometric properties with Cronbach's alpha .90, test-retest reliability .92, and convergent correlation with the Keane MMPI-PTSD of .80.[38]
Positive and Negative Affect. The Positive And Negative Affect Schedule (PANAS) is a 20-item self-report measure of positive and negative affect, reflecting positive mood and pleasurable engagement with the environment (Positive Affect), and subjective distress and unpleasurable engagement with the environment (Negative Affect). Higher scores indicate higher levels of either positive or negative affect. Respondents rate each emotion on a 5-point self-report scale (1 = *very slightly or not at* all to 5 = *extremely*). The Dutch version of the PANAS showed internal consistency scores of .83 for the Positive affect scale and .79 for the Negative affect scale.[39]

Personality

Personality styles of Neuroticism and Conscientiousness. The personality styles of Neuroticism and Conscientiousness were assessed using two subscales of the NEO Five-Factor Inventory (NEO-FFI), a self-report questionnaire designed to measure the five major domains of personality.[40] Each domain consist of 12 items rated on a 5-point Likert scale (1 = *totally disagree* to 5 = *totally agree*). Higher scores indicate higher levels of the personality style. In the Dutch version of the NEO-FFI Cronbach's alpha of the subscale Neuroticism ranged from .80 to .88 and of the subscale Conscientiousness from .69 to .81 depending on the study population.[41]

Coping

Avoidance, task oriented, and emotional coping styles. A short form of the Coping Inventory for Stressful Situations (CISS-SF) was used. The CISS-SF assesses three dimensions of responses to stressful circumstances: task-oriented, emotional, and avoidance coping.[42] The CISS-SF consists of 21-items with 7 items per subscale rated on a 5-point self-report scale (1 = *not at all* to 5 = *very much*). Higher scores indicate higher levels of the coping style. The Dutch version of the CISS has good psychometric properties with Cronbach's alpha of .87 for task oriented coping and emotional coping, and .82 for avoidance coping. Test-retest reliability is .78 for task oriented coping and avoidance coping, and .90 for emotional coping.[43]

Data Analysis

Factorial structure
To test the factorial structure of the TxEQ-NL a Confirmative Factor Analysis (CFA) was conducted using M-Plus 6.0 (Muthen & Muthen, Los Angeles, CA, 2010). Goodness of

fit was evaluated using several descriptive criteria: chi-square (X^2), chi-square/degrees of freedom (X^2/df), and root means square error of approximation (RMSEA). The X^2 statistic was used to evaluate the appropriateness of the structural equation model.
If the *P* value associated with the X^2 value is >.05, the model shows a good fit with the data. The relative chi-square (X^2/df) aims to make the test less dependent on the sample size. A ratio between 0 and 2 indicates a good fit; whereas a ratio between 2 and 3 indicates an acceptable fit. The RMSEA quantifies the divergence between data of this study and the original model per degree of freedom. Values below .05 indicate a close fit, whereas values up to .08 indicate an adequate fit.[44] Factor loadings of ≥.40 are considered sufficient. The Akaike Information Criterion (AIC) was used to compare different models. The AIC is a descriptive measure in which the model with the lowest AIC is the preferred model.
If one or more items on the subscales of the TxEQ-NL remained unanswered, data were excluded from analysis for that subscale. If one or more items were missing on all subscales of the TxEQ-NL the case was excluded from all analysis.

Descriptive statistics, reliability, and construct validity
Descriptive statistics, reliability, and construct validity analyses were performed using PASW 18.0. (SPSS inc., Chicago, IL, 2010). Differences between responders, non-responders, and the total eligible patient group were examined using the Mann-Whitney U-test for continuous data and Chi-square test for categorical variables. Reliability was examined using the internal consistency coefficient Cronbach's alpha (α) and the mean inter-item correlation coefficient (MICC) for each subscale. In general, Cronbach's alpha for diagnostic instruments are considered sufficient if ≥.80, but for instruments used for screening of individuals an internal consistency score >.90 is recommended.[45] For research instruments a Cronbach's alpha between .70 and .80 is considered acceptable.[46] However, the value of alpha is somewhat dependent on the number of items in a scale, whereas the inter-item correlation coefficient does not have this dependency. Briggs and Cheek[47] recommend that the MICC should fall in the range of .20-.40.
Analysis of convergent and divergent correlations between the TxEQ-NL and measures of psychological functioning, personality, and coping was performed using Spearman's correlation coefficients. Correlations between .50 and 1.00 were interpreted as strong, correlations between .30 and .50 as moderate, correlations between .10 and .30 as small, and correlations <.10 as weak.[48] To correct for the number of repeated tests, the significance level of .05 was adjusted by Bonferroni correction to <.01 for psychological functioning measures, <.025 for personality measures, and <.016 for coping measures. Squared correlation (r^2) also were computed for each correlation to indicate the percentage of overlap between constructs.

RESULTS

Participants

Of the 373 eligible liver transplant recipients, 281 completed the questionnaire, resulting in a response rate of 75%. One responder's data on the TxEQ-NL were insufficient and were excluded from analysis. Sociodemographic and medical data are presented in Table 2.

Men and women were equally present in the study population. Age at the time of survey and age at transplantation showed wide ranges of 26-80 and 16-68 years respectively. Mean time since transplantation was 9.9 years, again with a wide range of 6 months to 31.5 years. Most respondents lived together with a partner (79%) and were of Dutch nationality (89%). Diagnoses before transplantation were mainly primary sclerosing cholangitis, primary biliary cirrhosis, and cryptogenic liver cirrhosis. All responders were on immunosuppressive medication at time of the survey.

Although responders were older than the non- responders at the time of the survey and at the time of transplantation, and time since transplantation was shorter for excluded recipients, responders did not significantly differ from the total study population (Table 2).

Table 2. Characteristics of all eligible transplant recipients, excluded recipients, non responders and responders and comparisons between groups

Characteristic	All (n = 420) (%)	Excluded (n = 47) (%)	Non responders (n = 92) (%)	Responders (n = 281) (%)	Significance
Gender					
Male	51.0	46.8	51.1	51.6	ns#
Female	49.0	53.2	48.9	48.4	
Living situation	na	na	na		
With partner				79	-
Alone				21	
Nationality	na	na	na		
Dutch				89	-
Other				11	
Medical diagnosis	PSC 19 PBC 12 ALD 11	Hep. B 19 PBC 13 ALF 13	PSC 18 PBC 12 ALD 12	PSC 22 PBC 12 Crypt 12	ns#

	All (n = 420)		Excluded (n = 47)		Non responders (n = 92)		Responders (n = 281)		
Characteristic	Mean	Range	Mean	Range	Mean	Range	Mean	Range	Significance
Age	55.1	24.7-79.7	53.5	25.7-75.5	52.3*	24.7-77.8	56.4*	25.4-79.7	*p <.01^
Age at Tx	45.4	15.9-68.9	45.6	19.8-64.2	42.2	17.2-67.1	46.4	15.9-68.9	*p <.01^
Time since Tx	9.7	0.6-31.1	7.9*	0.8-23.0	10.1	0.9-28.6	9.9	0.6-31.1	*p <.05^

Note: Tx, transplantation; na, not available; ns, not significant; PSC, Primary Sclerosing Cholangitis; PBC, Primary Biliary Cirrhosis; ALD, Alcoholic Liver Disease; Hep. B, Hepatitis B Cirrhosis; ALF, Acute Liver Failure; Crypt, Cryptogenic Cirrhosis;

#X^2test, ^Mann-Whitney U-test, *Significant differences between groups

Table 3. Standardized factor loadings of the confirmatory factor analysis of the TxEQ-NL

Item	Factor and statement	Estimate	Standard error
Factor 1: Worry about the transplant			
1	With regard to my transplant I feel that I am carrying around something fragile	0.57	0.05
3	I am hesitant to engage in certain activities because I am afraid of doing harm to my transplant	0.55	0.05
9	I am worried about damaging my transplant	0.56	0.05
12	I monitor my body more closely than before I had the transplant	**0.30**	0.06
16	I worry each time my anti-rejection drug regime is altered by my doctor	0.61	0.05
18	I keep wondering how long my transplant will work	0.47	0.06
Factor 2: Guilt towards the donor			
8	I do not have any feelings of quilt toward the donor	**0.34**	0.07
14	I feel guilty about having taken advantage of the donor	0.55	0.06
17	The donor had to suffer to make me feel better	0.58	0.06
19	Sometimes I think that I have 'robbed' the donor of a vital part	**0.36**	0.07
23	I have the feeling that the donor/the donors' family has some control over me	0.65	0.06
Factor 3: Disclosure about having a transplant			
5	I am uncomfortable with other people knowing that I have a transplant	0.56	0.05
13	I have difficulty in talking about my transplant	0.75	0.04
15	I avoid telling other people that I have a transplant	0.96	0.04
Factor 4: Adherence to immunosuppressive medication			
2	Sometimes I think I do not need my anti-rejection medicines	**0.25**	0.06
7	Sometimes I forget to take my anti-rejection medicines	0.88	0.02
11	I find it difficult to adjust to taking my prescribed anti-rejection drug-regime	0.57	0.05
20	When I am too busy I may forget my anti-rejection medicines	0.84	0.02
22	Sometimes I do not take my anti-rejection medicines	0.77	0.03
Factor 5: Perceived responsibility towards others			
4	I think that I have a responsibility to the transplant team to do well	0.63	0.05
6	I feel that I owe the donor/the donor's family something that I will never be able to repay	0.50	0.06
10	I think that I have a responsibility to the donor/the donors' family to do well	0.66	0.05
21	I think that I have a responsibility to my friends and my family to do well	0.54	0.06

Note: Factor loadings <.40 are in boldface

Confirmatory factor analysis

The CFA was conducted using the five factor structure of the original English version of the TxEQ. Although the chi-square statistic showed a *P* value <.05 (X^2 466, *p* <.001), the other goodness of fit indices showed an adequate fit (X^2/df 466/220 = 2.1; RSMEA = .063; AIC = 19578) of the original model in our data. Table 3 shows the standardised factor loadings of the CFA on the items of the TxEQ-NL in our data.

Four items show a factor loading of <.40. This concerns item 12 ("I monitor my body more closely than before I had the transplant") of the subscale "Worry," item 8 ("I do not have any feelings of guilt towards the donor") and item 19 ("Sometimes I think that I have 'robbed' the donor of a vital part") of the subscale "Guilt," and item 2 ("Sometimes I think I do not need my anti-rejection medicines") of the subscale "Adherence." Additional CFAs, in which items with a factor loading <.40 separately were excluded from analysis, did not reveal a better fit with our data (X^2 *P* <.05; X^2/df between 2.02 and 2.31; RSMEA between .061 and .068; AIC between 15894 and 18722). Only when all items with a factor loading <.40 were excluded from analysis, did the CFA show a substantial decline in AIC from 19578 in the original model to 14143. However, the fit of this model was also adequate (X^2 325, *P* <.001; X^2/df 325/142 = 2.3; RSMEA = .068).

Reliability

The internal consistency scores were satisfactory for the subscales "Disclosure" and "Adherence," with Cronbach's alphas of .79 and .78 respectively (Table 4). The Cronbach's alphas for the subscales "Worry," "Guilt," and "Responsibility" were modest, ranging from .66 to .68, but sufficient given the MICCs of .26, .34, and .33 respectively. When the items with a factor loading <.40 were deleted from analysis, the internal consistency estimates improve for the subscales "Worry" (from .68 to .69) and "Adherence" (from .78 to .85). For the subscale "Guilt" the internal consistency score improved if item 8 was deleted (from .66 to .73), but decreased when item 19 was deleted (from .66 to .54).

The internal consistency scores are comparable to the scores of the English and German versions of the TxEQ for the subscales "Adherence" and "Disclosure" (Table 4), but lower for the other subscales.[10,11]

Table 4. Internal consistency scores of the TxEQ-NL and Cronbach's Alpha of the English version (TxEQ-E) and German version (TxEQ-D) of the Transplant Effects Questionnaire

Scale	n	Items	Possible score range	Observed score range	Mean	SD	MICC	Cronbach's Alpha		
								TxEQ- NL	TxEQ-E	TxEQ-D
Worry	278	6	1.0-5.0	1.0-4.5	2.80	0.73	.26	.68	.81	.73
Guilt	279	5	1.0-5.0	1.0-4.2	1.74	0.60	.34	.66	.76	.74
Disclosure	280	3	1.0-5.0	1.0-5.0	4.36	0.74	.57	.79	.86	.71
Adherence	279	5	1.0-5.0	1.8-5.0	4.17	0.80	.44	.78	.79	.79
Responsibility	280	4	1.0-5.0	1.0-5.0	3.49	0.86	.33	.66	.72	.73

Note: SD, standard deviation; MICC = mean inter-item correlation coefficient; α = Cronbach's alpha

Table 5. Observed convergent and divergent correlations and squared correlations between TxEQ subscales and measures of psychological functioning, personality, and coping

TxEQ subscale	Worry		Guilt		Disclosure		Adherence		Responsibility	
	r	r^2	*r*	r^2	*r*	r^2	*r*	r^2	*r*	r^2
Psychological functioning										
Depressive symptoms	**.29***	.08	**.17***	.03	**-.19***	.04	**-.12**	.01	.05	<.01
Anxiety	**.30***	.09	**.22***	.05	**-.22***	.05	**-.14**	.02	*.01*	<.01
Posttraumatic stress	**.27***	.07	**.16***	.03	**-.27***	.07	**-.08**	.01	*-.01*	<.01
Positive affect	*<.01*	<.01	*-.07*	<.01	*.08*	.01	.12	.01	*.22**	.05
Negative affect	**.29***	.08	**.20***	.04	**-.17***	.03	**-.11**	.01	*.04*	<.01
Personality										
Conscientiousness	**-.14***	.02	**-.28***	.08	**.24***	.06	**.20***	.04	.09	.01
Neuroticism	**.32***	.10	**.28***	.07	-.23*	.05	-.18*	.03	**<.01**	<.01
Coping										
Avoidant	**.20***	.04	**.17***	.03	**-.06**	<.01	**-.09**	.01	.22*	.05
Task-oriented	*.01*	<.01	*-.07*	<.01	*.07*	<.01	**.12**	.01	**.15***	.02
Emotional	**.34***	.12	**.36***	.13	**-.25***	.06	**-.20***	.04	-.09	.01

Note: * Bonferroni adjusted level of significance (two-tailed): psychological functioning p<.01, personality p <.025, Coping p <.016; expected convergent correlation are in boldface; Expected divergent correlations are in Italic typeface.

Construct validity

Table 5 summarises the findings regarding the convergent and divergent correlations of the subscales of the TXEQ-NL with measures of psychological functioning, personality, and coping.

Twenty-six of the 34 expected convergent correlations between the subscales of the TxEQ-NL and measures of psychological functioning, coping, and personality were confirmed. The expected convergent correlations between the subscale "Disclosure" and avoidance coping; between the subscale "Adherence" and measures of psychological functioning, and avoidance and task-oriented coping; and between the subscale "Responsibility" and the personality style of neuroticism were not supported by our data.

Thirteen of the 16 expected divergent correlations were confirmed. The subscale "Disclosure" was negatively correlated with the personality style of neuroticism, and the subscale "Responsibility" was positively correlated with positive affect and avoidant coping style. All expectations regarding the direction of the convergent correlations were met.

Overall, the correlations between the TxEQ-NL and measures of psychological functioning indicated significant, but small effect sizes (between .10 and .30), and the percentage of variance explained by these measures was low (r^2 = <.01-.09). This indicated that an association existed between these constructs, but that the constructs measured were different. This means that the TxEQ measures a distinguishable and independent construct when compared to other scales measuring psychological functioning.

Correlations between the subscale "Worry" and the personality style of neuroticism and emotional coping, and between the subscale "Guilt" and emotional coping, show moderate effect sizes (between .30 and .50). This indicates that coping style and personality style could be potential determinants of the emotional response to the receipt of an organ. However, the variance explained by these construct remains small (r^2 = <.01-.10). Comparison of the effect sizes of the convergent and divergent correlations per subscale showed satisfactory differences in strength of the correlations for four subscales. Only the subscale "Adherence" showed minimal differences in strength between convergent and divergent correlations.

DISCUSSION

The TxEQ-NL has been shown to be a valid and reliable instrument to measure the emotional response to the receipt of an organ in Dutch liver transplant recipients. The confirmatory factor analysis of the TxEQ-NL, revealed an adequate fit with the original English version of the TxEQ. The reliability of the TxEQ-NL was satisfactory for the subscales "Disclosure" and "Adherence," and given the MICC, was sufficient for the subscales "Worry," "Guilt," and "Responsibility." With respect to construct validity, overall small correlations were found between the subscales of the TxEQ-NL and measures of psychological functioning, personality, and coping.

Overall, the reliability scores of the TxEQ-NL were somewhat lower than in the English and German versions of the TxEQ.[10,11] Although the reliability scores of the TxEQ-NL were not perfect, the scores were within acceptable standards of reliability used for research instruments in social sciences.[46] However, there are some implications for the use of the TxEQ-NL as a screening tool. To make inferences about individuals, an internal consistency score >.90 is recommended.[45] Therefore, the use of the TxEQ-NL as a screening instrument should be done carefully.

The significant correlations of the subscales of the TxEQ-NL with coping and personality indicated that coping style and personality style are potential determinants of the emotional response to the receipt of an organ. The significant correlations of the subscales of the TxEQ-NL with measures of psychological functioning indicated that an association exists between these constructs. The overall small effect sizes, however, indicated that the constructs measured are different. This means that the TxEQ-NL measures a distinguishable and independent construct when compared to other scales measuring psychological functioning. Therefore, it can be argued that the TxEQ-NL adds a new dimension to the measurement of psychological functioning of transplant recipients.

However, the merely adequate fit of the TxEQ-NL with the original five factor model of the TxEQ-E indicates that there are a few differences regarding item-response between these two instruments. This could be due to cultural differences, but the rich tradition of translating English questionnaires into Dutch generally does not reveal issues regarding cultural differences.

Based on the results of the CFAs, it seems appropriate to measure the emotional

response to the receipt of a transplant with a version of the TxEQ-NL without the four items with a factor loading <.40. However, the CFA model without these items also had only show an adequate fit in our data. Because the TxEQ-NL was only validated in liver transplant patients, deleting these four items might be premature. Alternatively, the four items could be reformulated to make them less equivocal, which should be addressed in future research.

In this respect, some points regarding these items with poor factor loadings need to be addressed. First, Item 12 ("I monitor my body more closely than before I had the transplant") was also troublesome in the validation study of the German version of the TxEQ, because it loaded higher on the subscale "Responsibility" (.50) than on the subscale "Worry" (.22).[11] This might indicate that this item may not have a distinctive character when phrased in this way, because it can be seen as worrying about the transplant as well as taking responsibility, but also because transplant recipients have to monitor their body before the transplant as a consequence of their chronic illness. Therefore, rephrasing this item in a way that reflects worrying about the transplant more closely might be a solution to this problem.

Second, item 8 ("I do not have any feelings of guilt towards the donor") and item 19 ("Sometimes I think that I have 'robbed' the donor of a vital part") both refer to specific feelings of guilt towards the donor. These feelings may play a major role in cases where the transplant organ was donated by a living donor.[12] In our population of liver transplant recipients, nearly all transplanted organs were retrieved from cadaveric donors, which may have influenced the results on these items.

Third, in the subscale "Adherence," item 2 ("Sometimes I think I do not need my anti-rejection medicines") showed a factor loading <.40, and also minimal differences between convergent and divergent correlations were found. This may have been due to the broad focus of this subscale; it encompasses both emotional and behavioural aspects of medication adherence. Indeed, in the original version of the TxEQ, the items regarding emotional aspects of medication taking were originally placed in an additional factor, but finally grouped into the adherence subscale.[10] It might be worthwhile to differentiate between adherence behaviour and emotions regarding medication taking, or, as in the other subscales, focus solely on emotional aspects.

Some issues regarding the cutoff scores used for the TxEQ also need to be addressed. To identify problematic responses to the receipt of an organ, cutoff scores have been reported in the literature.[32] However, the rationale behind these cutoff scores has not been described, nor has validity regarding sensitivity and specificity of the cutoff scores been reported. Although the TxEQ has been shown to be able to identify different responses to the receipt of an organ in different types of organ transplant recipients[49] and in recipients who received an organ from a living or a cadaveric donor,[12] additional research is warranted to examine the validity of the cutoff scores.

Specific measures like the TxEQ are also believed to be more sensitive to small, but clinically relevant, changes in outcomes.[2] To our knowledge, no studies have been performed to test if the TxEQ is sensitive to detect changes in the emotional response over time. Prospective studies measuring the emotional response to the receipt of an organ over time are therefore required.

Strengths and limitations

Given the number of liver transplant recipients included (n = 281) and the response rate of 75%, it can be concluded that the TxEQ was validated in a representative sample of Dutch liver transplant recipients. Furthermore, the broad range of time since transplantation and age of recipients at follow-up increases the representativeness of the sample. The use of several psychological constructs and the concepts “Personality” and “Coping” to test the construct validity contributes to the validity of TxEQ.

Limitations of our study were that only liver transplant recipients were included and that almost all our recipients received an organ from deceased donors. Results may be different for other organ transplant groups or for transplant recipients who receive an organ from living donors. Therefore validation of the TxEQ-NL in other organ transplant recipients is required.

Conclusion

The TxEQ-NL is a valid and reliable research instrument for measuring the emotional response to the receipt of an organ in transplant recipients. However, future research in which issues regarding ambiguous items are addressed is needed to enhance the reliability and validity of the TxEQ-NL. Research to validate the TxEQ-NL in other organ transplant recipients, to test the sensitivity and specificity of the cutoff scores used to identify problematic responses, and to examine the sensitivity of the TxEQ-NL to detect changes over time also is warranted.

The TxEQ-NL adds a new dimension to the measurement of psychological functioning of transplant recipients and can be used as a transplant-specific research instrument to monitor emotional problems and adherence of liver transplant recipients. Using the TxEQ-NL as a screening instrument should be done carefully but makes it possible to identify transplant recipients with emotional problems with the receipt of a transplant organ and subsequently offer them adequate support.

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CHAPTER

4

OPINIONS OF DUTCH LIVER TRANSPLANT RECIPIENTS ON ANONYMITY OF ORGAN DONATION AND DIRECT CONTACT WITH THE DONOR'S FAMILY

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ABSTRACT

Background
In the Netherlands, anonymity of organ donation, which is currently protected by legislation, has come under discussion. In the Dutch society, a tendency to allow direct contact between transplant recipients and their donor's family is noticeable. As little is known about the opinion of Dutch liver transplant recipients on anonymity of organ donation and direct contact with the donor's family, this study examines their opinion.

Methods
A cross-sectional study was conducted in 244 liver transplant recipients. Their opinions were examined in relation to demographic, transplant-related and emotional variables. Data were collected by questionnaire. Transplant-related variables were retrieved from the hospital's liver transplant database.

Results
Fifty-three percent of the respondents (n = 177) agreed with anonymity of organ donation, mainly out of respect for the donor. Living situation, age, and level of positive affect influenced this opinion. The majority of the respondents (65%) indicated that they would like to receive some information about their donor, like age, sex, and health status. Only 19% of the respondents favored direct contact with the donor's family, mainly to express their gratitude personally. Respondents transplanted for alcoholic cirrhosis were less in favor of direct contact. Respondents with feelings of guilt doubted more about direct contact.

Conclusions
There is no need to change the current legislation on anonymity of organ donation. However, most liver transplant recipients would like to receive some general information about their donor. Therefore, clear guidelines on the sharing of donor data with recipients need to be established.

INTRODUCTION

In the Netherlands, the anonymity of organ donors and recipients is protected by legislation. The "Act on Safety and Quality of body materials" states that the identity of the donor or recipient of a donor organ may never be disclosed (www.st-ab.nl/wetten-nr06/0681-04_Eisenbesluit_lichaamsmateriaal_ 2006.htm; Article 9.1, lid1; Accessed February 2014). Anonymity is protected to avoid possible undesirable and adverse consequences for both the donor family and the transplant recipient, such as feelings of obligation to do something in return, emotional issues or disappointment when expectations are not met.[1-3] Based on the legislation, transplant programs forbid direct contact after deceased organ donation. Contact between transplant recipients and the donor's family is only possible indirectly, by means of sending an anonymous letter of appreciation. Sometimes information about sex and approximate age of the donor is given upon request of the recipient. However, because there are no uniform guidelines regarding the sharing of donor data, differences in practices can occur among and within transplant programs.

The current practice seemed sufficiently satisfying for both the transplant recipients and the donor families. However, the legislation on anonymity of organ donation has recently come under discussion. This discussion is influenced by documentaries on national television in which transplant recipients meet the family of their donor in person, and Internet networking websites that enable transplant recipients to search for their donor's family. As a result of this discussion, the public opinion in the Dutch society shows a tendency to allow direct contact. Also, health care workers increasingly receive requests from transplant recipients to provide more information about their donor.

These developments have also been described in other countries, like the United States and Israel, resulting in organ procurement organizations acting as an intermediary for contact between transplant recipients and donor families.[4-7] Recently, the anonymity of living donation to an unspecified recipient has also been brought to discussion.[3]

This made us wonder if health care workers in the field of transplantation should advocate for allowing direct contact between transplant recipients and donor families in the Netherlands. However, little is known about the opinions of Dutch transplant recipients on anonymity of organ donation and direct contact with their donor's family. To date, a few studies among (South-)American transplant recipients[5,6,8,9] have been performed, showing that the majority (~70%) of the recipients wished to have contact with the donor's family. In contrast to these studies, a survey among Belgian liver transplant recipients[2] found that 60.5% agreed with the principle of anonymity. Only 36% was interested in direct contact with the donor family, mainly to express their gratitude personally. A recent study from Israel showed that 29% of the transplant recipients had contact with the donor's family, of which 89% reported benefits of the contact, 49% reported disadvantages.[4]

The opinion of transplant recipients on anonymity of organ donation and direct contact may be influenced by variables like age, sex, and primary disease, as well as emotions.[2] To date, no studies have examined the influence of demographic, transplant-related or emotional variables on the opinion of transplant recipients regarding these issues.

Therefore, it is not known whether female recipients have different opinions on these topics than male recipients, whether younger or older recipients are more in favor of direct contact, or whether recipients transplanted for alcoholic liver disease feel less need to meet the donor's family because of feelings of guilt or embarrassment.
To be able to make an informed decision whether to advocate for a change in legislation regarding anonymity of organ donation, the aim of this study was to gain insight into the opinion of Dutch liver transplant recipients on anonymity of organ donation and direct contact with the donor's family. Additionally, reasons for being in favor or against anonymity, and the willingness for direct contact were examined. To place their opinions into context, it was examined in relation to demographic, transplant-related and emotional variables.

RESULTS

Study population

Of the 244 eligible liver transplant recipients, 179 (73%) returned the questionnaire. Data of two respondents were insufficient and therefore excluded from the analysis. Demographic and transplant-related variables of the study population are presented in Table 1.

Anonymity of organ donation

Fifty-three percent of the respondents agreed or strongly agreed with the principle of anonymity of organ donation, 17% disagreed or strongly disagreed, and 30% were neutral (Figure 1).
Reasons to be in favor or against anonymity are presented in Table 2. Overall, most respondents disagreed with the statements that they had feelings of guilt towards the donor (84%), or that they felt obliged to do something in return (66%). Significant differences in agreement between respondents with different opinions on anonymity of organ donation were found regarding three statements. Respondents in favor of anonymity of organ donation indicated more often that they found that anonymity of organ donation was an expression of mutual respect (P <0.001). Respondents who were against anonymity of organ donation agreed more often with the statements "Anonymity of organ donation should not be imposed by law, but should be decided upon by the transplant recipient and the donor's family" (P <0.001), and "I would like to support the donor's family"(P <0.001). None of the respondents added other reasons to be in favor or against anonymity of organ donation.
Respondents with a higher level of positive affect disagreed more frequently with the principle of anonymity of organ donation (P = 0.025), mainly because they found that this should not be imposed by law (P = 0.009). They also disagreed more often with the statement "I have feelings of guilt towards the donor" (P = 0.015). Respondents who lived alone (P = 0.043), and respondents who were younger than 40 years or older than 60 years (P = 0.019) were more in favor of anonymity of organ donation. For these variables no distinct underlying reasons were found.

Table 1. Demographic and transplant-related characteristics of the study population

	Respondents (n = 179)	Nonrespondents (n = 65)	*p*
Demographic characteristics			
Sex, %			
Male	57.0%	52.3%	0.516[a]
Female	43.0%	47.7%	
Age (mean±SD), yr	56.0 (± 12.6)	48.7 (± 17.6)	0.016[b]
Living status, %			
With partner	75%	NA	-
Alone	25%		
Education, %			
Low	27%	NA	-
Moderate	45%		
High	28%		
Region, %			
North-East NL	55%	54%	.744[a]
South-East NL	30%	28%	
West NL	15%	18%	
Country of origin, %			
The Netherlands	93%	NA	-
Other country	7%		
Transplant-related characteristics			
Time since transplantation (mean± SD),yr	6.4 (± 3.1)	6.9 (± 3.1)	0.312[b]
Number of transplants, %			
1	83.8%	80.0%	0.094[a]
2	13.4%	10.8%	
3 or 4	2.8%	9.2%	
Primary diagnosis, %			
Biliary cirrhosis	30.2%	27.7%	0.708[a]
Cirrhosis eci	10.1%	15.4%	0.248[a]
Viral hepatitis	8.9%	7.7%	0.759[a]
Metabolic disorders	14.5%	13.8%	0.894[a]
Alcoholic cirrhosis	15.1%	10.8%	0.390[a]
Acute liver failure	7.3%	9.2%	0.512[a]
Miscellaneous	14.0%	15.4%	0.780[a]

[a] X^2 test
[b] Mann-Whitney U-test
eci, of unknown etiology; NA, not available; NL, Netherlands; SD, standard deviation

Direct contact with the donor's family

Most respondents (85%) reported that they sometimes thought about their donor (often, 12%; regularly, 8%; occasionally, 31%; seldom, 34%), whereas 15% reported that they never thought about their donor. Sixty-five percent of the respondents reported

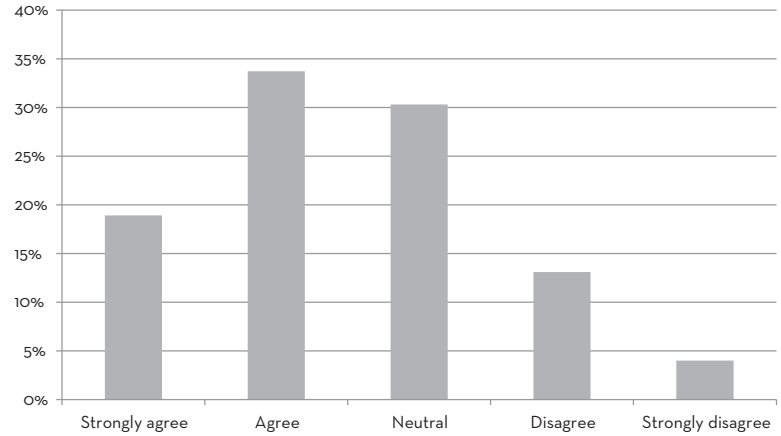

Figure 1. Percentage of respondents who (strongly) agree, are neutral, or (strongly) disagree with the principle of anonymity of organ donation (n = 177)

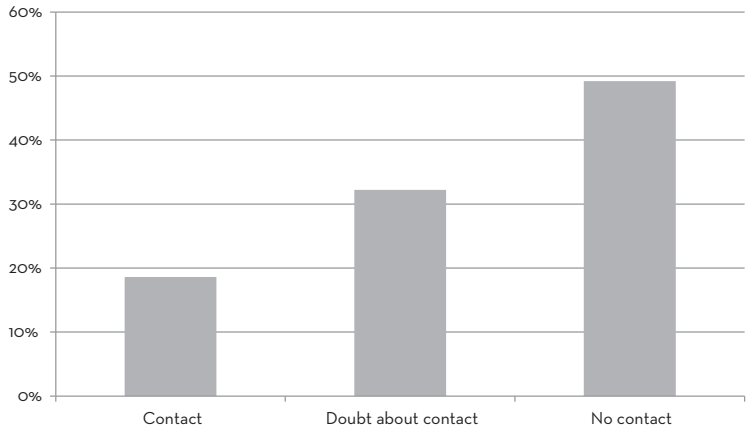

Figure 2: Percentage of respondents in favor of, with doubts about, or no wish for direct contact with the donor's family (n = 177)

that they would like to know more about their donor (general information 39%, personal information 26%), and 35% indicated that they did not wish to receive information about their donor. In the additional comments, respondents indicated that besides information about age and sex, they would like to receive information about the health status of the donor.

Although almost 30% percent of the respondents felt that contact with the donor's family should be possible in the Netherlands, only 19% of the respondents actually favored direct contact with their donor's family (Figure 2). Forty-nine percent indicated that they did not wish to contact the donor's family, and 32% had doubts about direct contact.

Table 2. Percentage of agreement with reasons in favor or against anonymity of organ donation in general, and in relation to the opinion on the principle of anonymity of organ donation.

		% Agreement overall (n = 177)			% Agreement in relation to opinion on anonymity[a]			
	Statement	**Agree**	**Neutral**	**Disagree**	**Agree with anonymity (n = 94)**	**Neutral about anonymity (n = 53)**	**Disagree with anonymity (n = 30)**	**X^2 test, *p***
1	I think that the principle of anonymity of organ donation is an expression of mutual respect	66%	21%	13%	83%	50%	43%	**<0.001**
2	I have feelings of guilt towards the donors and the donor's family	6%	10%	84%	6%	6%	7%	0.284
3	I would like to support the family of the donor	15%	35%	50%	7%	10%	47%	**<0.001**
4	I feel obliged to do something in return	9%	25%	66%	7%	8%	17%	0.118
5	Anonymity of the donor should not be imposed by law but should be decided upon by the transplant recipient and the donor's family	54%	18%	28%	38%	64%	87%	**<0.001**
6	I am afraid to become emotionally involved with the donor's family	42%	26%	32%	49%	41%	23%	0.101
7	I am afraid to cause additional grief to the donor's family	27%	27%	46%	27%	24%	33%	0.167
8	I am afraid that the donor's family might have expectations of me that I cannot live up to	36%	24%	41%	42%	28%	30%	0.202
9	I am worried about differences in social, political, or moral background between myself and the donor	19%	24%	58%	15%	22%	22%	0.313

[a] only the percentage of respondents who agreed with the statements is shown

Table 3. Percentage of agreement with reasons in favor or against direct contact in general, and in relation to the wish for direct contact with the donor's family

		% Agreement overall (n = 177)			% Agreement in relation to wish for direct contact[a]			
	Statement	**Agree**	**Neutral**	**Disagree**	**Wish for direct contact (n = 33)**	**Doubt about direct contact (n = 57)**	**No wish for direct contact (n = 87)**	**X^2 test, *p***
1	I want to express my gratitude directly towards the donor's family	28%	30%	42%	79%	33%	4%	**<0.001**
2	Contact with the family of the donor would help me to cope with the transplant experience	5%	16%	79%	18%	4%	0%	**<0.001**
3	I want to personally share the result of the transplantation with the family of the donor	19%	28%	53%	70%	12%	4%	**<0.001**
4	I am afraid that I will have feelings of guilt when I am confronted with the donor's family	26%	20%	54%	12%	23%	33%	0.062
5	I am afraid of the emotional consequences of contact with the family of the donor	38%	22%	40%	24%	36%	46%	**0.001**
6	Direct contact between transplant recipients and family of the donor can stimulate people to become an organ donor	34%	40%	26%	69%	39%	16%	**<0.001**
7	I doubt if I can handle the situation when I have contact with the family of the donor	39%	24%	37%	14%	36%	50%	**<0.001**
8	I find it difficult to be confronted with the grief of the donor's family	40%	29%	31%	21%	39%	49%	**0.001**

[a] only the percentage of respondents who agreed with the statement is shown

In Table 3, reasons to be in favor or against direct contact are presented. No distinct reasons for respondents to be in favor of or against direct contact could be identified (Table 3). However, respondents who favored direct contact with the donor's family differed significantly from respondents who doubted about or did not favor direct

contact on almost all reasons mentioned. Respondents who liked to get in touch with the donor's family reported significantly more often that they wanted to express their gratitude personally (P <0.001), that they would like to share the result of the transplant personally (P <0.001), that it would stimulate organ donation (P <0.001), and that contact with the donor's family would help them to cope with the transplant experience (P <0.001). Respondents who doubted about or did not favor direct contact reported significantly more often that they were afraid of the emotional consequences of contact with the donor's family (P = 0.001), found it difficult to be confronted with the grief of the donor's family (P = 0.001), or doubted if they could handle the situation (P <0.001). No additional reasons for wanting direct contact or not were mentioned, but a substantial part of the respondents stressed that direct contact should only be considered if both the recipient and the donor family have a wish for direct contact.
Respondents with more feelings of guilt toward the donor doubted more about direct contact with the donor's family (P = 0.018). This ambivalence is reflected in the underlying reasons. On the one hand, they indicated more often that they would like to express their gratitude directly (P = 0.028). On the other hand, they indicated more often that they doubted if they could handle the situation (P = 0.002), found it difficult to be confronted with the grief of the donor family (P = 0.011), and that they were afraid of the emotional consequences (P = 0.044). Respondents with a higher educational level (P = 0.003) felt significantly less need for direct contact with the donor's family, mainly because they felt no need to share the result of the transplant personally (P = 0.039). Respondents transplanted for alcoholic liver disease (P = 0.007) reported significantly more often that they felt no need for direct contact with the donor's family. Mainly because they felt no need to express their gratitude directly (P = 0.003) or to share the result of the transplant personally (P = 0.011). Also, they were more afraid of the emotional consequences (P = 0.003).

DISCUSSION

Our results show that the majority of the Dutch liver transplant recipients agreed with the principle of anonymity of organ donation, only a minority (17%) opposed to the principle of anonymity. Nevertheless, most recipients did express the wish to receive some general information about their donor. Only a small proportion (19%) of the Dutch liver transplant recipients was in favor of direct contact with the donor's family, whereas 32% had doubts about direct contact.
The reason to be in favor of or against anonymity of organ donation was based on personal values of either mutual respect or autonomy to make your own decisions. Recipients who favored direct contact mainly based this wish on positive expectations, such as showing gratitude and sharing the result of the transplantation. Whereas recipients who did not favor direct contact had negative expectations, such as being afraid of emotional consequences or of not being able to handle the situation.

Our study is the first to examine variables that are of influence on the opinion of transplant recipients regarding anonymity of organ donation and their wish for direct contact with the donor's family. Regarding demographic variables, we found that living situation and age were both of influence on the opinion on anonymity of organ donation. However, no distinct underlying reasons were found. Respondents with a higher educational level and those transplanted for alcoholic liver disease felt a less need to get in touch with the donor's family, mainly because they felt no need to express their gratitude or share the result of the transplantation personally. Although it was expected beforehand, the opinion of recipients transplanted for alcoholic liver disease was not related to feelings of guilt. Regarding emotional variables, we found that transplant recipients with a higher level of positive affect opposed more to anonymity of organ donation, mainly based on the moral value of autonomy to make their own decisions. Respondents with more feelings of guilt towards the donor doubted more about direct contact with the donor's family. This ambivalence is reflected by the underlying reasons indicated: they would like to express their gratitude personally, but were also afraid of the possible negative consequences.

Our findings are in line with the results from the study of Dobbels et al.[2] among Belgian liver transplant recipients, in which also the majority (60.5%) was satisfied with the principle of anonymity of organ donation and a minority (36%) favored the possibility of direct contact with the donor's family. However, our findings differ from the results of American studies.[5,6,8] Their results showed that majority of transplants recipients (52%-77%) favored direct contact with the family of the donor. This could be because of cultural differences between American societies, in which individual opportunities are highly appreciated, and European societies, in which collective norms play a more important role.[10]

A result that needs to be mentioned is that most respondents (65%) reported that they would like to receive at least some general information about their donor, such as age, sex, and health status. However, uniform guidelines about the type and amount of information which can be given to transplant recipients have not yet been established in the Netherlands. Providing this information to transplant recipients would not only satisfy their need for information, but could also facilitate the search for the donor's family. Therefore, when providing general information health care workers should be aware of the wish for direct contact of the transplant recipient and discuss the expectations of the recipient regarding direct contact, as well as the possible psychological strain and (dis)advantages of direct contact for both the transplant recipient and the donor family.

A limitation of our study is that the study was only performed among liver transplant recipients. Although the sample size was adequate and the response rate (73%) was reasonable, the results may be different for transplant recipients who had other types of organ transplants. In addition to this, only a small percentage of liver transplant recipients with a foreign descent were included in the study. Therefore, future research on this topic should focus on the opinion of heart, kidney, and lung transplant recipients, and transplant recipients with a foreign descent. Additionally, it would be interesting to assess the opinion on anonymity of organ donation and direct contact from

the perspective of the donor family, as this study only focuses on the perspective of transplant recipients.
In short, the findings of our study suggest that, from the perspective of transplant recipients, there is no need to change the current legislation regarding anonymity of organ donation in the Netherlands. A minority (17%) of the respondents opposed to the principle of anonymity of organ donation, whereas a small majority was in favor of anonymity of organ donation. The opinion of liver transplant recipients is based on the moral values of mutual respect (in favor of anonymity) or autonomy (against anonymity) and is influenced by age, living situation, and level of positive affect. A small percentage (19%) of the liver transplant recipients favored direct contact with the donor's family. The wish for direct contact is related to expectations, either positive or negative, recipients carry and is influenced by educational level, primary disease, and feelings of guilt. However, most liver transplant recipients would like to receive some general information about their donor. Therefore it is important to establish guidelines about the type and amount of information that can be given within the boundaries of the law.

MATERIALS AND METHODS

Participants and procedure

A cross-sectional study was performed among liver transplant recipients from our center in November and December 2012. Recipients were eligible for inclusion if they had undergone transplantation in our center between 2000 and 2010, were 18 years or older at the time of the survey, and still received post-transplant care at our center. Exclusion criteria were: not being able to fill in a Dutch questionnaire, having had a retransplantation after 2010, or being enlisted for retransplantation at the time of the survey. Eligible transplant recipients (N = 244) received an information letter explaining the purpose of the study, a questionnaire and a pre-addressed and stamped return envelope. Questionnaires were coded to guarantee confidentiality. After 4 weeks, a reminder was sent to nonrespondents and another 4 weeks were allowed for completion. The study met the criteria for an exemption from institutional review board approval (approval letter METc2012.306).

Measures

The questionnaire was composed for the purpose of the study under guidance of an experienced health psychology researcher (A.V.R.). Questions were based on questions from previous studies on this topic.[2,5,11,12] Firstly, recipients had to answer five questions regarding anonymity of organ donation and direct contact (Materials and Methods, SDC, http://links.lww.com/TP/B48). Next, the recipients were asked to report their level of agreement with nine statements with reasons in favor or against anonymity of organ donation and eight statements regarding direct contact. All statements could be answered on a five-point Likert scale (strongly agree to strongly disagree). A full description of all statements can be found in Tables 2 and 3. Additionally, respondents

had the possibility to add reasons for being in favor or against anonymity, regarding their wish for direct contact, or other comments.

To measure emotional variables two research instruments were used:

(1) Transplant Effects Questionnaire (TxEQ). The TxEQ is a 23-item self-report instrument measuring the emotional response of transplant recipients to the receipt of a transplant organ.[13] In this study, four subscales of the TxEQ were used: worries about the transplant, feelings of guilt toward the donor, disclosure about having undergone a transplantation, and perceived responsibility toward others. Items are scored on a five-point Likert scale (strongly disagree to strongly agree). A mean score is computed for each subscale. On the subscales "Worry" and "Guilt," a higher score indicates a problematic response. On the subscales "Disclosure" and "Responsibility," a lower score indicates a problematic response.[14] The Dutch version of the Transplant Effects Questionnaire (TxEQ-NL) showed acceptable internal consistency scores (0.66-0.79) and confirmatory factor analyses revealed an adequate fit of the TxEQ-NL with the original version.[15] In this study Cronbach's α ranged between 0.69 and 0.85.

(2) Positive And Negative Affect Schedule (PANAS). The PANAS is a 20-item self-report measure of positive affect (PA) and negative affect (NA) reflecting positive mood and pleasurable engagement with the environment (PA), and subjective distress and unpleasurable engagement with the environment (NA).[16] Each emotion is rated on a five-point Likert scale (very slightly or not at all to extremely). Higher scores indicate higher levels of PA or NA. Cronbach's α of the PANAS in the present study was 0.86 for the PA scale and 0.90 for the NA scale.

The questionnaire ended with questions about demographic characteristics. Transplant-related variables were retrieved from the hospital's liver transplant database.

Data analyses

Descriptive data are presented as means and standard deviations or percentages of respondents. The Pearson Chi-square test was used to examine differences between groups regarding categorical variables. Because the data were not normally distributed nonparametric test were used to examine differences in continuous variables; the Mann-Whitney *U* test to examine differences between two groups, and the Kruskal-Wallis test to examine differences between more than two groups. Questions and statements with answering categories with a five-point Likert scale were compiled into a three-point Likert-scale (Agree/Neutral/Disagree) to facilitate analyses of the relation between the opinion of transplant recipients and demographic, transplant-related, and emotional variables. *P* value was set at 0.05 two-sided. All analyses were performed using IBM SPSS statistics 20 (IBM SPSS Inc., Chicago, IL).

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CHAPTER

5

SHARED DECISION MAKING IN TRANSPLANTATION: HOW PATIENTS SEE THEIR ROLE IN THE DECISION PROCESS OF ACCEPTING A DONOR LIVER

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ABSTRACT

At the time of organ offer for transplantation, donor-related risks such as disease transmission and graft failure are weighed against the patient's risk of remaining on the waiting list. The patient's commonly inactive role in decision making and the timing and extent of donor-specific risk information have been discussed in the medical literature. This is the first study revealing the opinion of liver patients on these issues. Forty patients listed for liver transplantation and 179 transplanted liver patients participated in an anonymous questionnaire-based survey. The majority of patients wanted to be informed about donor-related risks (59.8%-74.8%). The preferred timing for being informed about donor-related risks was the time of the organ offer for 53.3% of the patients. Among these patients, 79.8% wished to be involved in making the decision to accept or not to accept a liver for transplantation, 10.6% wished to make the final decision alone, and only 9.6% did not want to be involved in the decision-making process. Implementing this knowledge through the standardization of the content, the manner of transfer, and the amount of information that we provide to our patients will improve opportunities for shared decision making at different time points during the transplant allocation process. This will enable us to provide the same opportunities and care to every patient on the waiting list.

INTRODUCTION

Liver transplant waiting lists increase more rapidly than the supply of donor organs, and this leaves many patients stranded and without access to what is often a lifesaving therapy. Efforts to increase the donor pool include the acceptance of more donors at the expense of diminished organ quality [ie, extended criteria donors (ECD)]. An ECD implies a higher donor-related risk in comparison with a standard criteria donor (SCD). This risk may manifest as an increased incidence of poor allograft function, allograft failure, or transmission of a donor-derived disease.[1]

To what extent such donor-related risks are discussed with the liver transplant candidate (informed consent) varies between countries and hospitals; whether or not the transplant candidate is involved in the decision-making process (shared decision making) at the time of donor offer also varies.[2-4]

In the United States, since the 2007 implementation of the guidelines from the Centers for Medicare and Medicaid Services (US Department of Health and Human Services), consent forms have been required for various stages of the transplant process, which starts with the initial evaluation and ends with the surgery. However, consent for ECD liver transplantation is not a requirement of the Centers for Medicare and Medicaid Services; it is offered at the discretion of the provider.[3] A recent study by Bruzzone et al.[2] has provided insight in the European implementation of informed consent for ECD liver donation: the majority of transplant centers inform transplant candidates about the ECD status of the donor, but great variations were observed in the timing of informing (before listing and/or at the time of organ offer), in the topics discussed, and in whether a special consent form was signed.

Standardization for the timing and content of the informed consent and for the transplant patient's role in the decision-making process is currently lacking, although both topics are receiving increasing attention in medical literature.[5-9] *Informed consent* is the term used for a patient's voluntary authorization, with full comprehension of the risks involved, for medical and surgical treatment.[10] *Shared decision making* is the process by which a health care provider communicates personalized information about options, outcomes, probabilities, and the uncertainties of the available options and a patient communicates values and the relative importance of benefits and harms.[11] For both informed consent and shared decision making, informing patients of all risks involved with a certain treatment is essential. Health researchers and policy-makers increasingly urge both patient and clinician engagement in shared decision making to facilitate the greater involvement of patients in their personal healthcare management.[12] Paternalistic health care has fallen out of favour and has been replaced by the patient-centered model, which emphasizes patient autonomy, informed consent and empowerment.[13]

Although shared decision making has been examined and implemented in numerous clinical settings,[14,15] it has received little attention in solid organ transplantation, especially in the field of (deceased donor) liver transplantation.[8,12] In a transplant setting, decisions often have to be made quickly, and the risks and benefits are difficult to explain fully at the time of an organ offer; this complicates informed consent and particularly patient involvement in shared decision making. Moreover, medical decision

making for liver transplantation raises additional challenges for shared decision making because liver transplant patients have no effective medical alternatives to transplantation such as dialysis in renal patients.[12]
Various ideas about the patient's role in decision-making and the timing and extend of informed consent have been proposed in medical literature.[6,8,16] However, there is a more fundamental question to be answered first: what do patients really want? There is very limited information on (1) the donor-related risk information that patients want to receive, (2) the preferred timing of ECD informed consent, (3) whether potential transplant candidates want to be involved in decision-making at the time of organ allocation, and (4) how much risk they are willing to accept. We, therefore, performed an anonymous questionnaire-based survey among patients listed for transplantation and liver transplant patients that addressed these questions.

PATIENTS AND METHODS

Participants and study design

All liver transplant recipients who underwent transplantation at an adult age at the University Medical Center in Groningen between 2000 and 2010, and who were still receiving posttransplant care at our center were invited to participate. In addition, adult patients that were actively listed for transplantation on February 1, 2013, were invited to participate. All eligible posttransplant and pretransplant patients received an information letter and a self-administered questionnaire by mail. Questionnaires were coded, and confidentiality was guaranteed. After 4 weeks, a reminder was sent to non-responders, and they were allowed another 4 weeks for completion. The study met the criteria for an exemption from approval (approval letter METc2012.306). The questionnaire was composed for the purpose of the study under guidance of an experienced health psychology researcher (A.V.R.) because no standard questionnaire was available for this topic. Internal validation questions were added to assess patients' understanding of the questionnaire, and the demonstrated conformity of 90% to 96%. The questionnaire was divided into two parts: (1) donor organ information, which contained 18 questions, and (2) general information, which contained 6 questions. All of the questions are addressed in the assessment section.

Assessment

All liver patients were approached by mail and asked to complete a 20 to 30 minute questionnaire. Patients were first reminded of the distinction between SCD livers and donor livers with an increased risk of complications after transplantation (so-called ECD livers). The difference between the general risk of a transplant procedure and (specific) donor-related risks was explained. An age >60 years, steatosis, and donation after cardiac death (DCD) were described as risk factors for liver failure and bile duct complications. Also, the potential risk of a transfer of a malignancy or an infectious disease from

the donor to the recipient was explained. After this introduction, patients were asked 4 personal questions concerning their time on the waiting list, previous experience with liver transplantation, and experience with complications after liver transplantation (questions 1-4).

Patients' acceptable risk of disease transmission (questions 5-8).
Next, patients were informed that the risk of a malignancy or infectious disease being transferred from a SCD livers is generally kept at less than 1%, and this leads to the discarding of livers that are otherwise suitable for transplantation. Patients then were asked to indicate on a visual proportion scale (1-50%) the risk of disease transmission that they considered high, and they were then asked to indicate the risk of disease transmission that they were willing to accept. The latter 2 questions were repeated (on the following page) after the patients were informed about the 15% mortality rate on the waiting list.

Informing patients about donor-related risks (questions 9-12)
In the subsequent questions, patients were asked whether they wished to be informed when a donor liver was offered with (1) an increased risk of transferring an infectious disease such as hepatitis or human immunodeficiency virus (HIV), (2) an increased risk of transferring a malignant disease (tumor), (3) an increased risk of bile duct strictures, or (4) an increased risk of early graft failure. Early graft failure was explained as requiring re-transplantation within 2 weeks after transplantation.

Timing of donor-specific informed consent (questions 13 and 14).
Next, it was explained that patients are informed (in general terms) about donor-related risks before waiting-list registration. It is currently not common practice to inform patients about specific donor-related risks at the time of donor offer. First, patients were asked to agree or disagree on a 5-point Likert scale (strongly disagree to strongly agree) with 4 statements through motives for wanting or not wanting information about donor-related risks were explored:

13a. It would cause distress (I would worry) if I received information about donor-related risks at the time of donor offer.
13b. I would like to receive information about donor-related risks at the time of donor offer, because it will allow me to be mentally prepared.
13c. I prefer not to receive information about donor-related risks at the time of donor offer, because I will already be overwhelmed.
13d. I would like to receive information about donor-related risks at the time of donor offer, since it will allow me to decide whether I do or do not want to receive that donor liver.

Subsequently, patients were asked whether they wished to be informed about donor-related risks of the liver offered to them for transplantation, with the following options for answers:

- No, I do not want to be informed about the donor-related risks.
- I want to be informed at the time of donor offer, even when this is at 3 AM.
- I want to be informed afterwards, when I have recovered from the transplant surgery.

The patient's role in the decision process (questions 15 and 16)

The patients who wished to be informed at the time of the donor offer, were asked what they planned to do with the acquired information:

- I just want to know, the decision on whether or not to accept the liver should be made by my physicians.
- I would like to make the decision together with my physician; we should decide together on whether or not to accept the liver.
- I would like to make the final decision alone (by myself).

Next, it was explained that in some countries, listed patients are allowed to exclude certain groups of livers (ECD livers) from being offered to them for transplantation, such as donation after cardiac death livers, livers from older donors, and livers from donors with an increased risk of infectious disease transmission. They were told that this would decrease the risk of complications after transplantation, but it would also increase the waiting time for a donor liver and thereby increase the mortality risk while on the waiting list. Patients were asked if they wanted to be able to exclude certain groups of donor livers before they were listed for transplantation.

Presented cases (questions 17 and 18)

Finally, two cases were presented to the patients: one concerning an 18-year old donor acquainted with intravenous drug use and the other concerning a healthy 81-year old donor (Table 1). First, patients were asked to assess the expected risk of infectious disease transmission and early graft failure, respectively, in those 2 cases. Next, the patients were asked whether they would accept these livers for transplantation if (1) their personal medical situation were stable and (2) their liver disease was progressively severe and the situation were, therefore, unstable.

Through 6 additional questions, information was obtained about patient age, sex, country of origin, civil status, education, and employment status. Data regarding the primary liver disease etiology and the time on the waiting list were extracted from medical databases.

Statistical analysis

Data were expressed as means and standard deviations, medians, or percentage of participants with specific responses. Categorical variables were compared with the Pearson Chi-square test or Fisher's Exact test as appropriate. Continuous variables were compared with the Student *t* test. Repeated measurements of ordinal variables within one group were compared using the Wilcoxon signed-rank test. The level of significance was set at a *P* value of 0.05. Statistical analyses were performed using SPSS 16.0 for Windows (SPSS, Inc., Chicago, IL).

Table 1. Two cases and situations: Would you accept this liver?

	Acceptable?		
	Yes	**No**	**Uncertain**
Case A. A young man (18 years old) died of an acute stroke (brain death). He was in good health, and his blood liver tests were normal. There is no evidence of a (endured) virus infection like Hepatitis B or C virus or HIV. However, the donor was acquainted with intravenous heroin use. Situation 1: You have been listed for transplantation for 8 months, and your condition is deteriorating: you are admitted to the hospital with significant jaundice, ascites and fatigue. There are concerns about whether there will be a liver available for transplantation in time**.**	74.3%	2.8%	22.9%
Case B. The donor profile is the same as that for case A. Situation 2. You have been listed for transplantation for 8 months, and your condition is fairly stable. You work part-time (half days) because of your liver disease, and you suffer mild jaundice. Arguably, you have some time to wait for a suitable organ offer.	40.7%	16.8%	42.5%
Case C. An 81-year-old woman died of an acute stroke. She lived more or less independently and relied on her neighbours only for help with groceries. She was healthy for her whole life. Her blood liver tests were normal. Situation 1. You have been listed for transplantation for 8 months, and your condition is deteriorating: you are admitted to the hospital with significant jaundice, ascites and fatigue. There are concerns about whether there will be a liver available for transplantation in time.	73.1%	3.3%	23.6%
Case D. The donor profile is the same as that for case C. Situation 2: You have been listed for transplantation for 8 months, and your condition is fairly stable. You work part-time (half days) because of your liver disease and you suffer mild jaundice. Arguably, you have some time to wait for a suitable organ offer.	39.2%	14.6%	46.2%

RESULTS

Respondent characteristics

Patients on the waiting list with an inactive status (n = 18) and patients who were <18 years old (n = 15) were excluded. In all, 243 transplanted patients and 66 patients on the waiting list were invited to participate. The overall response was 70.9% (n = 219); this included 60.6% (n = 40) of the approached waiting list patients and 73.7% (n = 179) of the transplant patients.

The study population was predominantly middle-aged, male, Dutch, married, and educated at an intermediate level (Table 2). The most common indications for transplantation were non-cholestatic cirrhosis (34.7%), cholestatic cirrhosis (33.3%), and metabolic disease (10.5%). The time since (last) liver transplantation was 6.4 ± 3.1 years (mean and standard deviation) for transplant patients and 9.4 ± 4.2 years for patients on the waiting list who had been transplanted before (n = 8; 20% of all participating listed patients). Ninety-nine of all transplant patients, 55.3% had developed 1 or more complications after transplantation, with biliary complications being the most common (n = 55 or 30.2%). The average time on the waiting list was 34.9 months (median = 26 months, interquartile range = 6-49 months) for the waiting-list patients. Nonresponders did not differ significantly from responders with respect to sex, liver disease before transplantation, or time since last transplantation. However, nonresponders were significantly younger (46.7 ± 16.6 versus 54.5 ± 13.1, *P* <0.001). During the study period, 2 nonresponders died, and 1 was admitted to the hospital.

Patient's view on acceptable risk of disease transmission

In general practice, the risk of disease transmission during organ transplantation is kept at less than 1% (no additional risk). Patients reported a significantly higher willingness to accept an increased risk of disease transmission after they had received information about the current 15% waiting-list mortality rate (Figure 1). The risk of disease transmission that patients were willing to accept was 7% ± 1% (mean and standard error), which increased to 12% ± 1% after they had received information about the current waiting-list mortality (*P* <0.001). No significant differences were found between subgroups based on patient status (transplant/waiting list), age, sex, level of education (low/intermediate/high), country of origin (Netherlands/other), or civil status (living alone/living with partner).

Informing about different types of donor-related risks

The vast majority wished to be informed when donor-related risks increased. When there was an increased risk of the transmission of an infectious disease or a malignant tumor, 73.5% and 74.8% of respondents, respectively, wished to be informed. In the case of an increased risk of bile duct strictures, 59.8% of respondents wished to be informed. When an increased risk of early graft failure was present, 70.1% of the patients wished to be informed (Table 3). Experience with bile duct complications or early graft failure after liver transplantation (the patient or an acquaintance) was not associated with an increased wish to be informed about an increased risk of bile duct strictures

Table 2. Patient characteristics

	Overall (n=219)	After transplantation (n=179)	Waiting list (n=40)
Age (years)*	54.5 ± 13.1	55.8 ± 12.8	48.6 ± 13.1
Sex: female {n/N(%)}	94/219 (42.9)	76/179 (42.5)	18 (45.0)
Country of origin			
Netherlands	203/219 (93.1)	164/179 (92.1)	39/40 (97.5)
Other	15/218 (6.9)	14/179 (7.9)	1/40 (2.5)
Civil status			
Married	145/217 (66.8)	120/177 (67.8)	25/40 (62.5)
De facto union	17/217 (7.8)	12/177 (6.8)	5/40 (12.5)
Partner, not living together	8/217 (3.7)	6/177 (3.4)	2/40 (5.0)
No partner	33/217 (15.2)	26/177 (14.7)	7/40 (17.5)
Divorced	7/217 (3.2)	6/177 (3.4)	1/40 (2.5)
Widow	7/217 (3.2)	7/177 (4.0)	0/40 (0.0)
Highest education achieved			
Lower vocational education or primary school	53/216 (24.5)	47/177 (26.6)	6/39 (15.4)
Intermediate vocational education	99/216 (45.8)	80/177 (45.2)	19/39 (48.7)
Higher vocational education or university	64/216 (29.6)	50/177 (28.2)	14/39 (35.9)
Occupation			
Full-time/part-time job	56/208 (26.9)	42/169 (24.9)	14/39 (35.9)
Retired	55/208 (26.4)	49/169 (29.0)	6/39 (15.4)
Partial or complete incapacity to work	58/208 (27.9)	44/169 (26.0)	14/39 (35.9)
Other†	39/208 (18.8)	34/169 (20.1)	5/39 (12.8)
Liver disease (before transplantation)			
Acute hepatic failure	13/219 (5.9)	13/179 (7.3)	0/40 (0.0)
Non-cholestatic cirrhosis	76/219 (34.7)	59/179 (33.0)	17/40 (42.5)
Cholestatic cirrhosis	73/219 (33.3)	55/179 (30.7)	18/40 (45.0)
Metabolic disease	23/219 (10.5)	22/179 (12.3)	1/40 (2.5)
Hepatocellular carcinoma	18/219 (8.2)	17/179 (9.5)	1/40 (2.5)
Congenital pediatric liver disease	4/219 (1.8)	3/179 (1.7)	1/40 (2.5)
Miscellaneous	12/219 (5.5)	10/179 (5.6)	2/40 (5.0)
Liver transplantation in the past	187/219 (85.4)	179/179 (100)	8/40 (20.0)
Time since (last) liver transplantation, years	6.5 ± 3.1	6.4 ± 3.1	9.4 ± 4.2 (n=8)
Time on waiting list, months	NA	NA	34.9 ± 43.2

The data are presented as n/total n (%).
*The data are presented as means and standard deviations.
†Student, volunteer, job seeker, etc.

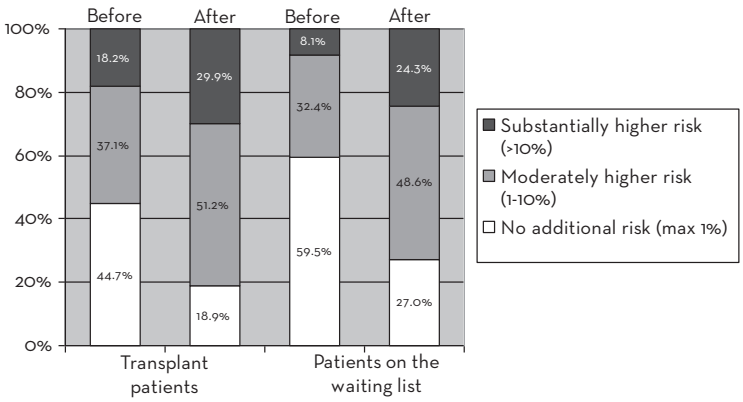

Figure 1. Risk of disease transmission that is viewed as acceptable: acceptable risk of disease transmission before and after the receipt of information about the 15% waiting-list mortality rate. No differences were observed between transplant patients and patients on the waiting list for liver transplantation

Table 3. Number of patients wishing to be informed about donor-related risks

Information about:	Overall	After transplantation	Waiting list	*P* value
Increased risk of infectious disease transmission	150/204 (73.5)	115/166 (69.3)	35/38 (92.1)	0.02
Increased risk of malignant tumor transmission	154/206 (74.8)	120/168 (71.4)	34/38 (89.5)	0.06
Increased risk of developing bile duct strictures	122/204 (59.8)	95/166 (57.2)	27/38 (71.1)	0.27
Increased risk of early graft failure*	143/204 (70.1)	109/166 (65.7)	34/38 (89.5)	0.02

NOTE: the data are presented as numbers and percentages.
* Re-transplantation was required within 2 weeks after transplantation

or early graft failure, respectively. No significant differences were found between subgroups based on age, sex, level of education (low/intermediate/high), country of origin (Netherlands/other) or civil status (living alone/living with partner). However, in comparison with transplant patients, significantly more waiting-list patients wished to be informed about donor-related risks (Table 3).

Preferred time for providing donor-related risk information

Approximately half of the patients (53.3%) wished to be informed at the time of the organ offer, 18.8% of the patients preferred to be informed after the transplant procedure, and 27.7% did not wish to be informed at all. Significantly more waiting-list patients wished to be informed at the time of organ offer (71.1%) in comparison with transplant patients (49.4%, $P = 0.02$; Figure 2). Younger patients (<40 years) wished to be informed at the time of the organ offer more often (70.3%), than older patients (55.6% for patients 41-60 years old and 44.0% for patients >60 years old). More pa-

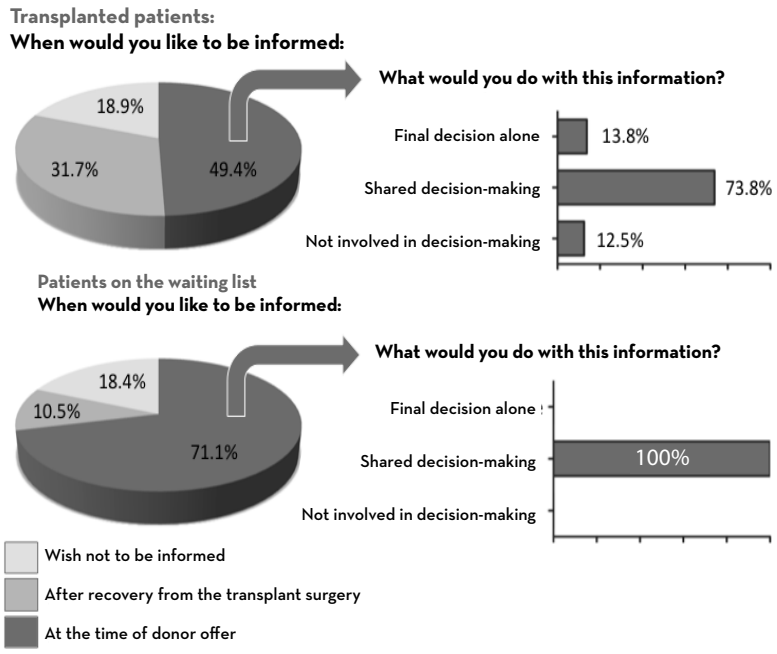

Figure 2. Timing and results of providing donor-related risk information. The majority of the patients wanted to be informed about donor-related risks at the time of organ offer (pie charts on left) and wished to be involved in the decision-making process (bars graphs on right).

tients with a lower level of education preferred not to be informed at all (43.8%) in comparison with intermediately educated patients (25.5%) or more highly educated patients (16.9%, $P = 0.03$). No significant differences were found between subgroups based on sex, country of origin (Netherlands/other), or civil status (living alone/living with partner). In comparison with waiting-list patients, significantly more transplant patients indicated that they would feel worried if donor-related risk information were provided at the time of organ offer (59.5% versus 39.5%, $P = 0.048$) and that they would feel overwhelmed (39.2% versus 18.4%, $P = 0.047$).

The patient's role in the decision process

All respondents who wished to be informed about donor-related risk at the time of organ offer were asked whether they wished to be actively involved in the decision-making process for accepting or declining the liver for transplantation. Overall, 79.8% of the respondents preferred shared decision-making, 10.6% wished to make the final decision alone, and only 9.6% did not want to be involved in the decision-making process. No significant differences were found between subgroups based on age, sex, level of education (low/intermediate/high), country of origin (Netherlands/other), or civil status (living alone/living with partner). As presented in Figure 2, significantly more

waiting-list patients wished to be involved in shared decision making (100%), when compared to transplant patients (73.8%, *P* = 0.02).
Patients were asked whether they want to be able to exclude certain groups of donor livers before they were listed for transplantation. Only 21.6% of the transplant patients and 31.6% of the waiting-list patients wished to be able to exclude certain groups of donor livers, before they were listed for transplantation. No differences were found between the aforementioned subgroups.

Presented cases

Finally, 2 potential donor cases were presented: a healthy 18-year-old previous heroin user who had tested negative for HIV and a healthy 81-year-old donor. Only 19.4% of all patients judged the risk of disease transmission associated with accepting the liver from the 18-year-old donor to be high. Similarly, only 16.5% of the patients judged the risk of potential nonfunction for the 81-year-old liver to be high. If the respondent's own condition were deteriorating, no less than 74.3% would accept the liver from the 18-year-old previous heroin user, and 73.1% would accept the liver from the healthy 81-year-old donor. If the respondent's own condition were moderately stable, still 40.7% would accept the 18-year-old liver, and 39.2% would accept the 81-year-old liver (Table 1).
In the case of the healthy 18-year-old previous heroin user, no significant differences were found between subgroups based on patient status (waiting list/transplant), age, level of education (low/intermediate/high), country of origin (Netherlands/other) or civil status (living alone/living with partner). However, significantly more male respondents were willing to accept this 18-year-old liver in comparison with female respondents: 50.4% versus 27.5% (*P* <0.001) if the respondent's condition were moderately stable and 80.5% versus 65.9% (*P* = 0.05) if the respondent's condition were deteriorating. In the case of the healthy 81-year-old donor, no significant differences were found between the aforementioned subgroups.

DISCUSSION

Various ideas about the patient's role in decision-making and the timing and extent of informed consent in transplantation have been proposed and discussed in literature by medical professionals.[5-9,16] This is the first study revealing the opinions of liver patients on these issues. The 4 main findings are as follows: (1) most liver patients want to be informed about donor-related risks, (2) half of the liver patients want to be informed at the time of organ offer, (3) the majority of these patients wish to participate in making decision to accept or decline a potential donor liver, and (4) liver patients are willing to accept a relatively high risk of disease transmission and graft failure in comparison with the risk commonly accepted by physicians.
The vast majority of patients (59.8%-74.8%) want to be informed when the donor-related risk of infectious disease, a malignant tumor, bile duct strictures, or early graft

failure is increased. The need for a full, clear, and frank explanation about general and donor-specific risks of transplantation is supported in the literature.[7,9] Moreover, better-informed patients may establish more realistic expectations, which in turn have been shown to improve postsurgical health outcomes and decrease legal claims.[10,17] This finding also supports the call for the standardization of informed consent before placement on the waiting list, which would promote the autonomy of recipients by helping to ensure that they are informed of all relevant donor risk factors.[6]

Interestingly, for more than 50% of the patients, the preferred timing of donor-related risk information is at the time of organ offer. Additionally, more than 90% of those patients want to be involved in making the decision to accept or decline a potential donor liver (shared decision making). This confronts medical teams with a dilemma: on one hand, the principles of patient autonomy and dignity require nothing less than complete disclosure, especially when potentially risky therapies are being offered,[16] but on the other hand, the disclosure of donor-specific risks requires extra time precisely when time is at a premium (during organ offer), and this could, therefore, prevent the optimal use of the organ supply.[6]

A suggested alternative to informed consent and shared decision making at the time of organ offer is to give patients the opportunity to accept or decline ECD organs as a group before transplantation.[6] However, a classification of organs into 2 groups might be inaccurate, because some of the standard organs would not be acceptable for certain recipients and not all ECD organs are of equal quality and risk.[8] It has, therefore, been suggested that ECD organs be classified in several groups, but it is still questionable whether the patient can understand the impact of these risks and make a good decision, especially because the patients' own medical condition is a dynamic process that will change his or her willingness to accept ECD livers, as shown in this study. Only a quarter of the patients in this study wished to be able to exclude certain groups of donor livers before they were listed for transplantation.

It is recognized that shared decision making may not suit all types of patients. Studies of shared decision making have found that patients with more serious or life-threatening illnesses and those for whom there are no alternative treatments do not wish to participate in the decision-making process.[18] In contrast to renal patients, patients with end-stage liver disease have no effective medical alternatives to transplantation such as dialysis. Interestingly, this study showed that the majority of the liver transplant patients actually did want to be involved in shared decision making at the time of organ offer.

This study also showed that patients are willing to accept a relatively high risk of disease transmission and potential graft failure, especially when their clinical situation is deteriorating. Previous studies have shown a similar high willingness of patients to accept donor-related risks such as ECD donor livers or donor kidneys at risk for viral infections.[19,20] Interestingly, we noticed that informing the patients of the 15% waiting-list mortality rate significantly increased their willingness to accept more donor-related risk. This suggests that providing information affects the decision-making process. Providing standardized information on the risks and benefits of the different types of ECD donor transplantation at the time of waiting-list registration, potentially in combination with comprehension assessment tools and e-health educational tools, might enable

liver patients to participate in shared decision making at the time of organ offer. Decision aids have been demonstrated to affect long-term behavior and appear to promote informed decision-making.[21]

A potential bias could reside in the fact that we do not know whether the nonresponders to this questionnaire would have given the same answers to the questions in comparison with the responders. We did, however, compare responder and nonresponder characteristics, and we found no significant differences with respect to sex, liver disease, or time since transplantation. On the other hand, non-responders were approximately 8 years younger. During the study period, 2 non-responders died, and 1 was admitted to the hospital.

This study is clinically relevant to anyone who is involved in transplantation. Decisions concerning the patient's role in decision making and the timing and extent of informed consent in transplantation need to be made by every transplant center. Both the physician's opinion and the patient's opinion on these issues should be taken into consideration. Standardization of both the information about the different donor types provided before patient listing and shared decision-making at the time of organ offer is important for providing the same opportunities and care to every patient. We are aware that the results of the current study only represent the opinion of liver patients in the Netherlands. This study was undertaken at a transplant center in the north of the Netherlands, an area that is known to be more culturally homogeneous than transplant centers in the south of the Netherlands. The opinion of patients elsewhere in the world could be different. We hope that this study stimulates other transplant centers to perform a similar survey to reveal the local need for information and involvement of patients in the decision-making process surrounding liver transplantation.

In the case of deceased donor liver transplantation, decisions often have to be made quickly, and the risks and benefits are difficult to explain fully at the time of an organ offer. The involvement in shared decision making should be consistent with patient preferences; the process of involvement may be as important as who eventually makes the decision.[11,22] On the basis of the results of this study, we suggest that information on risks related to SCD and ECD transplantation be provided in detail to all patients listed for transplantation. Moreover, patients who want to be informed and involved in shared decision making at the time of the organ offer should be identified at the time of listing for transplantation. Accordingly, these patients should receive additional information and potentially decision aids to allow shared decision making at the time of the organ offer.

In conclusion, the questionnaire presented in this paper provides unique information on the opinion of liver patients on donor-related risks. The majority of respondents wished to be informed about donor-related risks and wanted to be involved with shared decision making at the time of organ offer. Implementing this knowledge and standardizing the content, the manner of transfer, and the amount of information that we provide to our patients at different time points during the transplant allocation process will be important for providing the same opportunities and care to every patient on the waiting list.

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CHAPTER

6

TRAJECTORIES OF ANXIETY AND DEPRESSION IN LIVER TRANSPLANT CANDIDATES DURING THE WAITING-LIST PERIOD

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Submitted

ABSTRACT

Objectives
To explore whether distinct trajectories of anxiety and depression exist among liver transplant candidates, and to gain insight into demographic, clinical, and individual characteristics associated with these trajectories.

Design
A prospective cohort study among 216 liver transplant candidates. Respondents filled out a questionnaire at study entrance, and subsequently every six months until transplantation or removal from the waiting list.

Methods
Anxiety (STAI6), depression (CES-D), demographic, and individual variables were assessed by questionnaire. Clinical variables were retrieved by medical record review. The SAS TRAJ procedure was used to identify distinct trajectories. Chi-square, ANOVAs, and ordinal logistic regression analyses were used to explore associated variables.

Results
Regarding anxiety three stable trajectories were identified: below clinical level (51%), slightly above clinical level (34%), and high above clinical level (15%). Regarding depression four stable trajectories were identified: below clinical level (23%), slightly below clinical level (34%), slightly above clinical level (28%), and high above clinical level (6%). For anxiety as well as for depression, experiencing more liver disease symptoms, a lower level of personal control, making more use of emotional coping, and making less use of task-oriented coping increased the likelihood of membership in those trajectories with higher symptom levels.

Conclusion
Distinct trajectories for anxiety and depression are present in liver transplant candidates. However, the symptom level at baseline seems to be indicative of the symptom level during the waiting-list period. Screening of psychological symptoms and associated variables is warranted early in the transplant process. Subsequently, appropriate interventions should be undertaken to optimize psychological wellbeing.

INTRODUCTION

In the Eurotransplant region, over 2000 patients with end-stage liver disease are waiting for a liver transplant, while about 1600 patients per year receive a liver transplant.[1] More specifically, in the Netherlands about 200 patients are placed on the waiting list for a liver transplant per year, while approximately 145 patients receive a liver transplant.[2] Due to the gap between supply and demand for organ donors, transplant candidates may have to wait for a donor offer for a prolonged period of time. Each year approximately 15% of transplant candidates die while on the organ transplant waiting list.[2] Waiting for a new organ puts a lot of stress on patients. Not only are they confronted with deterioration in their physical health but they also have to deal with uncertainty – will the transplant come in time – and unpredictability – when will the transplant take place.[3-6] Although the prospect of a transplantation offers new hope for the future, transplant candidates often feel that their life is on hold.[3,7]

Given the stressors encountered by transplant candidates, it is not surprising that psychological problems, such as anxiety and depression, are common during the waiting-list period. Among liver transplant candidates, prevalence rates of 14%-52% regarding anxiety[8-12] and of 17%-60% regarding depression[8-13] have been described. Psychological problems before transplantation have been associated with poor psychological health after transplantation,[9,14,15] which in turn has been associated with poorer outcomes after transplantation regarding adherence,[16,17] quality of life,[9,16,18] and mortality.[19,20] Therefore, effective treatment of symptoms of anxiety and depression during the waiting-list period may contribute to an optimal preparation for transplantation and better outcomes after transplantation.

So far, little is known about the evolution of symptoms of anxiety and depression during the waiting-list period, since most studies describing prevalence rates of anxiety and depression have a cross-sectional design, and data are often assessed before or shortly after placement on the waiting list. Regarding liver transplant candidates, two studies have described the course of symptoms of depression and anxiety as remaining stable during the first six months after placement on the waiting list.[21,22] Three studies among lung, heart, and kidney transplant candidates revealed an increase in symptoms of anxiety and depression over time during the waiting-list period.[23-25] However, these studies examined the course of symptoms of anxiety and depression on a group level. Distinct trajectories, representing clusters of individual developmental courses for symptoms of anxiety and depression during the waiting-list period, have not been examined yet. Thus, we do not know whether transplant candidates become increasingly anxious over time, or whether transplant candidates who are already depressed remain depressed.

In addition to this, insight into the demographic, clinical, and individual characteristics that distinguish the distinct trajectories of symptoms of anxiety and depression can provide direction for the type of intervention needed. In the literature, several variables have been associated with higher levels of anxiety and/or depression in transplant candidates. These include demographic characteristics, such as age, sex, marital status, and employment status;[10,19,26,27] clinical characteristics, such as the Model for

End-stage Liver Disease (MELD) score, time on the waiting list, and perceived health status;[12,15,28] and individual characteristics, such as coping style, personal control, social support, and self-efficacy.[10,12,29] However, other studies have shown contradictory results regarding these factors.[30,31] Although these variables are associated with higher levels of anxiety and depression measured on a group level, we have to rely on these studies to identify possible predictors for distinct trajectories, since studies on distinct trajectories are lacking.
Knowing whether distinct trajectories are present in liver transplant candidates, how these evolve over time, and which demographic, clinical, and individual characteristics are associated with these trajectories can provide health care workers with valuable insights for interventions aimed at reducing distress during the waiting-list period.

MATERIALS AND METHODS

This study was part of a prospective cohort study on psychological aspects of liver transplantation among transplant patients of all three liver transplant centers in the Netherlands. All transplant candidates on the waiting list between October 2009 and April 2013 were eligible to participate if they were 18 years or older, and received pre-transplant care in one of the transplant centers. Exclusion criteria were: unable to fill out a questionnaire due to physical, mental, or cognitive functioning, or a language barrier.

Informed consent was obtained from all the individual participants included in the study. After written informed consent, respondents received a baseline questionnaire (T0), which they were asked to fill out within two weeks. A reminder was sent after two weeks, if necessary. The measurement of symptoms of anxiety and depression was repeated every 6 months (T1-T7) after inclusion in the study until either transplantation, removal from the waiting list, death during the waiting-list period, or the end of the study in October 2013.
The institutional review board of the transplant center that initiated the study approved the study, and a positive recommendation of local feasibility was obtained from the other transplant centers (METc2009.190).

Measurements

Outcome variables

The outcome variables of anxiety and depression were included in the questionnaire at all measurement points.
Symptoms of anxiety were measured using the short form of the State-Trait Anxiety Inventory (STAI-6).[32] The STAI-6 consists of 6 items rated on a 4-point intensity scale (1 = not at all, to 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 20 item scale cutoff of ≥40 for the general population,[33] a cutoff score of ≥12 was used to identify clinically relevant cases. 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 varied from 0.75 to 0.88 at the different measurement points.
Symptoms of depression were assessed using the Dutch version of the Center for Epidemiological Studies Depression scale (CES-D).[35] The CES-D consists of 20 items, scored on a 4-point self-report scale (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.[36] Cronbach's alpha of the CES-D in the present study varied from 0.79 to 0.94 at the different measurement points.

Predictor variables

All predictor variables were measured once at the baseline measurement (T0).
Demographic characteristics regarding age, sex, marital status, educational level, and employment status were retrieved by self-report.
Clinical characteristics regarding primary liver disease, presence of hepatocellular carcinoma (HCC), time since diagnosis, time on waiting-list, MELD score at time of listing, number of comorbidities, and the severity of liver disease symptoms were examined. Most of the variables were retrieved by medical record review. To measure comorbidity and liver disease symptoms, two research instruments were included in the questionnaire:

- To measure comorbidities, a checklist of twenty common medical problems adapted from the health survey of the Dutch central statistics office, Statistics Netherlands, was used (www.cbs.nl; accessed 01/15/2015). This checklist included common medical conditions such as pulmonary diseases, heart diseases, stroke, gastrointestinal disorders, kidney function disorder, diabetes mellitus, joint complaints, and cancer. Respondents were asked to indicate which medical conditions, in addition to the liver disease, they had (yes/no), and whether they had received treatment (yes/no) for any of these medical conditions in the past twelve months. The total number of co-morbidities was calculated by adding up all medical conditions for which treatment was received in the past year. Previous studies suggest that this method of self-reported comorbidity tends to be an accurate representation of actual comorbidity.[37,38] Moreover, it has been found to be applicable in a transplant population.[39]
- The Liver Disease Symptom Index 2.0 (LDSI)[40] was used to measure the severity of specific liver disease symptoms. The LDSI includes 18 items, of which 9 measure the severity of liver disease-related symptoms, such as itch, jaundice, and sleepiness during the day. The other 9 items measure the hindrance caused by these symptoms in terms of daily activities. All items are scored on a 5-point Likert scale ranging from "not at all" (0) to "to a great extent" (4). The LSDI has shown good feasibility and good test-retest reliability.[40] Two items, regarding depressive and anxious feelings, were removed from the analyses in order to avoid overlap with the outcome variables. In this study, only the severity scale of the LDSI was used. This score was calculated by summing up the scores of the remaining items.

Regarding *individual characteristics*, the level of personal control and coping style used were taken into account, since these are modifiable factors. In addition to these char-

acteristics, the number of life events was examined as a potential confounder variable.

- *Personal control,* the general perception of control over life, was measured using the Pearlin-Schooler Mastery Scale.[41] The Mastery Scale measures the degree to which individuals feel they can control things that happen to them, and it consists of seven items rated on a 5-point Likert scale (1 = totally disagree, 5 = totally agree). Total scores range from 7 (low personal control) to 35 (high personal control). The Mastery Scale is used in a variety of well and ill populations, and has shown good reliability and validity.[41] Cronbach's alpha in the present study was 0.80.
- *Coping style* was measured using the short-form of the Coping Inventory for Stressful Situations (CISS-SF). The CISS-SF measures three dimensions of responses to stressful circumstances: task-oriented, emotional, and avoidance coping. The CISS-SF consists of 21 items, where respondents can rate the extent to which they engage in various types of coping activities, when confronted with stressful situations, on a 5-point Likert scale (1 = not at all, to 5 = very much).[42] Higher scores on a subscale indicate more use of the specific coping style. In this study, the Cronbach's alphas of the subscales were: 0.79 for the task-oriented coping scale, 0.82 for the emotional coping scale, and 0.78 for the avoidance coping scale.
- Other *Stressful life events,* in addition to having end-stage liver disease, which may influence a person's life and psychological functioning, were measured using the Trauma and Life Event Self-report Inventory (TLESI).[43] The TLESI consists of a list of eleven stressful events, where a person can indicate which events happened in the past five years. Additional life events that had an influence on a person's life could be added. In the analyses, the number of reported life events was taken into account.

Data Analyses

Distinct trajectories were identified using a group-based modeling strategy for estimating developmental trajectories (PROC TRAJ) in SAS 9.4 (SAS Institute Inc., Cary, NC). PROC TRAJ identifies latent clusters of the time trajectories of maximally third-order polynomials in a population. Respondents are assigned to one of the identified trajectories by calculating the probability of membership in each latent class for each respondent using a normal mixture model.[44] This means that the response variables (anxiety and depression) are normally distributed within each cluster. In PROC TRAJ, the Bayesian Information Criterion (BIC) is used to identify the number of different clusters, by starting with one homogeneous cluster and stopping at the number of clusters that sequentially minimizes the BIC. The BIC measures the relative fit of different models, with lower levels indicating a better fit.

The waiting list cohort was a dynamic cohort, subjects were being continuously enrolled in or removed from the waiting-list group (in case of transplantation, removal from the waiting list, or death) during the follow up period. Therefore, the number of observations for each transplant candidate and the sample sizes per measurement point varied. However, PROC TRAJ uses maximum likelihood and can therefore handle missing data of the type Missing at Random (MAR). To check the robustness of our findings, sensitivity analyses were performed using data from five of the eight measurements points (T0-T4).

Cluster membership with respect to the trajectories of anxiety and depression, identified for each transplant candidate, was added to an IBM SPSS Statistics 22.0 database (SPSS Inc., Chicago, 2013), which was used for all other analyses. Descriptive statistics were used to calculate the mean scores or prevalence rates of the demographic, clinical, and individual characteristics. To examine whether these characteristics differed among the distinct trajectories, chi-square tests were used for categorical variables and ANOVAs were used for continuous variables. Characteristics that differed significantly between trajectories were entered into an ordinal logistic regression analysis to examine the independent effect of these characteristics on the distinct trajectories using proportional odds ratios.

To test the stability of the trajectories over time, the effect size of partial eta squared (η_p^2) was used. Partial eta squared describes the proportion of the total variability attributable to a factor.[45] GLM repeated measures ANOVA with time as a factor was used to calculate η_p^2. Because of the small sample sizes in the measurement points T5-T7, these analyses were performed using the data of the measurement points T0-T4. *P* value was set at 0.05, two-tailed, for all analyses.

RESULTS

Of the 474 liver transplant candidates on the waiting list between October 2009 and April 2013, 350 were eligible to participate in the study (Figure 1). Of these, 241 liver transplant candidates (68.9%) agreed to participate. Liver transplant candidates not willing to participate were significantly younger (48.0 years, ± 13.6; *P* = 0.02) than those willing to participate. Besides this, candidates with the primary diagnosis of biliary cirrhosis were more willing to participate (76%, *P* = 0.048), whereas candidates within the group of miscellaneous diseases were less willing to participate (54%, *P* = 0.03). Regarding sex, time since diagnosis, time on waiting list, and MELD-score no differences were found between participants and non-participants.

Two hundred and sixteen liver transplant candidates (93.1%) responded to the baseline questionnaire (T0); 25 did not return the baseline questionnaire for several reasons (Figure 1).

During the study period, 116 of the respondents received a transplant (53.7%), 15 respondents (6.9%) were removed from the waiting list, and 14 respondents (6.5%) died during the waiting-list period (Figure 1). At the end of the study, 71 respondents were still on the waiting list.

Demographic, clinical, and individual characteristics of the study population are presented in Table 1.

Trajectories of anxiety during the waiting-list period

Figure 2 shows the results of the trajectory analyses of symptoms of anxiety. The dotted line represents the predicted values of the cluster-specific trajectories, and the solid line the observed average values. Based on BIC (2 clusters: 1355.64; 3 clusters: 1349.24;

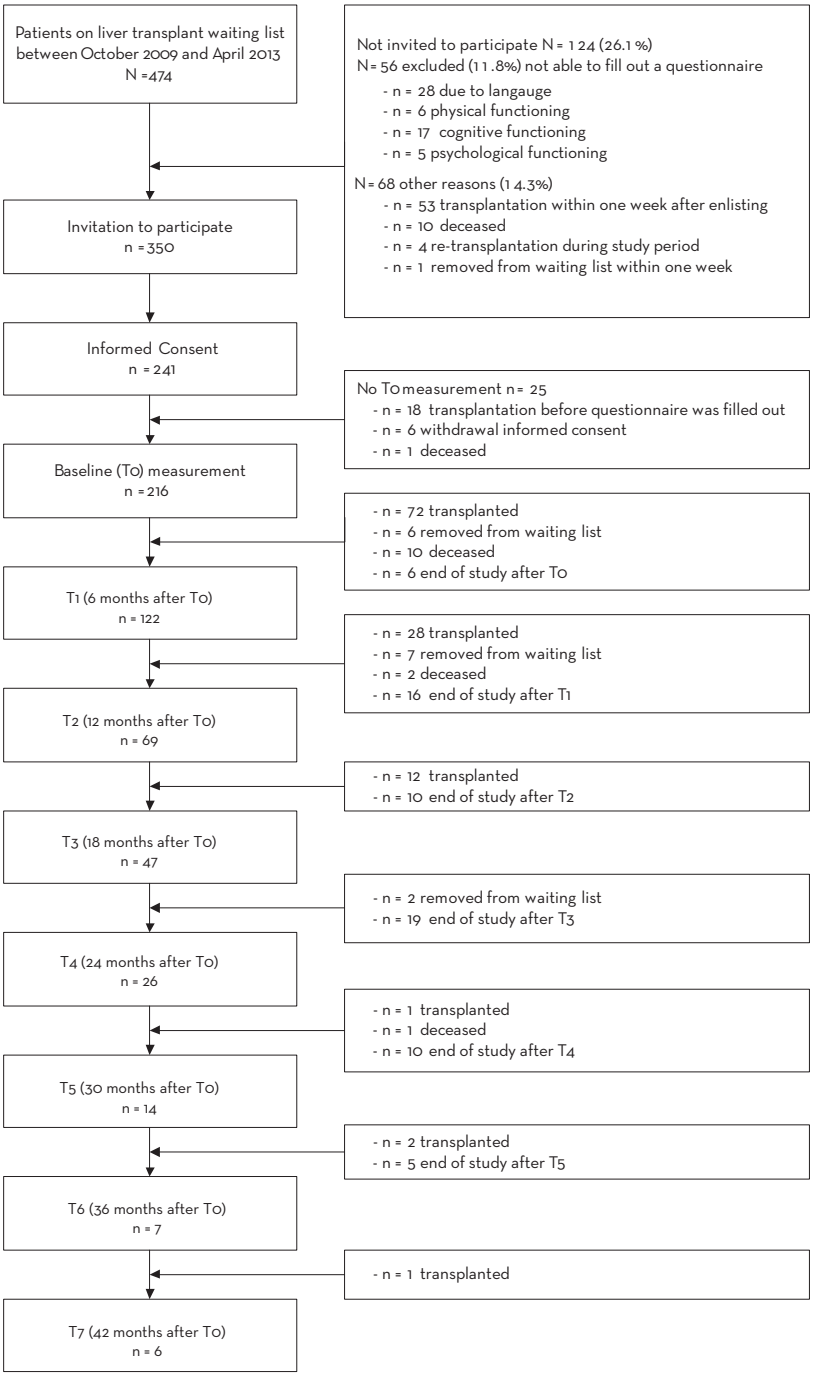

Figure 1. Study inclusion flow diagram.

Table 1. Baseline demographic, clinical, and individual characteristics of the study population

Characteristic	All n = 216
n (%)	
Gender: male	144 (66.7)
Marital status: with partner	168 (87.8)
Educational level	
Low	47 (21.8)
Moderate	96 (44.4)
High	73 (33.8)
Employment status: paid job	64 (29.6)
Nationality: Dutch	200 (92.6)
Primary disease	
Biliary cirrhosis	78 (36.1)
Alcoholic cirrhosis	51 (23.6)
Metabolic disorder	24 (11.1)
Viral hepatitis	28 (13.0)
Cirrhosis of unknown origin	18 (8.3)
Miscellaneous	17 (7.8)
Hepatocellular Carcinoma	34 (15.7)
Mean (SD)	
Age (in years)	51.6 (11.3)
Number of co-morbidities	1.9 (1.6)
Time since diagnosis (in years)	5.8 (6.3)
Time on waiting-list (in months)	7.8 (13.9)
MELD score	13.3 (5.3)
LDSI score	9.5 (5.4)
Personal control	23.9 (5.4)
Coping style	
- Emotional coping	19.2 (6.5)
- Task-oriented coping	25.1 (4.3)
- Avoidance coping	17.1 (5.0)
Number of life events	1.6 (1.3)

Note MELD = Model for End-stage Liver Disease; LDSI Liver Disease Symptom Index

4 clusters: 1354.92), three distinctive trajectories of anxiety were identified: 1) a group with average symptom scores below the clinical level, comprising 51.3% (n = 118) of the respondents; 2) a group with average symptom scores slightly above the clinical level, comprising 33.5% (n = 67) of the respondents; and 3) a group with average symptom scores high above clinical level, comprising 15.2% (n = 31) of the respondents. Sensitivity analyses using data of T0-T4 revealed three similar distinctive trajectories (BIC: 2 clusters: 1292.91; 3 clusters: 1288.92; 4 clusters: 1295.37), with an overlap in group membership in 94.4% of the cases. Regarding the stability of the trajectories over time,

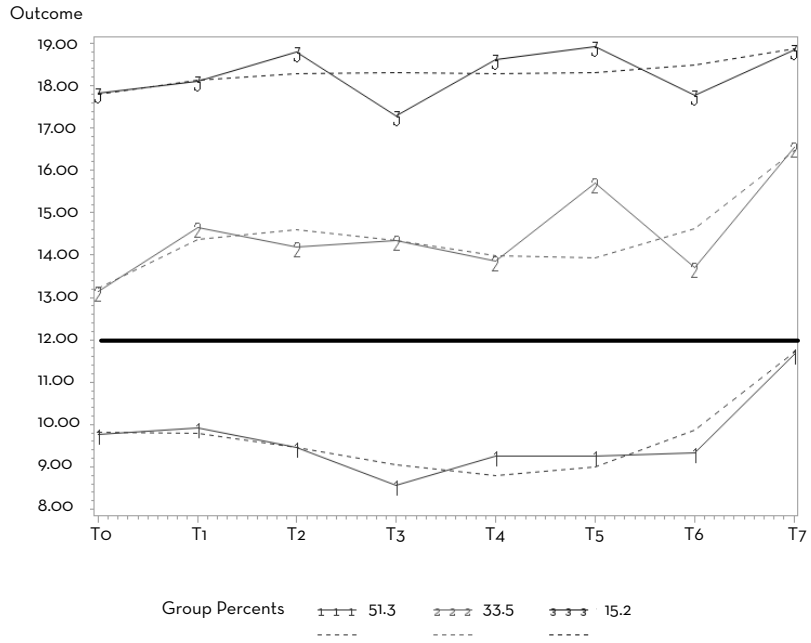

Figure 2. Distinct trajectories of symptoms of anxiety of liver transplant candidates during the waiting-list period.
Note: the bold black line represents the cutoff value (≥12) of the clinical level of symptoms of anxiety T0 = baseline measurement, T1 = 6 months after T0, T2 = 12 months after T0, T3 = 18 months after T0, T4 = 24 months after T0, T5 = 30 months after T0, T6 = 36 months after T0, T7 = 42 months after T0.

the effect sizes (η_p^2) were, respectively: 0.08 for trajectory 1, 0.15 for trajectory 2, and 0.20 for trajectory 3. This indicates that time accounted for 8% to 20% of the variability in anxiety scores within the trajectories.

Variables associated with the trajectories of anxiety

As shown in Table 2, the distinctive trajectories were independently associated with the variables: educational level, LDSI-score, personal control, emotional coping, task-oriented coping, and the number of life events. Investigating the effects of these variables simultaneously on trajectory membership, using ordinal logistic regression analyses, showed that educational level and the number of life events do not seem to help classify subjects when LDSI, personal control, emotional coping, and task-oriented coping are already provided (Table 3). A unit increase in LDSI score (OR = 1.16, CI 1.09-1.23), and a unit increase in emotional coping score (OR = 1.13, CI 1.07-1.19) increased the odds of membership in the trajectories with higher anxiety levels, while a unit increase in personal control score (OR = 0.89, CI 0.84-0.95) and a unit increase in the task-oriented coping score (OR =0.89, CI 0.82-0.96) reduced the odds of membership in trajectories with higher levels of symptoms of anxiety.

Table 2. Demographic, clinical, and individual characteristics of respondents within the distinct trajectories of anxiety

	Trajectory 1 Anxiety below clinical level n = 118	Trajectory 2 Anxiety slightly above clinical level n = 67	Trajectory 3 Anxiety high above clinical level n = 31	*P* value
n/%				
Gender: Male	78 (66.1)	46 (68.7)	20 (64.5)	0.90
Marital status: Partner	91 (77.1)	53 (79.1)	24 (77.4)	0.95
Educational level				
Low	23 (19.5)	11 (16.4)	13 (41.9)	**0.04**
Moderate	57 (48.3)	31 (46.3)	8 (25.8)	
High	38 (32.2)	25 (37.3)	10 (32.3)	
Currently employed: Paid job	38 (32.2)	22 (32.8)	4 (12.9)	0.09
Primary disease				
Biliary cirrhosis	45 (38.1)	25 (37.3)	8 (25.8)	0.43
Alcoholic cirrhosis	29 (24.6)	16 (23.9)	6 (19.4)	0.83
Metabolic disorder	11 (9.3)	8 (11.9)	5 (16.1)	0.54
Viral hepatitis	14 (11.9)	6 (9.0)	8 (25.8)	0.06
Cirrhosis of unknown origin	8 (6.8)	6 (9.0)	4 (12.9)	0.53
Miscellaneous	11 (9.3)	6 (9.0)	-	0.21
Hepatocellular Carcinoma	21 (17.8)	10 (14.5)	3 (9.7)	0.53
Mean (SD)				
Age	51.9 (11.3)	51.1 (11.7)	51.8 (11.0)	0.90
Number of co-morbidities	1.7 (1.4)	2.2 (1.9)	2.2 (1.5)	0.11
Time since diagnosis (in years)	6.4 (7.0)	5.0 (4.8)	5.2 (5.8)	0.28
Time on waiting list (in months)	6.9 (13.1)	7.9 (15.0)	9.5 (14.6)	0.63
MELD score	13.3 (5.5)	12.9 (5.4)	14.5 (4.5)	0.33
LDSI score	7.7 (4.9)	10.5 (4.3)	14.0 (5.7)	**<0.001**
Personal control	26.1 (4.8)	22.3 (5.0)	19.1 (4.4)	**<0.001**
Coping style				
- Emotional coping	16.8 (5.4)	21.3 (6.8)	23.5 (5.9)	**0.001**
- Task-oriented coping	25.9 (4.2)	25.0(4.0)	22.6 (4.3)	**<0.001**
- Avoidance coping	16.6 (5.4)	17.6 (4.7)	17.4 (3.8)	0.39
Number of life events	1.4 (1.1)	1.7 (1.4)	2.1 (1.5)	**0.02**

Note: MELD = Model for End-stage Liver Disease; LDSI = Liver disease Symptom Index

Trajectories of depression during the waiting-list period

Figure 3 displays the results of the trajectory analyses of symptoms of depression. Based on BIC (3 clusters: 1835.48; 4 clusters: 1824.75; 5 clusters: 1833.85), four distinctive trajectories of depression were identified: 1) a group with average symptom scores for depression below the clinical level, comprising 22.7% (n = 36) of the respondents; 2) a group with average symptom scores for depression slightly below clinical

Table 3. Unstandardized estimates, Odds ratios, and 95% Confidence Intervals of characteristics associated with the distinct trajectories of anxiety

Variable	Estimate	*P* value	Odds ratio	95% Confidence Interval	
				Lower	Upper
Low educational level	0.14	0.73	1.15	0.51	2.64
Middle educational level	-0.68	0.09	0.51	0.23	1.11
High educational level	reference				
LDSI score	0.14	**<0.01**	1.16	1.09	1.23
Personal control	-0.11	**<0.01**	0.89	0.84	0.95
Emotional coping style	0.12	**<0.01**	1.13	1.07	1.19
Task-oriented coping style	-0.12	**<0.01**	0.89	0.82	0.96
Number of life events	0.19	0.11	1.21	0.96	1.53

Note: LDSI = Liver Disease Symptom Index
Note: pseudo R^2 = 0.40 (Cox & Snell), 0.47 (Nagelkerke); Model X^2 (423) = 403.27, P = 0.75

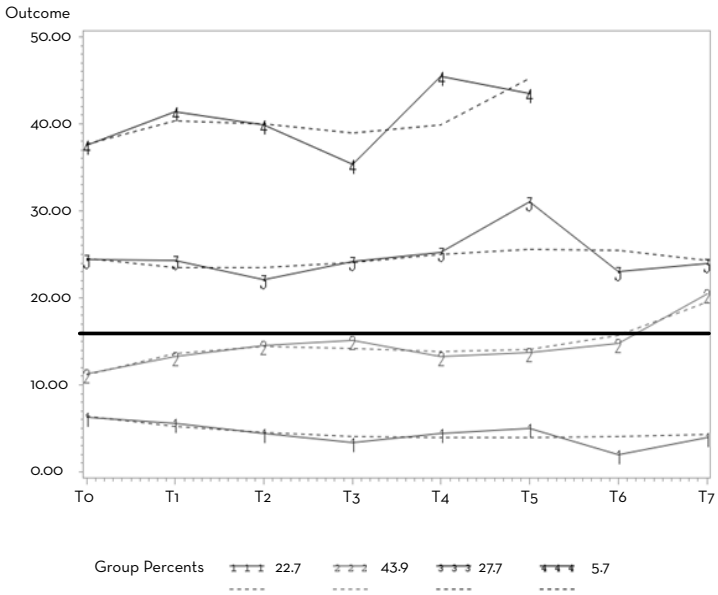

Figure 3. Distinct trajectories of symptoms of depression of liver transplant candidates during the waiting-list period.
Note: the bold black line represents the cutoff value (≥16) of the clinical level of depressive symptoms
T0 = baseline measurement, T1 = 6 months after T0, T2 = 12 months after T0, T3 = 18 months after T0, T4 = 24 months after T0, T5 = 30 months after T0, T6 = 36 months after T0, T7 = 42 months after T0.

Table 4. Demographic, clinical, and individual characteristics of respondents within the distinct trajectories of depression

	Trajectory 1 Depression below clinical level n = 36	Trajectory 2 Depression slightly below clinical level n = 104	Trajectory 3 Depression slightly above clinical level n = 66	Trajectory 4 Depression high above clinical level n = 10	*P* value
n (%)					
Gender: Male	21 (58.3)	71 (68.3)	45 (68.2)	7 (70.0)	0.71
Marital status: Partner	28 (77.8)	81 (77.9)	52 (78.8)	7 (70.0)	0.94
Educational level					
Low	9 (25.0)	17 (16.3)	16 (24.2)	5 (50.0)	0.14
Moderate	16 (44.4)	52 (50.0)	24 (36.4)	4 (40.0)	
High	11 (30.6)	35 (33.7)	26 (39.4)	1 (10.0)	
Employment status: Paid job	16 (44.4)	35 (33.7)	13 (19.7)	0 (0)	-
Primary disease					
Biliary cirrhosis	15 (41.7)	37 (35.6)	24 (36.4)	2 (20.0)	-
Alcoholic cirrhosis	9 (25.0)	23 (22.1)	16 (24.2)	3 (30.0)	
Metabolic disorder	5 (13.9)	10 (9.6)	5 (7.6)	4 (40.0)	
Viral hepatitis	3 (8.3)	14 (13.5)	10 (15.7)	1 (10.0)	
Cirrhosis of unknown origin	1 (2.8)	10 (9.6)	7 (10.6)	-	
Miscellaneous	3 (8.3)	10 (9.6)	4 (6.1)	-	
Hepatocellular Carcinoma	9 (25.0)	20 (19.2)	4 (6.1)	1 (10.0)	-
Mean (SD)					
Age (in years)	50.6 (11.2)	52.2 (12.0)	50.9 (11.1)	54.2 (5.7)	0.71
Number of co-morbidities	1.4 (1.1)	1.9 (1.6)	1.9 (1.7)	3.6 (1.6)	**<0.01**
Time since diagnosis (in years)	6.0 (6.0)	6.2 (6.7)	5.3 (5.7)	4.1 (6.5)	0.65
Time on waiting list (in months)	9.4 (16.2)	5.7 (11.7)	9.5 (16.1)	8.4 (7.3)	0.29
MELD score	11.1 (4.9)	13.5 (5.6)	14.3 (4.9)	13.7 (5.4)	**0.04**
LDSI score	4.8 (3.9)	8.5 (4.2)	13.0 (5.3)	13.1 (4.0)	**<0.01**
Personal control	28.1 (4.2)	25.1 (4.5)	20.9 (4.6)	15.5 (4.7)	**<0.01**
Coping style					
- Emotional coping	16.3 (4.8)	17.5 (5.5)	22.3 (6.4)	27.4 (7.2)	**<0.01**
- Task-oriented coping	26.8 (3.9)	25.4 (4.2)	24.3 (4.3)	21.9 (4.6)	**<0.01**
- Avoidance coping	17.5 (5.6)	17.0 (5.1)	17.1 (4.6)	15.7 (5.0)	0.80
Number of life events	1.3 (1.1)	1.5 (1.2)	1.8 (1.4)	1.5 (1.4)	0.27

Note: MELD = Model for End-stage Liver Disease; LDSI = Liver Disease Symptom Index

level, comprising 43.9% (n = 104) of the respondents; 3) a group with average symptom scores for depression slightly above clinical level, comprising 27.7% (n = 66) of the respondents; and 4) a group with average symptom scores for depression high above the clinical level, comprising 5.7% (n = 10) of the respondents. Sensitivity analyses, using data from T0-T4, revealed four similar distinctive trajectories (3 clusters: 1746.55; 4 clusters: 1740.71; 5 clusters: 1750.09), with an overlap in group membership in 89.4% of the cases. Regarding the stability of the trajectories over time, the effect sizes (η_p^2) were, respectively: 0.07 for trajectory 1, 0.04 for trajectory 2, 0.03 for trajectory 3, and 0.20 for trajectory 4. This indicates that time accounted for 3% to 20% of the variability in depression scores within the trajectories.

Variables associated with the trajectories of depression

As shown in Table 4, the trajectories were independently associated with the variables: number of co-morbidities, MELD score, LDSI score, personal control, emotional coping, and task-oriented coping. Investigating the effects of these variables simultaneously on trajectory membership, with ordinal logistic regression analyses, showed that the number of co-morbidities and the MELD score do not seem to help classify subjects, when LDSI, personal control, emotional coping, and task-oriented coping are already provided (Table 5). A unit increase in the LDSI score (OR = 1.24, CI 1.16-1.33) and a unit increase in the emotional coping score (OR = 1.13, CI 1.07-1.18) increased the odds of membership in trajectories with higher depression levels. Whereas, a unit increase in the personal control score (OR = 0.84, CI 0.78-0.90) and a unit increase in the task-oriented coping score (OR = 0.91, CI 0.85-0.98) reduced the odds of membership in the trajectories with higher levels of depressive symptoms.

Table 5. Unstandardized estimates, Odds ratios, and 95% Confidence intervals of characteristics associated with the distinct trajectories of depression

Variable	Estimate	*P* value	Odds Ratio	95% Confidence Interval	
				Lower	Upper
Number of comorbidities	0.01	0.90	1.01	0.84	1.21
MELD score	0.03	0.34	1.03	0.97	1.08
LDSI score	0.22	**0.00**	1.24	1.16	1.33
Personal control	-0.18	**0.00**	0.84	0.78	0.90
Emotional coping style	0.12	**0.00**	1.13	1.07	1.18
Task-oriented coping style	-0.09	**0.01**	0.91	0.85	0.98

Note: MELD = Model for End-stage Liver Disease; LDSI = Liver Disease Symptom Index
Note: pseudo R^2 = 0.52 (Cox & Snell), 0.58 (Nagelkerke); Model X^2 (639) = 426.10, P = 1.000

DISCUSSION

The results of our study showed that distinct trajectories of anxiety and depression are present in liver transplant candidates. Based on the level of anxiety symptoms during the waiting-list period, three distinct trajectories were identified: 1) below clinical level, 2) slightly above clinical level, and 3) high above clinical level. These comprised, respectively, 51%, 34%, and 15% of the respondents. With respect to depressive symptoms, four distinct trajectories were identified: 1) below clinical level, 2) slightly below clinical level, 3) slightly above clinical level, and 4) high above clinical level. Comprising, respectively, 23%, 34%, 28%, and 6% of the respondents. All trajectories were relatively stable over time. Time accounted for 8-20% of the variance in scores within the trajectories of anxiety and for 3-20% in the variance of scores in the trajectories of depression. The stability of the trajectories over time seems to indicate that the baseline measurement is indicative of the level of depression and anxiety of liver transplant candidates during the waiting-list period.

Of all the demographic, clinical, and individual characteristics examined, four variables were found to be independently associated with both the trajectories of anxiety and depression: the LDSI score, personal control, and emotional and task-oriented coping.

In contrast to studies that have analyzed associations at a group level,[10,19,26,27] we found no associations between demographic characteristics, such as age, sex, marital status, and employment status and the trajectories of either anxiety or depression. However, this result might be influenced by the small sample sizes in some of the identified trajectories. Because of this, we could not take all demographic variables into account in our analyses. Therefore, the influence of demographic variables needs to be taken into account in future research.

Regarding clinical characteristics, only the LDSI-score, the severity of liver disease symptoms as perceived by the transplant candidate, was found to be associated with the trajectories of anxiety and depression. Respondents, who perceived the liver disease symptoms as more severe, had a higher probability of being in the trajectories with higher levels of anxiety and depression. This finding emphasizes that adequate management of liver disease symptoms is necessary. However, the LDSI is a subjective measurement of disease severity, and this finding was not supported by an objective measurement of disease severity, such as the MELD score, in our study. This may imply that altering the cognitive appraisal of disease symptoms by giving adequate information about liver disease symptoms and possible self-management strategies may help transplant candidates to cope with their deteriorating health.

The individual characteristics of personal control and coping seem to play a major role in the development and maintenance of symptoms of anxiety and depression. Transplant candidates with a lower level of personal control, who feel that they have no control over the things that happen to them, and those who make more use of emotional coping, were more likely to be in the trajectories with high symptom levels of both anxiety and depression. Transplant candidates with a high level of personal control and who make more use of task-oriented coping, on the other hand, seem to be less anx-

ious and depressed. Therefore, interventions aimed at empowering transplant candidates by strengthening coping skills or sense of control may help to reduce symptoms of anxiety and depression during the waiting-list period. However, evidence regarding effective psychosocial interventions in transplant candidates is lacking.[46,47] So far, only a few studies, reporting (preliminary) findings regarding psychosocial interventions in transplant candidates and recipients, show that this may be effective in reducing distress.[48-51] In future studies the effectiveness of psychosocial interventions to address psychological problems in transplant candidates need to be examined.

The clinical implication of our study is that in the care of liver transplant candidates routine screening of psychological problems and associated variables is warranted early in the transplant process. Although the importance of screening for psychological problems has been widely recognized,[52] common practice may vary between transplant centers, and psychosocial screening is a less standardized procedure.[53] Based on the psychosocial screening, in which psychological problems as well as variables of influence on the psychological functioning of transplant candidates need to be examined, interventions tailored to the patient's needs should be undertaken to enhance the psychological wellbeing of transplant candidates. In addition to psychosocial interventions aimed at reducing distress, referral for psychological or psychiatric counseling may contribute to better psychological wellbeing during the waiting-list period, which ultimately may in turn contribute to better outcomes after transplantation.

The strength of our study was its prospective, longitudinal, and multicenter design which made it possible to study the evolution of psychological problems over time. The overall sample size (n = 216) was reasonable, and the response rate of 69% was satisfactory. Furthermore, a full range of associated variables (demographic, clinical, and individual) was examined. However, by using a trajectory approach we limited ourselves in the number of variables that could be taken into account because of the small sample sizes in some of the trajectories, especially in the trajectories regarding depressive symptoms. Therefore, differences between trajectories regarding some of the categorical variables could not be examined. Also, the generalizability of our results may be limited. Replication of our findings in larger sample sizes is needed to be able to generalize our results.

In conclusion, distinct trajectories of symptoms of anxiety and depression are present in liver transplant candidates. However, the stability of the trajectories over time seems to indicate that the baseline measurement is indicative of the trajectories for the symptoms of anxiety and depression during the waiting-list period. Experiencing more liver disease symptoms, a lower level of personal control, making more use of emotional coping, and making less use of task-oriented coping increased the odds of membership in trajectories with higher symptom levels for both the trajectories of anxiety and of depression. Based on our results, screening of psychological problems early in the transplant process – if not already established – is recommended. Subsequently, appropriate interventions aimed at reducing distress should be undertaken in order to optimize the psychological well-being of the transplant candidate. These interventions should be aimed at diminishing the perceived severity of the liver disease symptoms and the use of emotional coping, and enhancing the level of personal control and the

use of task-oriented coping. However, evidence regarding the effectiveness of psychosocial interventions in organ transplant candidates is lacking and needs to be studied in future research.

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CHAPTER

7

A PROSPECTIVE COHORT STUDY ON POSTTRAUMATIC STRESS DISORDER IN LIVER TRANSPLANTATION RECIPIENTS BEFORE AND AFTER TRANSPLANTATION: PREVALENCE, SYMPTOM OCCURRENCE, AND INTRUSIVE MEMORIES

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Submitted

ABSTRACT

Objective

This study aimed at increasing the understanding of posttraumatic stress disorder (PTSD) in liver transplant patients by describing the course of PTSD, symptom occurrence, psychological co-morbidity, and the nature of re-experiencing symptoms.

Methods

A prospective cohort study was performed among 95 liver transplant recipients from the waiting-list period, up until one year post-transplantation. Respondents filled out a questionnaire regarding psychological functioning (PTSD, anxiety, and depression) before, and at 3, 6, and 12 months post-transplantation. Both quantitative and qualitative methods were used to analyze the data.

Results

Before transplantation, full PTSD was present in 10.5% and partial PTSD in 6.3% of the respondents. In all cases, co-morbid conditions of anxiety and/or depression were present. After transplantation, no new onset of full PTSD was found. New onset of partial PTSD was found in six respondents. Arousal symptoms were the most frequently reported symptoms, but were found not to be distinctive for PTSD in transplant patients because of the overlap with disease- and treatment-related symptoms. Re-experiencing symptoms before transplantation were mostly related to waiting for a donor organ and the upcoming surgery; after transplantation this was related to aspects of the hospital stay.

Conclusions

In liver transplant patients, PTSD is more often present before transplantation than after transplantation. Being diagnosed with a life-threatening disease seems to be the main stressor. If a diagnosis of PTSD is suspected, assessment by a clinician is warranted because of the overlap with symptoms of anxiety and depression, and disease- and treatment-related symptoms.

INTRODUCTION

Since the introduction of the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV)[1] in 1994**,** being diagnosed with a life-threatening illness has been introduced as a potential stressor event for posttraumatic stress disorder (PTSD). Since then, PTSD has been described in a variety of somatic diseases and treatments, including organ transplantation.[2-7] However, contrary to other stressful events that may lead to PTSD, such as rape or car accidents, being diagnosed with a life-threatening illness is not a single event but a process, comprising a number of stressors that may lead to a traumatic experience.

In patients diagnosed with end-stage liver disease, liver transplantation is the only treatment option. In the liver transplant process several stressors that may be traumatic are present. First, transplant candidates find themselves diagnosed with a potentially life-ending disease, for which a donor organ is needed to survive, but where it is uncertain if this donor organ will arrive in time. Each year approximately 15% of transplant candidates die while on the organ transplant waiting list.[8] Second, if a donor organ becomes available, patients have to undergo major surgery, often followed by known risk factors for PTSD: a stay on the intensive care unit (ICU)[9,10] and delirium.[11,12] Third, after a successful transplantation, patients have to adjust to a life with a life-long regimen of immunosuppressive drugs and life-style rules but they may as well have to deal with serious, potentially life-ending, complications, such as rejection of the graft, or the development of cardiovascular diseases or cancer.[13,14] All these factors make PTSD a reasonable concern for the transplant population.

So far, the focus of the studies on PTSD after organ transplantation has mainly been on assessing prevalence rates, identifying risk factors for the development of PTSD, and the impact of PTSD on outcomes after transplantation. A recent systematic review[15] showed that, after organ transplantation, clinically relevant symptom levels of PTSD were present in 0-46% of transplant recipients, while clinician-ascertained PTSD was present in 1-16% of the cases. Studies on transplant candidates are limited and mainly retrospective in nature, showing that clinically relevant symptom levels of PTSD are present in 7-25%,[16,17] while 2-6% of transplant candidates satisfy the criteria for PTSD.[18,19]

Little attention has been paid to which aspects of the transplant process are traumatic in nature, to the occurrence of specific symptoms of PTSD, and to the overlap of PTSD symptoms with other psychological disorders. Furthermore, prospective studies examining the course of PTSD in the same patient group, before and after transplantation, are lacking. Examining these aspects may help to gain a better understanding of the concept of PTSD in the transplant population.

PTSD is characterized by symptoms of re-experiencing, avoidance, and arousal.[1] Symptoms of re-experiencing include recurrent dreams, intrusive memories, or flashbacks related to the event. Since symptoms of intrusive re-experiencing are seen as the core symptom of PTSD,[20] examining the nature of these symptoms in transplant patients can provide valuable insight into stressors associated with PTSD in this population.

The symptom clusters of avoidance and arousal are more general in nature, and show an overlap with mood and anxiety disorders.[21] Avoidance symptoms refer to the avoid-

ance of distressing memories, thoughts, feelings, or reminders of the event, but also detachment from others, and hopelessness about the future. Arousal symptoms are characterized by aggressive behavior, sleep disorders, and hyper-vigilance. Because of the overlap with mood and anxiety disorders, it might be hard to disentangle the differences between them. Therefore, examining comorbidity between PTSD, anxiety, and depression, and the overlap of symptoms of anxiety and depression with the symptom clusters of PTSD may help to differentiate between these problems.

Another important aspect to consider is that PTSD symptoms should not be the result of another medical condition, medication, drugs, or alcohol.[22] In liver transplant patients, arousal symptoms like sleeping disorders and concentration problems may also be disease-related. Sleeping disorders are common in liver transplant patients. Before transplantation, 35-73% of the transplant candidates reported poor sleep quality,[23,24] mainly due to hepatic encephalopathy or to the underlying liver disease.[23] Among transplant recipients, 41-73% reported poor sleep quality mostly due to physical problems.[25-27] Concentration problems and irritability may also interfere with symptoms of encephalopathy before transplantation.[28] Therefore, examining the occurrence of PTSD symptoms, and the contribution of specific symptom clusters to the diagnosis of PTSD in transplant patients can add to the understanding of PTSD in the transplant population.

The aim of this study was to increase the understanding of PTSD in liver transplant candidates and recipients by describing the course of PTSD from the waiting-list period up until the first year after transplantation, which symptoms of PTSD contribute the most to a diagnosis of PTSD in liver transplant patients, the overlap of PTSD with anxiety and depression, and to examine the nature of re-experiencing symptoms in liver transplant patients.

METHODS

A prospective cohort study on psychological aspects of liver transplantation was performed among transplant patients in all three liver transplant centers in the Netherlands. Transplant candidates who were on the waiting list between October 2009 and April 2013 were asked to participate. Inclusion criteria were: ≥18 years, and receiving medical treatment in one of the three transplant centers. Exclusion criteria were: unable to fill out a questionnaire due to physical, mental, or cognitive functioning, or due to a language barrier.

Eligible transplant candidates (n = 350) received a letter explaining the purpose and procedure of the study, together with an informed consent form and a pre-addressed, stamped return envelope. After written informed consent, respondents received a baseline questionnaire (T0). Measurements of psychological functioning were repeated every six months after inclusion in the study until transplantation. In this study, data from the last measurement-point before the transplant were used to describe PTSD symptoms of liver transplant candidates (T0). After transplantation respondents filled

out a questionnaire at three (T1), six (T2), and twelve (T3) months after the transplant surgery. The institutional review board of the transplant center that initiated the study approved the study, and a positive recommendation of local feasibility was obtained from the other transplant centers (METc2009.190).

Research instruments

To measure symptoms of PTS, the Self-Rating Inventory for Posttraumatic Stress Disorder (SRIP) was used,[29] a Dutch screening instrument that registers symptoms of PTSD. The 22 items, corresponding to the DSM-IV criteria for PTSD, are rated on a 4-point self-report scale (1 = not at all, to 4 = extremely). The SRIP has satisfying psychometric properties: validity (.90), reliability (.92), sensitivity (83%), and specificity (72%).[29] In this study Cronbach's alphas of the SRIP were, respectively, 0.89 (T0), 0.88 (T1), 0.87 (T2), and 0.87 (T3).

The items of the SRIP are stated in general terms, by referring to a stressful experience that happened in the past. In order to be able to examine symptoms of PTSD related to the end-stage organ disease (T0) or to the transplantation (T1-T3), the items were adjusted by replacing "stressful event" with either "my disease" or "my transplantation." Respondents who reported having re-experiencing symptoms, such as intrusive thoughts or recurrent dreams, were asked to briefly describe the nature of these re-experiencing symptoms.

In the SRIP, five of the PTSD symptoms mentioned in the DSM-IV are split into two separate items. For example, "having difficulty falling or staying asleep" is split into two items: "having difficulty falling asleep" and "having difficulty staying asleep." To correspond to the DSM-IV criteria, SRIP items that belong to the same PTSD symptom were merged into one item.

A cutoff score of ≥39 was used to identify respondents with clinically relevant symptom levels of PTS.[30] To be able to identify cases of PTSD, all items were recoded into 0 (no symptom of PTSD, scores 1 or 2) and 1 (symptom of PTSD, scores 3 or 4). For each symptom cluster, the number of symptoms was calculated by adding up the recoded symptom scores. Based on DSM-IV-criteria, caseness of full PTSD was defined as the presence of one symptom of re-experiencing, three avoidance symptoms, and two arousal symptoms.[1] Regarding partial PTSD, different criteria have been used in the literature, either satisfying symptom clusters at two of the three symptom clusters,[31] or having one symptom in each symptom cluster.[32] Because intrusive re-experiencing is recognized as the core symptom of PTSD, the latter definition of partial PTSD was used in this study.

To measure psychological co-morbidity, symptoms of anxiety and depression were assessed using, respectively, the short form of the State-Trait Anxiety Inventory (STAI-6)[33] and the Center for Epidemiological Studies Depression Scale (CES-D).[34]

The STAI-6 consists of 6 items rated on a 4-point intensity scale (1 = not at all, to 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 20 item scale cutoff of ≥40 for the general population,[35] a cutoff score of ≥12 was used to identify clinically relevant cases. The convergent validity of the STAI-6 with the full form of the STAI showed

a correlation of 0.95.[36] Cronbach's alpha of the STAI-6 in the present study varied from 0.87 to 0.89 at the different measurement-points.
The CES-D consists of 20 items, scored on a 4-point self-report scale (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.[37] Cronbach's alpha of the CES-D in the present study varied from 0.91 to 0.92 at the different measurement-points.
Demographic variables regarding age, sex, marital status, educational level, nationality, and employment status were retrieved by self-report. Clinical data regarding primary liver disease and time on waiting-list were obtained from the medical record.

Statistical analyses

Descriptive statistics were used to calculate mean or median scores, and prevalence rates regarding demographic and clinical characteristics, and prevalence and incidence rates of full and partial PTSD. Differences between groups were analyzed using Fisher's exact test or X^2-test for nominal variables. Because of non-normal distribution, the Mann-Whitney U-test was used to analyze differences between groups on continuous variables.
Ordinal Logistic Regression (OLR) analysis was used to identify which symptom clusters contributed the most to the diagnosis of full or partial PTSD, using odds ratios. Pearson's correlation coefficient was used to examine the association between the symptom clusters of PTSD with symptoms of anxiety and depression.

To analyze the qualitative data regarding re-experiencing symptoms, content analysis was performed by two researchers (GD/CA), independent of each other. Data were examined using a direct approach with a priori categories based on the re-experiencing symptoms in the DSM-IV diagnostic criteria for PTSD. Consensus on the coding was reached if the coding corresponded completely or after discussion about the differences in coding. If no consensus was reached, a third researcher (MJS) was asked to examine the specific data. Data were discussed with all researchers involved to reach final consensus.

RESULTS

Study population

Of the 350 eligible transplant candidates, 241 (69%) agreed to participate. Of these, 116 received a transplant within the study period. However, for 21 respondents, datasets were incomplete and therefore excluded from analyses. Reasons for missing data were: deceased (n = 12), hospitalization at measurement-point (n = 3), lost to follow-up (n = 3), questionnaire not returned (n = 2), and re-transplantation (n = 1). Demographic and clinical characteristics of the total study population, and included and excluded respondents are shown in Table 1. No significant differences were found between respondents included or excluded from the analyses.

Table 1: Demographic and clinical characteristics of the study population

	All respondents n = 116	Respondents included in analyses n = 95	Respondents excluded from analyses n = 21	*P* value
n (%)				
Sex: Male	76 (65.5)	63 (66.3)	13 (61.9)	0.80
Living situation: With partner	89 (76.7)	71 (74.7)	18 (85.7)	0.40
Educational level				
Primary	21 (18.3)	15 (16.0)	6 (28.6)	0.18
Secondary	54 (47.0)	43 (45.7)	11 (52.4)	
University	40 (34.8)	36 (38.3)	4 (19.0)	
Employment status				
Working	32 (27.6)	28 (29.5)	4 (19.0)	0.53
Sick-leave/disabled	59 (50.9)	48 (50.5)	11 (52.4)	
Retired/homemaker/student	25 (21.6)	19 (20.0)	6 (28.6)	
Nationality: Dutch	109 (94.0)	91 (95.8)	18 (85.7)	0.11
Primary liver disease				
Biliary cirrhosis	40 (34.5)	36 (37.9)	4 (19.0)	0.10
Metabolic disorder	14 (12.1)	11 (11.6)	3 (14.3)	0.72
Cirrhosis unknown etiology	9 (7.8)	6 (6.3)	3 (14.3)	0.21
Alcoholic cirrhosis	26 (22.4)	22 (23.2)	4 (19.0)	0.78
Viral hepatitis	17 (14.7)	11 (11.6)	6 (28.6)	0.08
Other	9 (7.8)	9 (9.5)	0 (0)	0.36
Mean (SD)/median (range)				
Age (at time of transplantation)	50.8 (11.4)	50.3 (11.3)	53.4 (12.2)	0.20
Time on waiting-list (in months)	9.4 (0.2-77.5)	9.5 (0.2-77.5)	8.5 (1.0-24.2)	0.49

Table 2. Prevalence rates based on cutoff score (≥39), and prevalence and (cumulative) incidence rates of full, partial, and no PTSD, based on DSM-IV criteria before and during the first year after transplantation

	Waiting list	3 months after transplantation	6 months after transplantation	12 months after transplantation	
Point-prevalence (n/%)					
Cutoff ≥39	30 (31.6)	15 (15.8)	14 (14.7)	14 (14.7)	
Full PTSD	10 (10.5)	1 (1.1)	0 (0)	0 (0)	
Partial PTSD	6 (6.3)	5 (5.3)	6 (6.3)	3 (3.2)	
No PTSD	79 (83.2)	89 (93.6)	89 (93.6)	92 (96.8)	
Incidence (n/%)					Cumulative Incidence
Full PTSD	10 (10.5)	0	0	0	10 (10.5)
Partial PTSD	6 (6.3)	1 (1.1)	3 (3.2)	2 (2.1)	12 (12.7)
Total	16 (16.8)	1 (1.1)	3 (3.2)	2 (2.1)	22 (23.2)

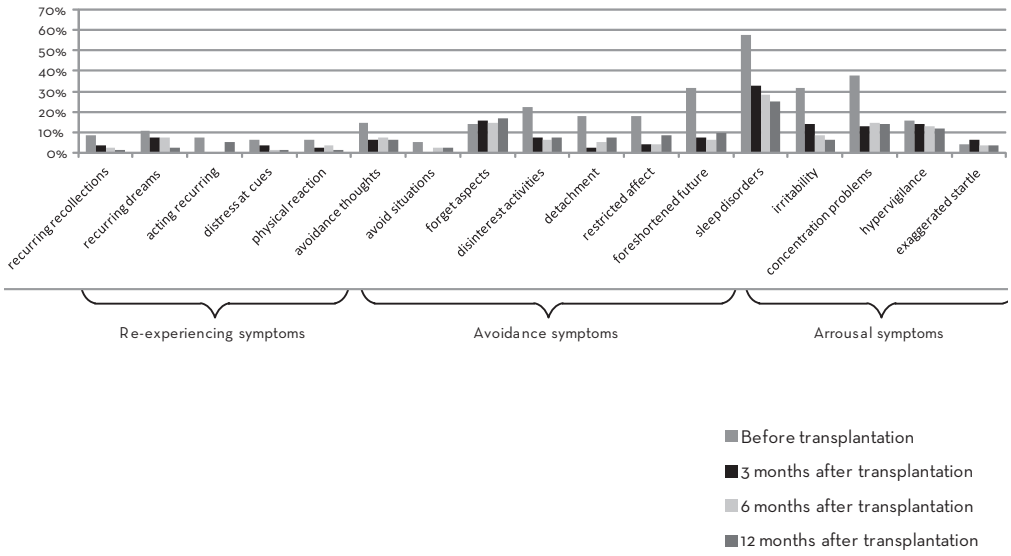

Figure 1. Overview of respondents (%) with specific PTSD symptoms at the different measurement-points.

Prevalence and incidence rates of PTSD

Table 2 shows the prevalence rates of PTSD at the different measurement-points. Clinically relevant symptomatology, based on the cutoff score (≥39), as well as caseness for PTSD, based on criteria for full and partial PTSD, were more present in the waiting-list period, when compared to the period after transplantation. The cumulative incidence, the proportion of individuals newly diagnosed with full or partial PTSD during the waiting-list period and in the first year after transplantation, was 23.2% (Table 2). After transplantation, no new onset of full PTSD was found, whereas new onset of partial PTSD was found in six transplant recipients.

Symptom occurrence

Figure 1 provides an overview of the percentage of respondents with clinically relevant symptoms (scores 3 or 4) of all PTSD symptoms at the four measurement-points. Regarding re-experiencing symptoms, “recurring dreams” and “intrusive memories” were the most frequently reported symptoms at all measurement-points. In the avoidance symptom cluster, “sense of foreshortened future” and “disinterest in activities” were the most reported symptoms before transplantation. After transplantation, the symptom “forgot important aspects” became most prevalent. The most reported symptoms in the arousal cluster were “having difficulty falling or staying asleep” and “problems concentrating.”

Table 3. Unstandardized estimates, 95% Confidence Intervals, and Odds Ratios of the predictive value of the number of symptoms in each cluster to satisfy criteria for partial of full PTSD compared to no PTSD

Variable	Estimate	*P* value	95% Confidence Interval		Odds ratio
			Lower	Upper	
Number of re-experiencing symptoms	1.61	0.002	0.59	2.64	5.01
Number of avoidance symptoms	1.37	0.002	0.51	2.23	3.93
Number of arousal symptoms	1.04	0.015	0.20	1.87	2.83

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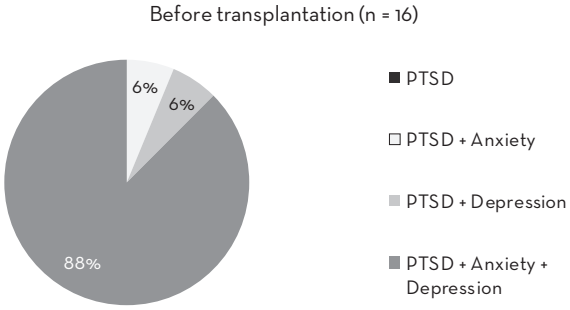

Figure 2. Percentage of respondents with full or partial PTSD and comorbidity of anxiety and/or depression before transplantation.

To identify which symptom cluster contributed the most to the diagnosis of either full or partial PTSD, compared to no diagnosis, an OLR analysis was performed. Because of the few cases of full and partial PTSD in the post-transplant period, we were only able to perform this analysis using data from the waiting-list period. The OLR showed that a unit increase in the number of re-experiencing symptoms increased the odds of caseness for partial or full PTSD the most (OR 5.0), when compared to a unit increase in the number of avoidance symptoms (OR 3.9) or arousal symptoms (OR 2.8) (Table 3).

Psychological comorbidity

Before transplantation, almost all respondents who met the criteria for either full or partial PTSD, also showed clinically relevant symptoms levels of both depression and anxiety (Figure 2). Again, because of the few cases of full and partial PTSD in the post-transplant period, we only performed these analyses using data from the waiting-list period.

To identify which symptom clusters of PTSD showed an overlap with either anxiety or depression, correlations between the number of symptoms in each cluster with the total score on the STAI and the CES-D were examined. Regarding anxiety, all symptom clusters of PTSD were significantly correlated with the STAI-6 total score. The strength of the correlation was moderate for the re-experiencing cluster (r = 0.32), and large for both the avoidance symptom cluster (r = 0.55) and the arousal symptom cluster (r = 0.57). Regarding depression, all symptom clusters of PTSD were also significantly cor-

related with the CES-D total score. The strength of these correlations was moderate for the re-experiencing cluster (r = 0.39), and large for both the avoidance symptom cluster (r = 0.62) and the arousal symptom cluster (r = 0.61).

Nature of re-experiencing symptoms

Because re-experiencing symptoms are seen as the core symptom of PTSD, we were interested in the nature of these symptoms. Of the 95 respondents, 49 (52%) described the content of their re-experiencing symptoms at one or more of the measurement-points. Some respondents mentioned the same symptoms at several measurement-points. Symptoms were therefore merged at the individual level at two measurement-points in time: before and after transplantation.

Symptoms of re-experiencing before transplantation

Before transplantation, intrusive thoughts related to the transplant were reported by fourteen (15%) of the respondents. These thoughts were mainly related to the period of waiting for an organ, such as concerns about timely availability of an organ and waiting for "the call." One respondent experienced a failed attempt to transplant, prior to a successful transplant, because the donor organ was rejected at the final decision, leaving the respondent with concerns about the success of any upcoming organ offer. Other respondents reported that they worried about the transplantation itself. They were concerned about being physically unable to undergo a transplantation because of their deteriorating health status or about the success of the transplant surgery. In addition, concerns about their family were described, mostly in terms of leaving their loved ones behind in case the transplant would not be in time or would be unsuccessful.

Two respondents mentioned that they had recurrent dreams about the transplantation or about death. Three respondents mentioned that they felt distress from cues related to medical complications or to the death of a family member with the same liver disease, leaving them with feelings of anxiety for their own future.

Symptoms of re-experiencing after transplantation

After transplantation, 32 (34%) of the respondents reported one or more re-experiencing symptoms. Twenty-one respondents reported having intrusive memories or thoughts about the transplant, mostly related to the clinical phase after the transplantation, such as the stay on the ICU or the nursing ward, but also regarding specific aspects of the clinical phase, such as experiencing delirium, interventions that restricted freedom of movement, or the feeling of being totally dependent upon others. Besides this, fears concerning the future, for example about the physical recovery or the possibility of graft loss, were described. Intrusive thoughts related to the death of the donor were also reported.

Recurrent dreams or nightmares about the transplantation were reported by fourteen respondents. These dreams were mostly about aspects of the transplant process, such as the surgery or the ICU stay, but unrealistic dreams were also present (eg, being hunted by sharks, horror-like dreams). One respondent described a feeling of reliving that consisted of a sensation of choking, which reminded of an experience during the stay

on the ICU. Distress at cues was mentioned by eight respondents. These cues were related to medical complications, such as recurrence of liver disease or signs of rejection, but also sounds or situations that reminded them of the hospital stay. Only one respondent reported physiological reactions to cues. This respondent felt nausea when confronted with reminders of the hospital stay.

DISCUSSION

The results of our study showed that in liver transplant patients clinically relevant PTS symptomatology is more present than caseness for full and partial PTSD, and that both PTSD symptomatology and caseness is more prevalent in liver transplant candidates than in liver transplant recipients during the first year after transplantation. Remarkably, we found no new onset of full PTSD after transplantation, and only a few cases of new onset of partial PTSD. All respondents with partial or full PTSD before transplantation also showed clinically relevant symptom levels of anxiety and/or depression.

Regarding symptom occurrence, arousal symptoms were most present at all measurement-points, especially sleeping disorders and concentration problems.

Our qualitative data showed that symptoms of re-experiencing before transplantation were mainly related to the wait for a suitable donor and the upcoming transplant surgery; after transplantation mainly to the clinical phase after the transplant surgery and concerns about the future.

Our findings regarding prevalence rates are in line with other studies that show that PTSD symptomatology is higher than PTSD caseness in patients after medical illness and treatment,[38] and after liver transplantation.[31,39] However, we found more PTSD caseness before the transplantation than previous studies among transplant candidates.[16,18,19]

Based on our qualitative data, the most prominent stressor for the development of PTSD in liver transplant candidates seems to be “being diagnosed with a life-threatening disease.” The nature of the re-experiencing symptoms, as described by the respondents, showed that, before transplantation, the unpredictability of the timing of the transplantation, along with deterioration in health status, left transplant candidates not only with concerns about the timely availability of a donor organ but also with concerns about leaving their loved ones behind.

Symptoms of re-experiencing after the transplantation were mostly related to the clinical phase after the transplantation (eg, ICU stay, delirium) but also represented current stressors like concerns about the recovery, or conceived future events like fear of graft loss. Although 34% of the respondents reported having intrusive thoughts, dreams, or distress at cues after the transplantation, this did not lead to the onset of full PTSD; furthermore, new onset of partial PTSD was found in 6% of the respondents. This might indicate that, after a successful transplantation, most recipients are capable of successfully processing their transplant experience.

Although arousal symptoms were most present at all measurement-points, OLR analyses showed that experiencing more arousal symptoms increased the odds of partial or

full PTSD only to a small extent, whereas experiencing more avoidance symptoms and re-experiencing symptoms increased the likelihood of PTSD to a greater extent. This emphasizes that re-experiencing symptoms are the core symptoms of PTSD and implies that the presence of arousal symptoms is not indicative of PTSD in the liver transplant population. Sleeping disorders and concentration problems are common in both transplant patients, mainly due to physical problems. Therefore, when transplant patients report arousal symptoms, causes other than PTSD should be kept in mind. Moreover, we found that PTSD in liver transplant patients is often accompanied by co-morbid conditions of anxiety and/or depression, and that, especially, avoidance and arousal symptoms show strong correlations with high symptom levels of anxiety and depression.
Due to the overlap between symptoms of PTSD with disease and treatment-related symptoms, and with other psychological disorders, the prevalence of PTSD in the transplant population could easily be overestimated. Because it is difficult to disentangle differences between them, it is important to carry out an assessment by a clinician when a diagnosis of PTSD is suspected. In this assessment, anxiety and depression should also be considered. Furthermore, alternative diagnoses, such as an acute stress disorder should be hold in mind, because some of the re-experiencing symptoms described by the respondents were related to current or conceived events (medical complications, fear of graft failure), which could be indicative of an acute stress disorder.

Strengths and limitations

The strength of our study is the prospective, longitudinal design, the satisfactory response rate (69%), and adequate sample size (n = 95), which made it possible to follow the course of PTSD in our patient group over time. To our knowledge, no other studies have investigated PTSD in a transplant population during the waiting-list period and after the transplantation. However, because of the prospective design, we could not include transplant recipients who were transplanted soon after placement on the waiting list or patients with acute liver failure. In this specific patient group, the transplantation itself may have a different impact, as shown by Guimaro and colleagues,[40] who found high symptom levels of PTS (46%) in patients transplanted for acute liver failure. Therefore, the course of PTSD in patients with an acute onset of their liver disease or who were on the waiting list for a short period of time, needs to be examined in future research.
A limitation of our study is that, because the start of the study was before the introduction of the DSM-5,[22] we were not able to examine PTSD in our population based on the latest insights. However, a study by O'Donnell and colleagues[41] showed that the prevalence scoring under DSM-5 was not significantly different from DSM-IV. Therefore, the results of our study may also be representative for DSM-5 criteria.
Another limitation was that we only used self-report to assess symptoms of PTSD. A clinician-ascertained diagnosis of PTSD may have added value. Also, the nature of the re-experiencing symptoms was only assessed by self-report. As a consequence of this, not all respondents, who indicated having intrusive memories or dreams, described the content of these thoughts or dreams. In addition, probing questions aimed at gaining more in-depth understanding of the nature of the re-experiencing symptoms was not

possible. For future research, we suggest using interviews to obtain a more in-depth understanding of these symptoms.

In conclusion, in liver transplant patients PTSD symptomatology is more present than PTSD caseness. During the waiting-list period, more patients satisfy the criteria for either full or partial PTSD – often accompanied by co-morbid conditions of anxiety and/or depression – than after the transplant. Having a life-threatening disease was found to be the main stressor for PTSD in transplant patients. Although aspects related to the transplantation itself, such as the stay on the ICU or delirium, were described as stressors after the transplant, this did not lead to development of full PTSD after transplantation. Arousal symptoms, such as sleeping disorders and concentration problems, were most frequently reported by transplant patients. However, these symptoms were not found to be unique to PTSD, whereas symptoms of re-experiencing and avoidance contributed the most to caseness for PTSD. Therefore, when patients report symptoms of re-experiencing transplant, healthcare workers should be aware of the possibility of PTSD. However, because of the overlap with disease and treatment-related factors, and with other psychological disorders, it is difficult to disentangle differences. Therefore, when PTSD is suspected, it seems important to refer to a clinician in order to confirm the diagnosis and subsequently initiate appropriate interventions.

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CHAPTER

8

RISK FACTORS AND IMPACT ON OUTCOMES OF TRAJECTORIES OF ANXIETY AND DEPRESSION AFTER LIVER TRANSPLANTATION: A PROSPECTIVE COHORT STUDY

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Submitted

ABSTRACT

Although the burden of psychological problems among liver transplant recipients is recognized, little is known about the course of symptoms of anxiety and depression over time. The aim of this study was to examine whether distinct trajectories of anxious and depressive symptoms are present among adult liver transplant recipients from before transplantation to two years afterwards; to identify associated demographic, clinical, and individual characteristics; and to examine the influence of distinct trajectories on outcomes. Data were retrieved by questionnaire before and at 3, 6, 12, and 24 months after transplantation. Clinical data were retrieved by medical record review.

Using Latent Class Growth Analysis, three distinct trajectories for symptoms of anxiety and depression were identified: "no symptoms," "resolved symptoms," and "persistent symptoms." The trajectory of persistent anxiety comprised 23% of the transplant recipients, the trajectory of persistent depression 29%. Several clinical and individual variables were found to be associated with the trajectories of persistent anxiety and depression: experiencing more side-effects from the immunosuppressive medication, a lower level of personal control, more use of emotional coping, less use of task-oriented coping, less disclosure about the transplant, and more stressful life events. Transplant recipients within the trajectories of "persistent symptoms" reported worse medication adherence and lower scores for all domains of health-related quality of life.

In conclusion, a significant subset of liver transplant recipients showed symptoms of persistent anxiety and depression. Our results emphasize the importance of psychological care in the transplant population. Assessment of risk factors early in the transplant process and continuous follow-up of psychological functioning are warranted. Based on these assessments appropriate interventions should be undertaken to enhance psychological functioning in liver transplant patients.

INTRODUCTION

Among liver transplant candidates clinically relevant symptom levels of 19%-55% have been described for symptoms of anxiety,[1-3] and 17%-62% for symptoms of depression.[2,4] After transplantation, prevalence rates of clinically relevant symptoms of anxiety have been described in 6%-35%[5-7] of the transplant recipients, while 3%-58%[6,8-10] have shown clinically relevant symptoms of depression. These prevalence rates show the burden of psychological problems among transplant patients, 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-transplant and post-transplant, and a stable situation thereafter,[2,8,11] although some studies have shown an increase in symptoms levels after the initial decrease.[12,13] However, these studies all describe the course of symptoms of anxiety and depression based on mean symptom levels or prevalence rates for the whole population under study. Given the individual variation in symptom levels among transplant recipients, distinct trajectories of anxiety and depression may be present within this general pattern. Exploring whether distinct trajectories are present in liver transplant recipients and examining their influence on outcomes after transplantation may help to gain a better understanding of the burden of anxiety and depression for transplant recipients. Moreover, examining variables associated with distinct trajectories may provide insight into risk factors related to the persistence or development of psychological problems after transplantation, and provide direction for interventions aimed at improving psychological functioning.

So far, only two studies have reported on distinct trajectories of anxiety and depression in liver transplant recipients over time. Miller et al.[14] reported on trajectories of resolved, unresolved, and no anxiety or depression, measured before and at six months after liver transplantation. DiMartini et al.[15] identified three trajectories of depression from three to twelve months after transplantation: constantly high symptom levels, increasing symptom levels, and constantly low symptom levels. Studies on trajectories of anxiety and depression in adult liver transplant recipients with measurement-points both before and at several time points after transplantation are lacking. Given the paucity of studies on this subject, little is known about trajectories of symptoms of anxiety and depression in liver transplant recipients, their associated risk factors, and their influence on outcomes after transplantation. Therefore, this study aims to: 1) examine whether distinct trajectories of anxious and depressive symptoms are present in liver transplant recipients from before transplantation to two years afterwards; 2) gain insight into the demographic, clinical, and individual characteristics associated with the distinct trajectories; and 3) examine the influence of the distinct trajectories of anxiety and depression on medication adherence and health-related quality of life after transplantation.

METHODS

A prospective, longitudinal cohort study was performed among adult liver transplant recipients of all three liver transplant centers in the Netherlands. 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 receiving medical treatment in one of the three transplant centers. Exclusion criteria were: unable to fill out a questionnaire due to physical, mental, or cognitive functioning or due to a language barrier. In addition, recipients receiving a re-transplant within the study period were excluded. Transplant recipients who could not be included in the study before transplantation (eg, in cases of acute liver failure) were invited to participate in the study, starting at 3 months after transplantation.

Eligible transplant candidates and transplant recipients received a letter explaining the purpose and procedure of the study, together with an informed-consent form, which also granted permission to obtain medical data from the medical record. After written informed consent, the participants received a baseline questionnaire. Measures of psychological functioning were repeated every six 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, transplant recipients filled out a questionnaire at three, six, twelve, and 24 months. The study ended in October 2015. The institutional review board of the transplant center that initiated the study 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).[16] The STAI-6 consists of 6 items rated on a 4-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 for the general population found in the 20-item scale,[17] a cutoff score of ≥12 was used to identify clinically relevant cases. Cronbach's alpha in this study varied from 0.84 to 0.87.

Symptoms of depression were assessed using the Dutch version of the Center for Epidemiological Studies Depression scale (CES-D).[18] The CES-D consists of 20 items, scored on a 4-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 was used to identify clinically relevant cases.[19] Cronbach's alpha in this study varied from 0.92 to 0.93.

Predictor variables

In studies measuring anxiety and depression on a group level, a variety of demographic variables, such as sex, age, marital status, education, and employment,[6,9,10,20] clinical

variables, such as primary liver disease, medical complications, and side-effects of the immunosuppressive medication (ISM),[9,10,21,22] along with individual variables, such as previous psychiatric disorders, coping style, and health beliefs,[11,12,20,22] have been found to be associated with symptoms of anxiety and depression. Because little is known about the risk factors associated with trajectories of anxiety and depression, we had to rely on these studies to identify possible predictors of distinct trajectories. In this study several demographic, clinical, and individual variables were taken into account as predictor variables.

Demographic variables were retrieved by self-report in the baseline questionnaire. *Sex, age, marital status, and educational level* were included in the analysis.

Regarding c*linical variables,* several variables that may be influential in the first two years after transplantation were considered. The presence of *transplant-related medical complications* in the first two 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 two years after transplantation. Hospital admissions which were part of the protocolled follow-up care after transplantation, were not taken into account.

Perceived side-effects of the ISM were measured at 24 months after transplantation by the Dutch version of the Modified Transplant Symptom Occurrence and Symptom Distress Scale (MTSOSD-59R).[23] This questionnaire assesses the occurrence of symptoms associated with ISM side-effects. Each item is scored on a 5-point scale (0 = never; 4 = always). Validation of the MTSOSD-59R showed excellent construct and discriminant validity.[23] In this study, data of the MTSOSD-59R were dichotomized to distinguish between side-effects occurring less often (score 0 to 2) and often (score 3 or 4). In the analyses, the number of ISM side-effects occurring often was taken into account by counting all ISM side-effects with a score of 3 or 4.

With respect to *individual variables,* three variables that are amenable to change were considered.

Personal control was measured before the transplant and at three, twelve, and 24 months after the transplantation using the Pearlin-Schooler Mastery Scale.[24] 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 5-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.[24] Cronbach's alpha in this study ranged from 0.80 to 0.82.

Coping style was measured at all measurement-points using the short-form of the Coping Inventory for Stressful Situations (CISS-SF).[25] The CISS-SF measures three dimensions of coping: task-oriented, emotional, and avoidance coping. The CISS-SF consists of 21 items, in which the respondents rate the extent to which they engage in various types of coping activities, using a 5-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,

Cronbach's alphas ranged between 0.79-0.86 for the task-oriented coping scale, 0.82-0.86 for the emotional coping scale, and 0.78-0.86 for the avoidance coping scale.

The emotional response to the receipt of a transplanted organ was measured at three, twelve, and 24 months after transplantation, by using three subscales of the Transplant Effects Questionnaire (TxEQ): worries about the transplant, feelings of guilt towards the donor, and disclosure about having had a transplant.[26] Items are scored on a 5-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.[27] The Dutch version of the TxEQ (TxEQ-NL) showed acceptable internal consistency scores (0.66-0.79), and an adequate fit with the original TxEQ.[27] In this study Cronbach's alphas were 0.71-0.78 for the subscale "Worry," 0.65-0.66 for the subscale "Guilt," and 0.70-0.86 for the subscale "Disclosure."

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 two years after the liver transplant was taken into account as a confounding variable. These data were retrieved by questionnaire at twelve and 24 months after transplantation using the Trauma and Life Event Self-report Inventory (TLESI).[28] The TLESI consist of a list of eleven stressful events (eg, death of a loved one, losing one's job) on which a person can indicate which events happened in the past five years. We adjusted this to "past year" in order 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.

Transplant outcomes

Regarding outcomes after transplantation, anxiety and depression have been associated with worse outcomes regarding quality of life, adherence, and survival in liver transplant recipients.[9,10,22,29,30] In this study, medication adherence and health-related quality of life (HRQoL), measured at 24 months after transplantation, were used as transplant outcomes.

Adherence to the immunosuppressive medication was measured using the adherence subscale of the TxEQ,[26,27] which measures behavioral as well as emotional aspects of adherence to the ISM-regimen. Higher scores indicate better adherence. Cronbach's alpha in this study was 0.76.

Health-related quality of life was measured using the World Health Organization Quality of Life–BREF questionnaire (WHOQOL-BREF).[31] The WHOQOL-BREF consists of 24 items covering 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 5-point Likert scale. For each subscale a mean value was computed, with higher scores indicating a better quality of life. In this study Cronbach's alpha's for the subscales were, respectively, 0.87, 0.87, 0.65, and 0.85.

Statistical analyses

Descriptive statistics were used to calculate mean scores and prevalence rates. For continuous data, differences between groups were examined with the Student t-test

(normally distributed variables) or the Mann-Whitney U test (non-normally distributed variables). Categorical data were examined with either the X^2-test or Fisher exact test, where appropriate.

Latent Class Growth Analysis (LCGA) with robust maximum likelihood estimation was used to identify trajectories of anxiety and depression using Mplus 7.1. (Muthen & Muthen, Los Angeles, CA). LCGA can identify unobserved differences in growth trajectories over time.[32] To select the best model, several criteria were used: 1) the Bayesian Information Criterion (BIC) and the Akaike Information Criterion (AIC) 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 (BLRT) and the Vuong-Lo-Mendel Rubin Likelihood Ratio Test (VLMR), 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.[33] 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 examine which demographic, clinical, and individual variables differed significantly between the distinct trajectories, X^2-tests and ANOVAs were used. Given the longitudinal study design, multivariate analyses of the variables significantly differing between trajectories was performed using General Linear Mixed Models (GLMM). In the GLMM analyses a polynomial approach was used, with either one of the trajectories of anxiety or depression as target variables entered as a nominal variable. Covariates were entered as fixed effects. ANOVAs were also used to examine the influence of the trajectories of anxiety and depression on health-related quality of life and adherence at two years after transplantation. The *P* value was set at 0.05, 2-sided, for all analyses.

RESULTS

Study population

Figure 1 provides an overview of the study inclusion, the available data, and the reasons for missing data. Demographic and clinical characteristics of the study population are shown in Table 1. Because of the number of missing data at baseline (37/153, 24%), the differences between patients with and without a baseline-measurement was 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 MELD-score at transplantation, and were more often transplanted for acute liver failure than were respondents with a baseline-measurement.

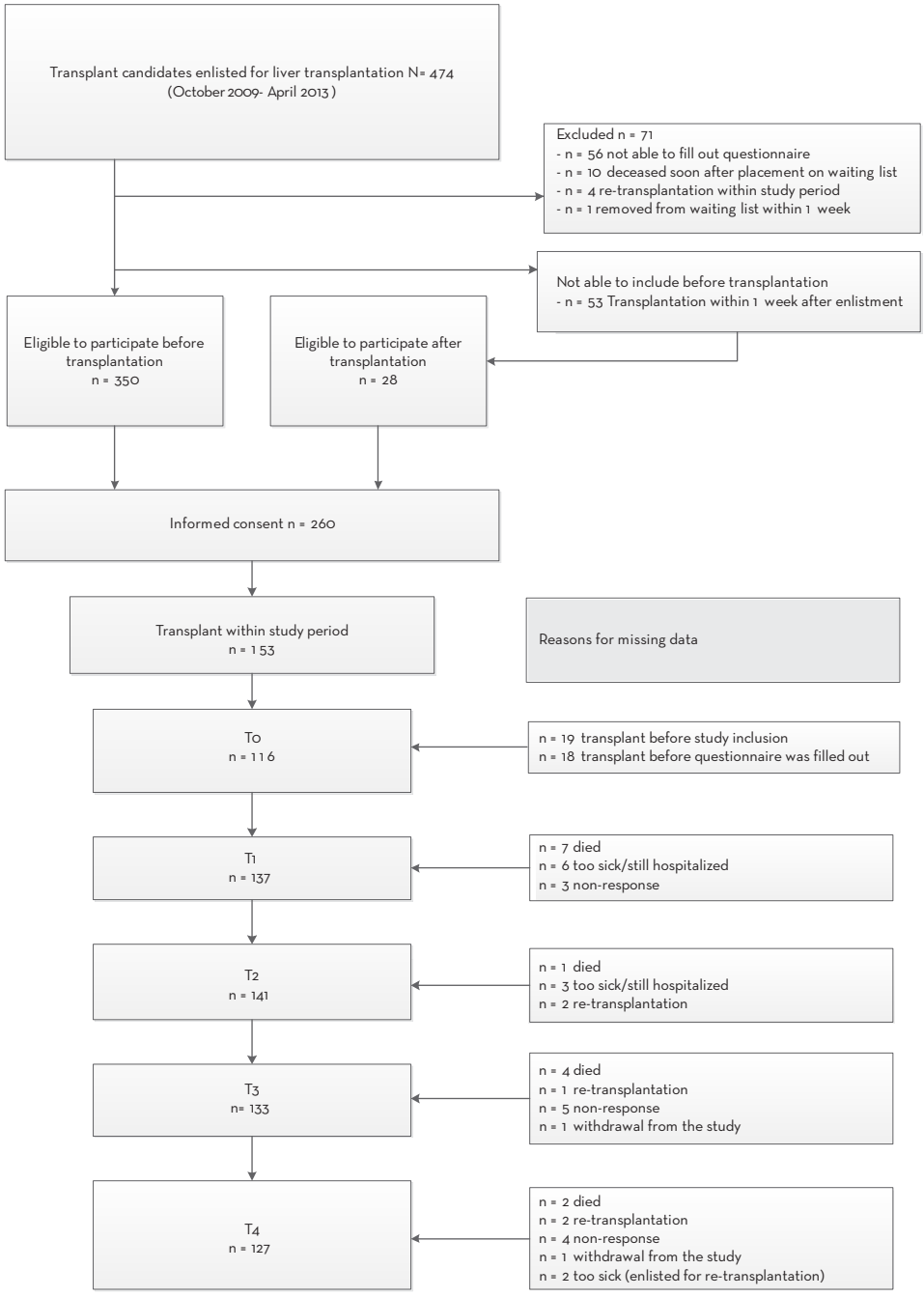

Figure 1. Overview of study inclusion and data.

Table 1. Demographic and clinical characteristics of the total study population, 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 value
n (%)				
Sex: Male	103 (67.3)	76 (65.5)	27 (73.0)	0.40
Marital status: Partner	117 (76.5)	90 (77.6)	27 (73.0)	0.57
Educational level:				
Primary	28 (18.5)	21 (18.3)	7 (19.4)	0.85
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)	0.33
Employment status:				
Working	35 (23.0)	33 (28.4)	4 (10.8)	0.09
Sick leave/ work disability	82 (53.9)	58 (50.0)	22 (59.5)	
Other	35 (23.0)	25 (21.6)	11 (29.7)	
Primary disease:				
Biliary cirrhosis	54 (35.3)	42 (35.2)	12 (32.4)	0.68
Metabolic liver disease	19 (12.4)	16 (13.8)	3 (8.1)	0.57
Cryptogenic liver cirrhosis	12 (7.8)	9 (7.8)	3 (8.10	0.59
Viral hepatitis	17 911.1)	15 (12.9)	2 (5.4)	0.17
Alcoholic liver disease	36 (23.5)	26 (22.4)	10 (27.0)	0.57
Acute live failure	4 (2.6)	0	4 (10.8)	**0.003**
Miscellaneous	11 (7.2)	8 (6.9)	3 (8.1)	0.73
Hepatocellular Carcinoma	32 (20.3)	25 (21.6)	6 (16.2)	0.48
Re-transplantation	15 (9.8)	11(9.5)	4 (10.8)	0.81
Immunosuppressive medication at discharge				
Corticosteroids	140 (94.0)	104 (92.9)	36 (97.3)	0.45
Tacrolimus	125 (83.9)	93 (83.0)	32 (86.5)	0.62
Cyclosporine	15 (10.1)	11 (9.8)	4 (10.8)	>0.99
Mofetil	71 (47.7)	50 (44.6)	21 (56.8)	0.20
Other	11 (7.4)	8 (7.2)	3 (8.1)	>0.99
Use of psychiatric drugs				
Anti-depressants	10 (6.5)	8 (6.9)	2 (5.4)	>0.99
Benzodiapines	12 (7.8)	10 (8.6)	2 (5.4)	0.73
Other	7 (4.6)	5 (4.3)	2 (5.4)	0.68
Mean (SD)				
Age at transplantation (years)	51.0 (11.8)	50.8 (11.4)	51.5 (13.1)	0.78
Time on waiting-list (days)	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 the transplant surgery (days)	32.9 (33.5)	34.1 (37.2)	29.1 (17.7)	0.43
Duration of ICU stay after the transplant surgery (days)	9.6 (21.6)	10.6 (24.3)	6.2 (7.9)	0.27

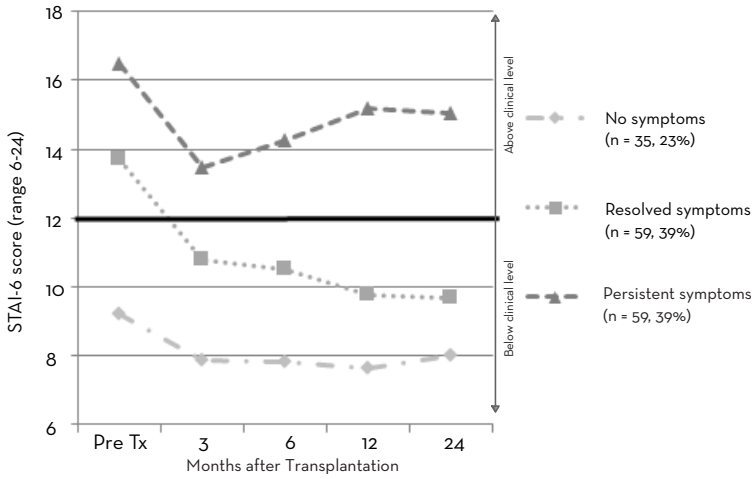

Figure 2. Trajectories of symptoms of anxiety from before transplantation to 24 months after transplantation.

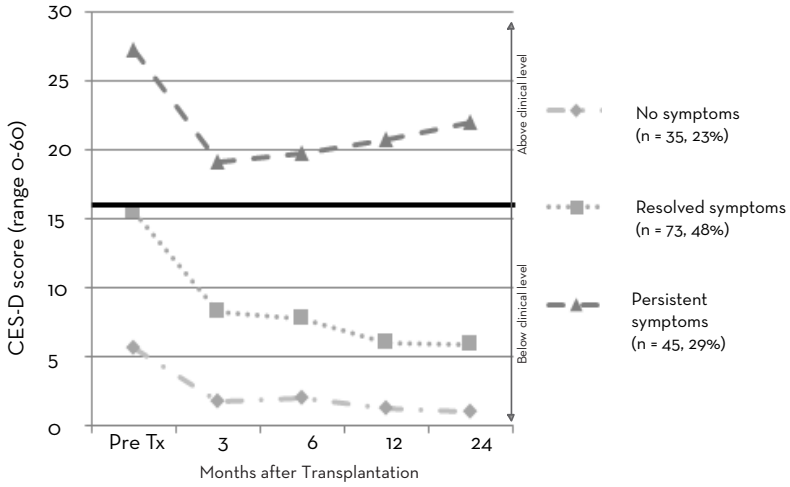

Figure 3. Trajectories of symptoms of depression from before transplantation to 24 months after transplantation.

Trajectories of symptoms of anxiety and depression

The parameter estimates of the LCGA analysis showed that the 3-class model was the best model for both symptoms of anxiety and depression (Table 2). Regarding symptoms of depression, the 4-class model seemed to be the best model, but the VLMR was not significant and the additional class was not meaningful conceptually; it distinguished two classes with depressive symptoms below the clinical cutoff score at all measurement-points.

The distinct trajectories of symptoms of anxiety and depression are depicted in, respectively, Figure 2 and Figure 3. Trajectory 1 (no symptoms) represented transplant recipients who did not show clinically relevant symptom levels of anxiety or depression at any measurement-point. Transplant recipients in Trajectory 2 (resolved symptoms) showed clinically relevant symptom levels of anxiety or depression around the cutoff score before transplantation but not after transplantation. In Trajectory 3 (persistent symptoms) the transplant recipients showed clinically relevant symptom levels of anxiety at all measurement-points. The trajectories regarding symptoms of anxiety comprised respectively 38.6% (n = 59), 38.6% (n = 59), and 22.9% (n = 35) of the transplant recipients. Those involving depressive symptoms comprised, respectively, 22.9% (n = 35), 47.7% (n = 73), and 29.4% (n = 45) of the transplant recipients.

Within all trajectories, of both symptoms of anxiety and depression, a significant decrease (P <0.001) in symptom level was found between the measurements before transplantation and at three months after transplantation, but not at subsequent measurement-points.

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 side-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, emotional coping, task-oriented coping, and the emotional response to the receipt of a transplanted organ differed significantly between the trajectories of anxiety and/or depression. The number of other life events also differed significantly between trajectories of anxiety and depression.

Multivariate analysis (Table 4) showed that the influence of some of the variables examined was comparable for the trajectories of anxiety and depression. Transplant recipients in the trajectories of no and resolved anxiety and depression reported less side-effects of the ISM, a higher level of personal control, and made less use of emotional coping compared to those in the trajectories of either persistent anxiety or depression.

Furthermore, transplant recipients within the trajectories of no or resolved anxiety made more use of task-oriented coping and disclosed more often that they had received a transplant compared to those in the trajectory of persistent anxiety. Transplant recipients within the trajectory of resolved anxiety encountered more biliary complications, but were readmitted to the hospital for fewer days compared to those in the tra-

Table 2. Parameter estimates for model selection of the trajectories of anxiety and depression

	BIC	AIC	Entropy	VLMR (df)	BLRT (df)	Size (%)				
						1	2	3	4	5
Symptoms of anxiety										
2-class	3302.113	3238.474	0.85	285.826**	285.826**	72.8	27.2	-	-	
3-class	**3283.078**	**3186.104**	**0.77**	**74.370****	**74.370****	**38.6**	**38.6**	**22.8**	**-**	
4-class	3298.421	3168.113	0.80	33.099	33.099	37.3	25.5	13.7	23.5	
Depressive symptoms										
2-class	4469.150	4405.511	0.88	469.088**	469.088**	52.9	47.1	-	-	-
3-class	**4332.732**	**4235.757**	**0.88**	**191.754****	**191.754****	**22.9**	**47.7**	**29.4**	**-**	**-**
4-class	4192.687	4162.378	0.89	95.739	95.379**	9.8	23.5	37.9	28.8	-
5-class	4309.403	4145.759	0.85	38.619	38.619*	10.5	26.1	18.9	26.1	18.3

Note: BIC = Bayesian Information Criterion; AIC = Akaike Information Criterion; VLMR = Vuong-Lo-Mendel Rubin Likelihood Ratio Test; BLRT = Bootstrapped Likelihood Ratio Test; * = significant at $P = 0.05$ level; ** = significant at $P = 0.001$ level

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* value	Trajectory of No depression n = 35	Trajectory of Resolved depression n = 73	Trajectory of Persistent depression n = 45	*P* value
n/%								
Sex: Male	42 (71.2)	38 (64.4)	23 (65.7)	0.72	24 (68.6)	51 (69.9)	28 (62.2)	0.68
Marital status: Partner	43 (74.1)	49 (83.1)	25 (71.4)	0.35	26 (76.5)	60 (82.8)	31 (68.9)	0.25
Educational level:								
Low	9 (15.3)	9 (15.5)	10 (29.4)	0.41	4 (11.4)	15 (20.5)	9 (20.9)	0.21
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)	**0.01**	12 (34.3)	36 (49.3)	18 (40.0)	0.30
vascular complications	18 (30.5)	19 (32.2)	12 (34.3)	0.93	12 (34.3)	18 (24.7)	19 (42.2)	0.13
rejection	9 (15.3)	14 (23.7)	10 (28.6)	0.28	6 (17.1)	14 (19.2)	13 (28.9)	0.35
graft failure	7 (11.9)	10 (16.9)	5 (14.3)	0.73	2 (5.7)	11 (15.1)	9 (20.0)	0.19
disease recurrence	5 (8.5)	7 (11.9)	3 (8.6)	0.79	1 (2.9)	11 (15.1)	3 (6.7)	0.10
Mean (SD)								
Age at transplantation (years)	53.4 (11.0)	49.8 (12.0)	48.9 (12.3)	0.12	52.4 (12.0)	52.1 (11.4)	48.0 (12.0)	0.13
Number of ISM side-effects	2.0 (3.7)	3.9 (4.1)	6.3 (6.0)	**0.001**	0.8 (1.0)	3.5 (4.3)	6.4 (5.7)	**<0.001**
Number of days re-hospitalization#	13.4 (20.0)	20.6 (24.6)	28.2 (33.3)	**0.03**	10.7 (17.8)	21.4 (25.5)	23.8 (34.1)	0.07
Personal control	28.4 (3.9)	25.2 (4.4)	20.2 (4.4)	**<0.001**	28.6 (3.7)	26.5 (4.5)	20.7 (4.2)	**<0.001**
Coping style								
Task-oriented coping	26.2 (5.0)	25.3 (3.9)	22.7 (5.4)	**0.01**	26.2 (4.3)	25.2 (4.8)	23.9 (5.3)	0.14
Emotional coping	14.2 (4.7)	16.4 (5.5)	21.9 (6.5)	**<0.001**	14.0 (4.1)	15.2 (4.5)	21.6 (7.3)	**<0.001**
Avoidance coping	15.4 (5.6)	17.5 (4.7)	15.8 (4.2)	**0.08**	15.8 (5.4)	16.4 (4.8)	16.5 (5.2)	0.81
Emotional response to the receipt of a transplanted organ								
Worry about transplant	2.5 (0.8)	2.8 (0.6)	3.2 (0.7)	**0.001**	2.4 (0.8)	2.7 (0.7)	3.3 (0.7)	**<0.001**
Guilt towards donor	1.6 (0.5)	1.7 (0.5)	2.0 (0.7)	**0.001**	1.7 (0.5)	1.7 (0.5)	2.0 (0.7)	**0.02**
Disclosure transplantation	4.6 (0.5)	4.4 (0.7)	3.9 (0.8)	**<0.001**	4.6 (0.5)	4.6 (0.5)	4.0 (0.9)	**<0.001**
Number of life events #	1.4 (1.4)	2.5 (2.2)	2.4 (2.1)	**0.01**	1.3 (1.2)	2.0 (1.8)	2.8 (2.5)	**0.01**

Note: ISM = immunosuppressive medication; # = in first two years after transplantation

Table 4. Odds ratios and 95% confidence interval (CI) of variables associated with trajectories of persistent anxiety compared to no anxiety and resolved anxiety, and of trajectories of persistent depression compared to no depression and resolved depression

	Odds ratio	95% CI		Odds ratio	95% CI	
		Lower	Upper		Lower	Upper
	Persistent anxiety vs. no anxiety			*Persistent anxiety vs. resolved anxiety*		
Variable						
Biliary complications#	1.83	0.52	6.44	**6.79**	**2.23**	**20.70**
Number of ISM side-effects	**0.78**	**0.70**	**0.87**	**0.90**	**0.83**	**0.97**
Number of days re-hospitalization#	0.98	0.95	1.00	**0.98**	**0.96**	**0.99**
Personal control	**1.35**	**1.21**	**1.50**	**1.14**	**1.04**	**1.25**
Task-oriented coping	**1.25**	**1.13**	**1.39**	**1.18**	**1.07**	**1.30**
Emotional coping	**0.85**	**0.78**	**0.93**	**0.89**	**0.82**	**0.96**
Worry about the transplant	1.44	0.71	2.89	1.51	0.80	2.82
Guilt towards donor	0.44	0.19	1.02	0.72	0.35	1.48
Disclosure about transplantation	**2.39**	**1.21**	**4.71**	**2.35**	**1.34**	**4.13**
Number of life events#	**0.66**	**0.53**	**0.82**	0.98	0.82	1.16
	Persistent depression vs. no depression			*Persistent depression vs. resolved depression*		
Number of ISM side-effects	**0.56**	**0.46**	**0.70**	**0.92**	**0.86**	**0.98**
Personal control	**1.30**	**1.18**	**1.43**	**1.19**	**1.11**	**1.29**
Emotional coping	0.93	0.86	1.02	**0.90**	**0.85**	**0.96**
Worry about the transplant	**0.33**	**0.17**	**0.62**	0.92	0.57	1.50
Guilt towards donor	0.77	0.39	1.55	0.58	0.34	1.00
Disclosure about transplantation	1.70	0.91	3.17	**1.56**	**1.01**	**2.43**
Number of life events#	**0.59**	**0.47**	**0.73**	**0.98**	**0.68**	**0.90**

Note: ISM = immunosuppressive medication; # = in first two years after transplantation

jectories of persistent anxiety. Transplant recipients in the trajectory of no anxiety reported fewer other life events compared to those in the trajectory of persistent anxiety. Transplant recipients in the trajectory of no depression worried less often about their transplant compared to those in the trajectory of persistent depression. Those in the trajectory of resolved depression made less use of emotional coping and disclosed more often that they had received a transplant compared to those in the trajectory of persistent depression. Compared to transplant recipients in the trajectory of persistent depression, those in the trajectories of no or resolved depression reported fewer other life events.

Influence of distinct trajectories on medication adherence and health-related quality of life

Transplant recipients within the distinct trajectories of anxiety and depression differed significantly on the level of medication adherence ($P = 0.02$ and $P = 0.01$, respectively). Transplant recipients in the trajectories of "no symptoms" showed the highest scores for adherence (4.6, ± 0.5 and 4.7, ± 0.5, respectively), compared to 4.4 (± 0.6) in both the trajectories of "resolved symptoms", and respectively 4.0 (± 0.9) and 4.1 (± 0.9) in the trajectory of "persistent symptoms."

Regarding HRQoL, significantly different mean scores ($P < 0.001$) in all domains of HRQoL at 24 months after transplantation were found between transplant recipients within the distinct trajectories. In the trajectories of "no symptoms," the highest scores in all domains of HRQoL were found. The trajectories of "persistent symptoms" showed the lowest scores. Posthoc-analyses revealed that for the social domain, the trajectories of "no symptoms" and "resolved symptoms" did not differ significantly for the trajectories of anxiety ($P = 0.53$) as well as depression ($P = 0.47$).

DISCUSSION

Three distinct trajectories of symptoms of both anxiety and depression in adult liver transplant recipients were identified: a trajectory of "no symptoms," "resolved symptoms," and "persistent symptoms." A significant subset of liver transplant recipients showed persistent symptoms of anxiety (23%) or depression (29%) after transplantation. These 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] we did not find a trajectory resembling an increase in symptom levels after transplantation. This might be due to the sample size, but differences in study population and design might also have been responsible for this. DiMartini et al.[15] included only transplant recipients transplanted for alcoholic liver disease and did not include a pre-transplant measurement-point. In our study, the study population was comprised of transplant recipients with various primary liver diseases and included a pre-transplant measurement-point.

In our study, all trajectories showed a significant decrease in symptom level between the measurements before and at three months after transplantation, implying a beneficial effect of the transplantation on psychological functioning for all recipients. Despite this beneficial effect, transplant recipients with high symptom levels of either anxiety or depression before transplantation seem to benefit less and to be most at risk for maintaining high symptom levels after transplantation. Moreover, transplant recipients within the trajectories of persistent symptoms, reported lower HRQoL and lower medication adherence. These results show not only the burden of psychological problems in transplant patients, but also that they are at risk for worse outcomes regarding (graft) survival due to their non-adherence.

In contrast to previous studies,[6,9,10,20] we found no associations between demographic

variables and the distinct trajectories of anxiety and depression in this study. Regarding clinical complications, of all medical complications examined, only having had biliary complications was associated with the trajectory of resolved anxiety. This seems to indicate that transplant-related medical complications after transplant surgery do not contribute to the persistence of symptoms of anxiety and depression. However, the number of days readmitted to the hospital differed significantly between the trajectories of anxiety. This might indicate that medical complications that require prolonged hospitalization, regardless of the underlying reason, may contribute to the persistence of symptoms of anxiety. However, it remains unclear whether anxiety leads to longer hospitalizations or vice versa.

Recipients in the trajectories of persistent symptoms of both anxiety and depression reported more severe ISM side-effects. This finding is in line with an earlier study among liver transplant recipients, in which was found that the number of ISM side-effects was associated with symptoms of anxiety and depression regardless of time since transplantation.[21] This result highlights the importance of the effective management of ISM side-effects. However, little is known about the treatability of these side-effects, and effective management strategies to decrease ISM side-effects are lacking.[34] This needs to be further addressed in future research.

Regarding individual variables, we found that respondents in the persistent symptom trajectories had a lower level of personal control, made more use of emotional coping, less use of task-oriented coping, and less often disclosed 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, personal control, or social support may help to improve their psychological functioning. However, evidence regarding effective psychosocial interventions in transplant recipients is limited.[35] Only a few studies report findings concerning psychosocial interventions, showing that these interventions may well be effective in reducing distress in transplant recipients.[35] Given this scarcity of evidence based interventions for the transplant population, psychosocial interventions need to be developed and examined for their effectiveness.

The strength of our study is its prospective, multicenter design, the adequate response rate (69%) and the reasonable sample size (n = 153). Although, data for pre-transplant 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 the study population.

Despite this, the generalizability of our results may be limited. Replication of our findings in larger samples is needed to be able to generalize our result to the liver transplant population as a whole. Larger sample sizes may also be needed to be able to identify additional trajectories (eg, increasing symptoms) of anxiety and depression. Furthermore, a longer follow-up is needed to be able to analyze the influence of the distinct trajectories on survival after transplantation.

In conclusion

Three distinct trajectories of symptoms of both anxiety and depression in adult liver transplant recipients were identified: a trajectory of "no symptoms," "resolved symptoms," and "persistent symptoms." A significant subset of liver transplant recipients 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 influenced by clinical variables, especially ISM side-effects, as well as 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. Individual risk factors associated with symptoms of anxiety and depression need to be assessed early in the transplant process and continuous follow-up on the psychological functioning of transplant recipients is warranted. If necessary, interventions aimed at managing ISM side-effects and empowerment can be offered to enhance the psychological functioning of transplant candidates and recipients. However, psychosocial interventions for transplant patients still need to be developed and examined for their effectiveness.

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CHAPTER

9

GENERAL DISCUSSION

Due to improvements in medical and surgical procedures and immunosuppressive medications, the clinical outcomes and survival of liver transplantation patients have improved over the past decades. As a consequence of this, other outcomes such as health-related quality of life and psychosocial consequences of transplantation have become increasingly important targets of evaluation.[1]

So far, the emphasis of psychosocial research in the field of transplantation has been mainly on health-related quality of life, the functional capacities involved in performing everyday tasks, and on a return to daily living. Relatively little attention has been paid to the psychological functioning of liver transplant patients.[2] Therefore, knowledge about the psychological functioning of this patient group is limited. In order to provide appropriate care to transplant candidates and recipients, it is important to understand the problems patients encounter, and to know what their opinions are regarding the provision of care. This emphasizes the need for empirical data on psychological problems and opinions of liver transplant candidates and recipients, the main focus of this thesis.

The psychological functioning of liver transplant recipients was examined in the "Psychological Aspects of Transplantation"-study that comprised two studies: 1) a prospective cohort study, in which liver transplant patients from all three liver transplant centers in the Netherlands were followed during the waiting-list period up until two years after transplantation; and 2) a cross-sectional study among all patients transplanted at the University Medical Center Groningen between 1979 and October 2009.

Exploring the opinions of transplant candidates and recipients enable transplant professionals to adapt the provision of care or, if necessary, to advocate changes in policies. Knowledge of the opinions of transplant candidates and recipients regarding transplant-related topics that are of interest to them is scarce. Therefore, the cross-sectional study "Communication about Donation" was performed to examine the opinions of transplant patients regarding the principle of anonymity of organ donation and shared decision making at the time of the organ offer.

MAIN FINDINGS

Psychological Aspect of Transplantation-study

In this study, we focused on the prevalence, associated variables, and impact on outcomes of three psychological problems: symptoms of anxiety, depressive symptoms and posttraumatic stress symptoms. Symptoms of anxiety, such as feeling tense, upset, or worried, may interfere with the daily functioning of transplant patients. Symptoms of depression, such as persistent feelings of sadness and worthlessness, and loss of interest in previously enjoyed activities, affect how people feel, think, and behave. This may lead to a variety of emotional and physical problems but can also be caused by physical illness. Symptoms of posttraumatic stress, such as intrusive memories, avoidance of reminders of the event, hopelessness, and hyper-arousal, can be seen as a failure to adapt to extreme stress and may lead to a posttraumatic stress disorder (PTSD). The main findings of the "*Psychological Aspect of Transplantation"-study* are presented in Figure 1.

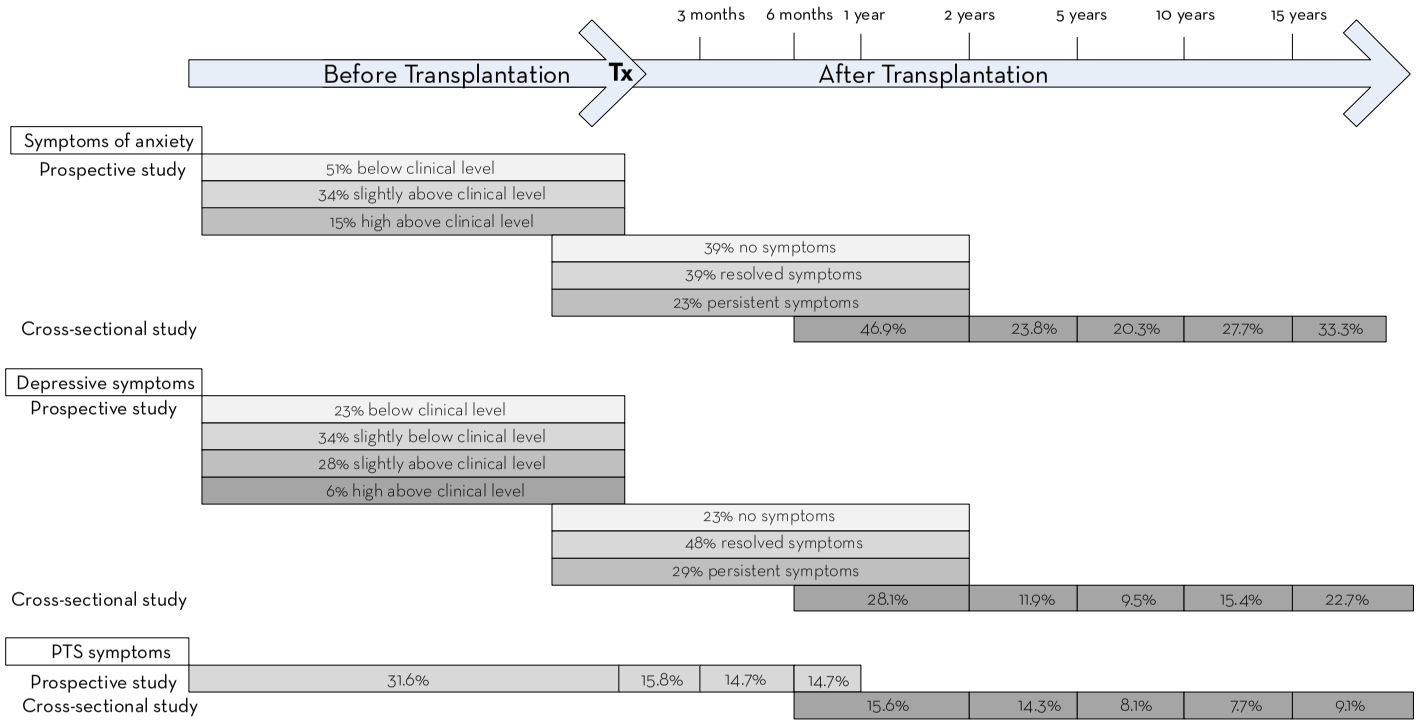


Figure 1. Main findings regarding prevalence rates "Psychological Aspects of Transplantation"-study.

Prevalence rates

In the prospective study, we examined the course of symptoms of anxiety and depression of liver transplant patients during the waiting-list period and in the first two years after transplantation (Chapters 6 & 8). The results showed that 34% of the transplant candidates had symptoms of anxiety slightly above clinical level throughout the waiting-list period, and 15% had symptoms of anxiety high above the clinical level (Chapter 6). When the post-transplant period was also taken into account, we found that 23% of the recipients showed persistent symptoms of anxiety above the clinical level (Chapter 8)
Regarding depression, 28% of the transplant candidates showed depressive symptoms slightly above the clinical level and 6% high above the clinical level throughout the waiting-list period (Chapter 6). After transplantation, 29% of the transplant recipients showed persistent symptoms of depression above the clinical level (Chapter 8).
With respect to posttraumatic stress, we found that 32% of the transplant candidates showed symptom levels above the clinical level, 10.5% of them fulfilled the criteria for full PTSD, and 6.3% fulfilled the criteria for partial PTSD. In the first year after transplantation, about 15% of the transplant recipients showed posttraumatic stress symptom levels above the clinical level, but no new onset of full PTSD was found. New onset of partial PTSD was found in six patients (6.3%) (Chapter 7).
In the cross-sectional study, we found that clinically relevant symptom levels of anxiety, depression, and posttraumatic stress were most present in the first 2 years after transplantation (Chapter 2). Regarding symptoms of anxiety and depression, the prevalence rates decreased in the years thereafter; a slight, but not significant, increase was shown in the patient groups in the long-term after transplantation. Posttraumatic stress symptoms remained at the same symptom level during the first 5 years but decreased in the years thereafter (Chapter 2).

Generally, we found that psychological problems are more common in transplant candidates than in transplant recipients. This implies, one the one hand, that the majority of transplant recipients are capable of successfully processing the transplant experience and that the transplantation itself provides health benefits regarding psychological functioning for a subset of the transplant recipients. On the other, a significant subset of transplant recipients encounters psychological problems, and may be in need of supportive care or psychological counseling.
However, the prevalence of PTSD in the transplant population can easily be overestimated due to the overlap between symptoms of PTSD and disease- and treatment-related symptoms, such as sleeping disorders and concentration problems, and with symptoms of anxiety and depression. Because it is difficult to disentangle differences between them, psychological problems other than PTSD should be kept in mind when PTSD is suspected.
When compared to Dutch population norms for lifetime prevalence rates, the prevalence rates of anxiety exceed the population norms of 19.6%,[3] in both transplant candidates and transplant recipients. Regarding depression, the percentage of transplant patients with symptom levels above the clinical level exceeds the population norm of 20.2%[3] before transplantation, shortly after, and in the long run after transplantation.

With respect to posttraumatic stress, the prevalence rates exceed the lifetime prevalence rate of 7%-8% during the waiting-list period, as well as in the first 5 years after transplantation, but in the long-term these prevalence rates are comparable.

Demographic, clinical, and individual variables associated with psychological problems

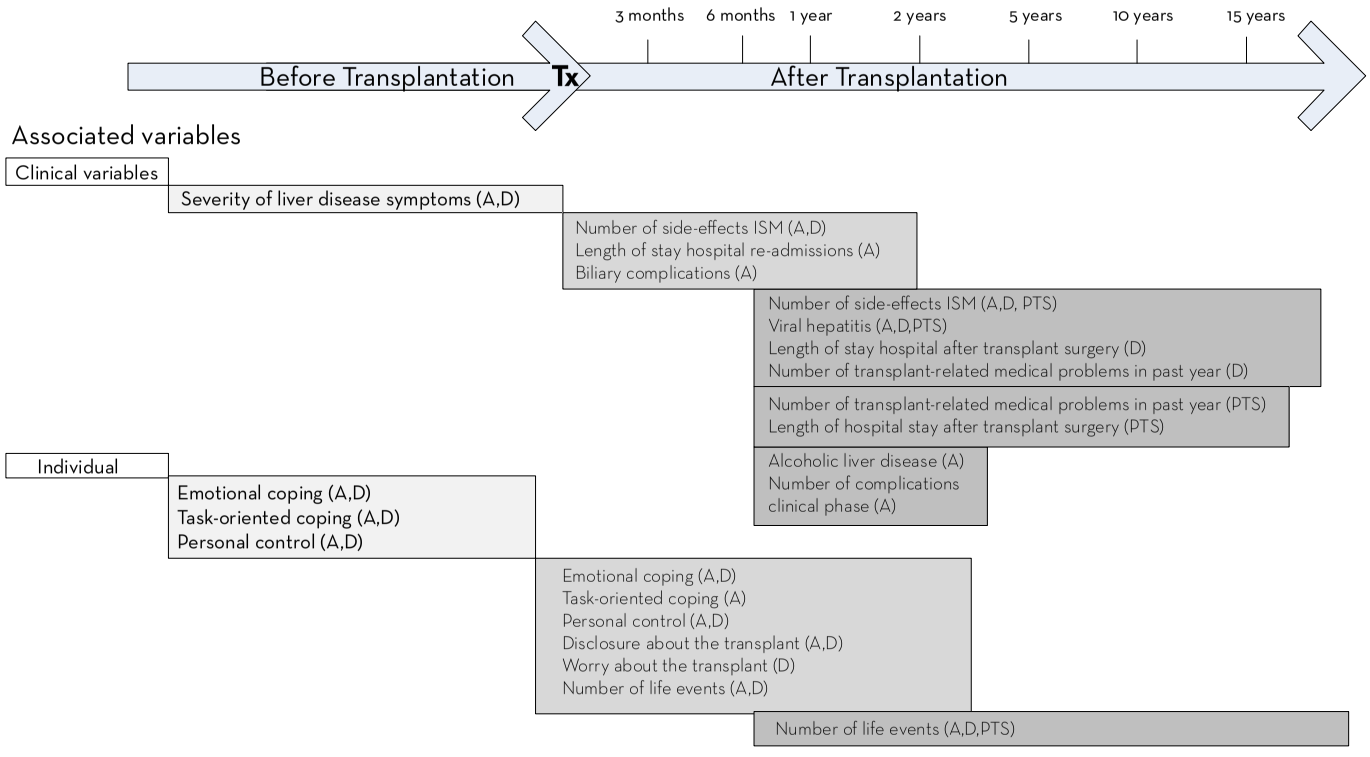
As depicted in Figure 2, several clinical and individual variables, but no demographic variables, were found to be associated with symptoms of anxiety, depression, and/or posttraumatic stress.

Regarding clinical variables, the most important risk factors for anxiety and depression seem to be the severity of the liver disease symptoms as experienced by the transplant candidates and the number of side-effects of the immunosuppressive medication after the transplantation. Among liver transplant candidates, experiencing more liver-disease symptoms was associated with the trajectories of anxiety and depression with symptom levels above the clinical level (Chapter 6). The number of side-effects from the immunosuppressive medication, was found to be associated with the trajectories of anxiety and depression after transplantation in the prospective study (Chapter 8) as well as with symptoms of anxiety, depression and posttraumatic stress regardless of time since transplantation in the cross-sectional study (Chapter 2). Furthermore, the length of hospital stay after the transplant surgery and of re-hospitalizations seem to play a role. Although transplant-related medical problems and primary liver diseases, such as viral hepatitis and alcoholic liver disease, were found to be associated with psychological problems in the cross-sectional study, these results were not confirmed in the prospective study.

With respect to individual variables, we found that a lower level of personal control, making more use of emotional coping, and making less use of task-oriented coping were associated with the trajectories of higher levels of symptoms of anxiety and depression in transplant candidates (Chapter 6) and with trajectories of persistent symptoms of anxiety or depression after transplantation (Chapter 8). In addition, disclosure about having had a transplant was associated with the trajectories of persistent symptoms of anxiety and depression after transplantation (Chapter 8). Life events other than the transplantation were also associated with psychological problems, in both the prospective and the cross-sectional study (Chapter 2 & 8).

In contrast to the literature, we found no associations of demographic variables with psychological problems after liver transplantation.

These results indicate that individual variables, such as coping style and sense of control, but also the severity of physical complaints (eg, disease symptoms or medication side-effects) are important risk factors in relation to the psychological well-being of transplant candidates and recipients. Interventions aimed at improving psychological well-being should, therefore, focus on effective disease management and side-effect management, and on empowering transplant recipients by strengthening coping skills and/or sense of control.



A = anxiety, D = depression, PTS = posttraumatic stress, ISM = immunosuppressive medication

Figure 2. Main findings regarding associated variables "Psychological Aspects of Transplantation'-study.

Influence of psychological problems on outcomes after transplantation

Transplant recipients within the trajectory of persistent symptoms of either anxiety or depression reported a significant lower level of adherence to the immunosuppressive medication and a significant lower level of health-related quality of life at two years after transplantation (Chapter 8).

This indicates that transplant recipients who show symptoms of anxiety or depression above the clinical level before and in the first two year after transplantation seem to benefit less from the transplantation in terms of quality of life. In addition, they are more at risk of medical complications, such as rejection, due to their medication non-adherence.

The emotional response to the receipt of a donor organ

To be able to examine patient reported outcomes, it is necessary to have valid and reliable research instruments. So far, no Dutch research instrument has been made available to measure the emotional response of transplant recipients to the receipt of a donor organ. Therefore, the Transplant Effects Questionnaire (TxEQ) was translated and validated for the adult Dutch liver transplant population. The Dutch version of the TxEQ was found to be an adequate fit with the original version of the TxEQ, showed acceptable validity, and was found to add a new dimension to the measurement of psychological functioning of transplant recipients (Chapter 3).

Communication about Donation-study

Opinions on anonymity of organ donation

Regarding anonymity of organ donation we found that a slight majority (53%) of the patients agreed with this principle, mainly out of respect for the donor (Chapter 4). Despite this opinion, the majority (65%) of transplant recipients would like to receive some information about their donor. A minority (19%) favoured direct contact with the donor's family. Respondents with a higher level of positive affect were less in favour of the principle of anonymity of organ donation, whereas respondents without a partner and those younger than 40 years or older 60 years were more in favour of anonymity or organ donation. Respondents with a higher level of education and those transplanted for alcoholic liver disease felt less need to get in touch with the donor's family, whereas respondents with more feelings of guilt towards the donor doubted more about direct contact.

Based on our results there is no need to advocate for a change in the current legislation on anonymity of organ donation. However, most liver transplant recipients would like to receive some general information about their donor. Therefore, clear guidelines on the sharing of donor data with recipients need to be established.

Need for information about donor related risk and shared decision making

The majority of patients (60%-75%) would like to be informed about donor-related risk at the time of the offer of a donor organ (Chapter 5). A small majority (53%) would like to be involved in the process of decision making on the acceptance of an organ offer, 80% of them preferred an active role in the decision making process whether to accept

or not to accept the organ offer. Transplant candidates, younger patients, and those with a higher level of education were found to be more willing to be involved in shared decision making. Therefore, patient preferences regarding the provision of information regarding donor-related risk and their wish for shared decision making needs to be assessed. Besides this, education and decision aid tools need to be provided to enable transplant patients to make informed decisions.

METHODOLOGICAL CONSIDERATIONS

The strengths and limitations of the studies are described in more detail in the separate chapters of this thesis. A short overview of the main issues is presented below.

The strength of the "Psychological Aspects of Transplantation"-study was the use of different approaches to gain insight into psychological problems of liver transplant candidates and recipients. In the cross-sectional study, we were able to examine clinically relevant symptom levels of anxiety, depression, and posttraumatic stress, in the short-, intermediate-, and long term after liver transplantation. Data on long-term psychological problems are especially scarce, and so ours have added value to the body of knowledge concerning psychological problems of liver transplant recipients. Another strength is the use of a prospective, longitudinal, multi-center design to study the course of psychological problems over time. Studies measuring psychological problems in the same liver transplant patient group before and at several time-points after transplantation are scarce. Therefore, little is known about the course of symptoms of psychological problems over time. By using a prospective design, we were able to identify different trajectories of symptoms of anxiety and depression, both during the waiting-list period and throughout the first two years after transplantation. Moreover, examining the influence of demographic, as well as clinical, and individual variables on psychological functioning jointly enhances the understanding about which aspects influence the psychological functioning of transplant patients the most.

The response rates in the separate studies were satisfactory; respectively, 69.5% (260/378) in the prospective cohort study and 75% (281/373) in the cross-sectional study of the PATx-study, and 73% (179/244) in the "Communication about Donation"-study. Compared to sample sizes in other prospective, longitudinal studies on psychological functioning in the field of liver transplantation, with sample sizes between 25 and 186 respondents, the sample size in our study was reasonable.

Despite the satisfactory response rates and the reasonable size of the study population, the sample sizes were still small from a statistical point of view. Given the number of variables associated with psychological problems in the transplant population, a larger sample is needed to be able to examine all demographic, clinical, and individual variables jointly. Furthermore, by using a time-group and trajectory approach, we limited ourselves as to the number of variables that could be taken into account because of the small sample sizes in some of the time-groups and trajectories. These aspects limit the generalizability of our results. Therefore, replication of our analyses in a larger cohort is

warranted so as to be able to generalize the results to the liver transplant population. Our sample size was also too small to make any inferences about the impact of psychological functioning on outcomes after transplantation in terms of survival and graft survival.

The multi-center approach used in the prospective study added to the representativeness of this study for adult Dutch liver transplant patients. However, the representativeness of our studies may be limited for liver transplant candidates and recipients with a different cultural background. Of the transplant candidates, 6% could not be included because of a language barrier and only ~7% of our study population originated from other countries. Therefore, no inferences about differences based on cultural background could be made. Besides this, the cross-sectional studies were only performed among transplant candidates and recipients of the UMCG, which may limit the generalizability of our results.

Another limitation of this study is that only self-report measurements were used. Although validated research instruments were used, only prevalence rates based on clinically relevant symptoms levels could be determined. Studies using clinician-ascertained diagnosis of depression, for instance, often show lower prevalence rates.[4,5] Therefore, additional evaluation of psychological functioning by a clinician may provide added value in future research.

CLINICAL IMPLICATIONS

The prevalence rates of symptoms of anxiety, depression, and posttraumatic stress in our studies, showed the burden of psychological problems among liver transplant candidates and recipients. Our results emphasize the importance of a psychosocial evaluation and psychosocial support in the routine care of transplant recipients throughout the transplant process. Psychosocial care should begin early in the transplant process, with the assessment of psychological problems and associated risk factors during the screening for transplantation, followed by continuous monitoring of psychological problems throughout the transplant process. Based on these assessments, psychosocial interventions to optimize the psychological well-being of transplant candidates and recipients can be undertaken. Furthermore, the incorporation of a psychologically- or psychiatrically-oriented healthcare professional in the transplant team is recommended.

A structured pre-transplant psychosocial assessment during the screening for a transplant can be used to identify possible risk factors associated with adverse outcomes after transplantation. In the literature, several instruments to assess psychosocial risk factors have been described, of which the “Stanford Integrated Psychosocial Assessment for Transplantation” (SIPAT) seems the most promising.[6] Implementing a structured pre-transplant assessment gives transplant professionals not only the opportunity to identify possible psychosocial risk factors that influence outcomes after transplantation, such as coping style, social support, and psychological functioning, but also the opportunity to optimize the psychosocial situation of transplant candidates by provid-

ing supportive care or offering appropriate interventions.
Assessment of psychological problems should be part of an on-going process of the provision of information both before and after transplantation. This information should preferably be provided by the patient before each appointment at the outpatient clinic. However, measuring psychological problems by means of standardized research instruments is time consuming, and may be a burden for patients to complete on a regular basis. Making use of modern research techniques such as, the Patient-reported Outcomes Measurement Information System® (PROMIS®), developed by the National Institute of Health (USA), seems auspicious to obtain information about "what is the matter" in a way that reduces the burden for patients, and provides transplant professionals with information on problem areas. PROMIS® is an information system designed to measure generic health-related quality of life across multiple chronic diseases.[7] In PROMIS® measurements computer adaptive testing is used, in order to customize the items a participant sees, by choosing each successive item based on the response to the proceeding item. For example, when a participant indicates having depressive feelings, extra items are provided to gain additional information about these depressive feelings. A recent study among heart transplant candidates showed promising results for the use of PROMIS® in the transplant population, although the item bank needs to be adjusted to encompass the specific problems of the transplant population.[8]
Based on the assessment of psychological functioning by either SIPAT or routine screening, the transplant patient can be referred for an intake by a psychologist, psychiatrist, or a psychiatrically trained nurse practitioner, and, if needed, treatment can be offered to the patient. The type of treatment -pharmacological or non-pharmacological- will depend upon the severity of the symptoms and underlying causes. Moreover, preventive measures can also be undertaken.

In the literature, several interventions aimed at reducing psychological distress in transplant candidates and recipients are mentioned, for example, providing sensory and procedural information, enhancing coping skills, and stress management training.[1] However, evidence regarding effective psychosocial interventions in transplant candidates and recipients is lacking.[1,9,10] So far, only a few studies have reported on (preliminary) findings regarding psychosocial interventions in transplant candidates and recipients, which show that these interventions may be effective in reducing distress.[11-16] Therefore, further research is required concerning the effectiveness of non-pharmacological interventions in addressing the psychological needs of transplant patients.
Based on our results the need for psychological counseling is evident. However, within the transplant team counseling by a psychologist or psychiatrist is often provided on an as-needed basis and a psychologists is not an integral part of the transplant team. Incorporating a psychologically oriented healthcare professional into the transplant team (eg, health psychologist, psychiatrically-oriented nurse practitioner) may provide added value, because this professional can not only design and carry out interventions to enhance psychological well-being, but can also could advise and support other transplant-team members. In what way such a healthcare professional can possibly be embedded in the transplant team in an effective and efficient way needs to be examined.

However, to fully integrate psychosocial care into the routine care of transplant candidates and recipients, a re-design of current clinical practice may be needed. In a recent report on the psychosocial care for patients with serious somatic diseases by the Ministry of Health, Welfare and Sport in the Netherlands, it was emphasized that psychosocial care should be an integral part of somatic care, be of high quality, and be tailored to the patient's needs. However, at the same time, it was stressed that, at the moment, the organization of care and the reimbursement of the costs of psychosocial care do not sufficiently address the psychosocial care needs of patients with serious somatic diseases.[17]

In the field of transplantation, care for transplant patients is usually provided by a multidisciplinary team, but the focus here is mainly on the detection and treatment of somatic problems both before and after transplantation.[18,19] In this traditional care approach, based on an acute care model, not only has less attention been given to psychosocial care, preventive measures, and effective self-management,[19] but optimal clinical outcomes may also not be achieved.[18] Moreover, transplant recipients trade a chronic disease for a chronic condition. Therefore providing care from a biopsychosocial model might better address the needs of transplant candidates and recipients. This might be best addressed by a model of care based on the principles of the Chronic Care Model[20] (Figure 3): a "Transplant Care Management System."

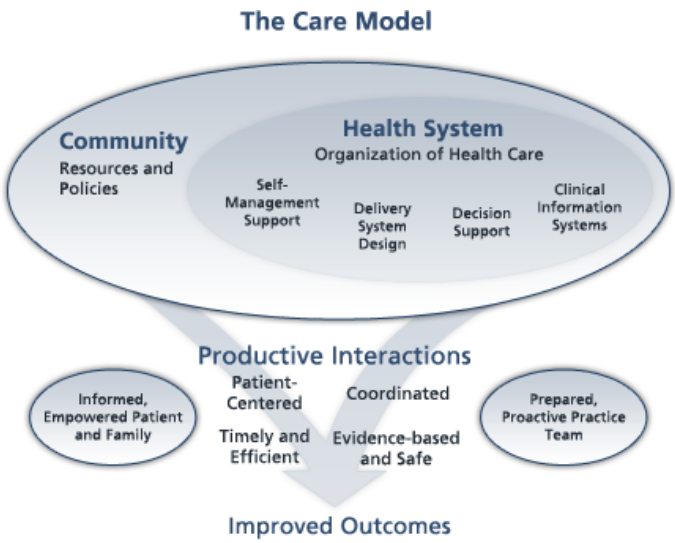


Figure 3. The Chronic Care Model.

This Transplant Care Management System could be based on the principles of the Chronic Illness Management (CIM) model. Chronic Illness Management is based on the principles of the Chronic Care Model and combines the following components: 1) ensuring access to and continuity of care; 2) increasing opportunities for patients and their families to participate in the care process; 3) coordinating care between care settings, and 4) providing continuous self-management support.[21]

The basis of the success of CIM in improving long-term outcomes is the building of relationships between informed, motivated, and involved patients and their families, a dedicated transplant team, and well-informed partners in care. In CIM, patient participation is crucial in the provision of care and the decision-making process. Therefore, integration of preferences and opinions of transplant candidates and recipients into care and policies is an integral part of the care process.

CIM is not a "one-size-fits-all concept" but can be adjusted to the patient's individual circumstances. The level of care needed, may depend upon the complexity of care. For most patients, provision of self-management support will be sufficient to fulfill their needs, whereas patients with complex care needs probably require intensive case management.

In CIM, nurses play a pivotal role in terms of treatment and coordination of care, improvement in outcomes, and in reducing healthcare costs.[19] The nurse, as a member of the multidisciplinary team, spends the most time with patients and is capable of maintaining an affective bond with patients and their families. In a recent study, Bisonnette et al.[18] showed that a collaborative care approach, led by an advanced practice nurse in the care of kidney transplant recipients, was successful in targeting clinical outcomes (blood pressure control, diabetes control, adherence) better than the usual care approach.

Psychological well-being may benefit from CIM as well, by establishing a partnership between the patient and the transplant professional, providing supportive care, and enhancing the perceived control over health and daily life.

Patient preferences, for instance with respect to shared decision making, can be put into practice within the CIM model. As shown in the "Communication about Donation"-study, liver transplant recipients do have different opinions about transplant-related topics and are willing to participate in shared decision making. However, to be able to make informed decisions, patients need to be educated about relevant topics, such as donor-related risks, and decision aid tools need to be developed. Also guidelines about the provision of information to patients need to be developed.

Effective integration of psychosocial care in the care of transplant patient will also depend upon the funding of this type of care. In the Netherlands, funding of healthcare is based on, so called, DBC's. (in Dutch: Diagnose Behandel Combinatie). A DBC is a predefined average care package, with a fixed price based on a specific medical diagnosis (www.nza.nl). In the DBC for liver transplantation, supportive care for transplant recipients is taken into account. However, the reimbursement of psychosocial care may be insufficient when it becomes a more integral part of the care for transplant patients. Therefore, the reimbursement needed for supportive care for transplant patient needs to be reconsidered.

FUTURE RESEARCH

Future studies on psychological aspects of transplantation in transplant candidates during the waiting-list period should focus on gaining a deeper understanding of the psychological functioning of transplant candidates in relationship with their illness and the concept of waiting for a transplant.
In future studies, the role of the social environment of the transplant patient also needs to be taken into account. Not only the influence of the support from significant others (eg, partner or family) on psychological problems of the transplant patient needs to be examined, also the psychological well-being of those family members themselves needs to be examined.
For transplant recipients, future studies should focus on the effect of psychological problems on clinical outcomes after transplantation, such as patient survival, graft survival, adherence, and health-related quality of life. Furthermore, the impact of psychological problems on outcomes in the long term after transplantation needs to be determined. So far, few studies have studied the impact of psychological distress on these outcomes, and those that have, have shown inconclusive results.[22] Psychological problems after transplantation, especially depression, seem to influence outcomes more than psychological distress before transplantation,[23] but additional research is warranted.
Furthermore, interventions to improve psychological health in transplant candidates and recipients need to be designed and evaluated. In these studies, not only does the effectiveness of the intervention need to be established, but also the question as to which interventions have beneficial outcomes for which patients needs to be answered. Patient preferences regarding the provision of care also need to be determined, not only regarding interventions, but also regarding the provision of information and resources. Also, the effect of educational programs and/or the use of decisions aid tools on the process of shared decision making need to be evaluated
When a Transplant Care Management System, based on the principles of Chronic Illness Management, is implemented, the effects of this model of care also need to be examined. The results of studies examining the effects of CIM on outcomes in chronically ill patient populations seem promising.[24-27] However, evidence as to their effectiveness in a transplant population is limited.[18] Future studies should focus on the embedding of a CIM model in the care of transplant patients, as well as on the effectiveness of specific parts of the care model in achieving the set goals, and on the effects on clinical outcomes for both transplant candidates and recipients.

CONCLUDING REMARKS

This thesis has addressed several topics related to the emotions and perceptions of liver transplant candidates and recipients. Therefore, for a large part we now know "What's on their mind". From the studies included in this thesis we know that:

- Symptoms of anxiety and depression are prevalent in adult Dutch transplant patients, especially during the waiting-list period (~49%, and ~34%, respectively) and to a smaller extent after transplantation (~23%, and ~29%, respectively);
- Distinct trajectories of symptoms of anxiety and depression can be distinguished in both transplant candidates and recipients
- PTSD is more prevalent in transplant candidates than in transplant recipients, but can be easily overestimated due to the overlap between symptoms of PTSD and disease- and treatment-related symptoms, and other psychological problems;
- Symptoms of anxiety and depression are mainly influenced by clinical variables, such as the severity of disease symptoms and the number of side-effects of the immunosuppressive medication, as well as individual variables, such as personal control and coping;
- Transplant recipients with persistent symptom levels of anxiety or depression within the first two years after transplantation report lower medication adherence and a lower level of health-related quality of life at two years after transplantation;
- The majority of liver transplant recipients is in favour of anonymity of organ donation. Although the majority of transplant recipients would like to receive some information about their donor, only a small subset of transplant recipients would like direct contact with the donor's family;
- A significant subset of transplant candidates and recipients would like to be informed about donor-related risks and would like to be involved in shared decision making regarding the acceptance a donor organ.

To address these topics that are on the minds of transplant patients, it is necessary to integrate psychosocial care into the routine transplant care. The time has come to proceed from "What is the matter" to "What matters". In this thesis several recommendations have been made:

- Use a structured assessment tool to identify psychosocial risk factors in the screening process of liver transplant candidates;
- Monitor psychological problems on a routine basis throughout the transplant process. Preferably, this should be done by modern research techniques using computer adaptive testing;
- Incorporate a psychologically and/or psychiatrically-oriented healthcare professional into the multidisciplinary transplant team;
- Design and evaluate interventions to address the psychological needs of transplant patients;
- Implement a model of care based on the principles of a Chronic Illness Management to better address the needs of transplant patients;
- Assess patient preferences and incorporate these in the provision of care;
- Provide education and decision aid tools to enable transplant patients to make informed decisions;
- Establish guidelines on the sharing of donor data with recipients;
- Reconsider the costs of psychosocial care in the DBC for liver transplantation.

To conclude, medical and technological progress has led to improved procedural and survival outcomes after liver transplantation, but the success of transplantation can no longer be determined solely by an extended life span.[28] It is the quality of that life span that matters too. The integration of psychosocial care into the care for transplant candidates and recipients, by using a biopsychosocial model of care, can offer a valuable contribution to the healthy ageing of the transplant population.

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APPENDICES

ENGLISH SUMMARY

Having to undergo a liver transplantation is a major event in a person's life. Although the transplantation itself, generally, is beneficial for the health and quality of life of the transplant patient, the transplant process is accompanied with significant stressors. These comprise for instance, learning about having a life threatening disease, having to wait for a suitable donor organ, undergoing a major surgery, adjusting to a life with a life-long regimen of immunosuppressive drugs and adherence to strict guidelines, and, possibly, experiencing complications related to the treatment. Given these stressors, it is not unlikely that the transplant process causes psychological distress in a subset of transplant candidates and recipients, such as symptoms of anxiety, depression, and/or posttraumatic stress (PTS). However, so far relatively little is known about psychological problems in Dutch liver transplant candidates and recipients. To be able to optimize the psychosocial care for liver transplant patients, more insight into the psychological functioning of this patient group is needed. Besides this, it is important to know how patients think about topics related to the transplant process which might be of influence on the care or policies for this patient population.

In this thesis the results of two studies on emotions and perceptions of liver transplant candidates and recipients are described. The first study, the "Psychological Aspects of Transplantation"-study (PATx-study) aimed to examine psychological problems among Dutch adult liver transplant candidates and recipients by: 1) gaining insight into prevalence rates of symptoms of anxiety, depression, and posttraumatic stress, 2) identifying demographic, clinical, and individual characteristics associated with these psychological problems, and 3) examining their influence on outcomes after transplantation. This study comprised a cross-sectional study among liver transplant recipients (n = 281), transplanted between 1979 and 2009, of the University Medical Center Groningen (UMCG) and a prospective cohort study among transplant patients (n = 260) from all three liver transplant centers in the Netherlands. In the prospective study, patients were followed during the waiting-list period up until the first two years after transplantation.

The aim of the second study, the "Communication about Donation"-study, was to gain insight into four topics related to the transplant process: 1) the principle of anonymity of organ donation; 2) direct contact with the donor's family; 3) shared decision making regarding accepting a donor offer; and 4) information about donor-related risks. This cross-sectional study was performed among adult liver transplant candidates and recipients receiving treatment at the UMCG. Liver transplant recipients transplanted between 2000 and 2010 and liver transplant candidates who were actively listed for transplantation in February 2013 were invited to participate in the study.

In Chapter 2, the results of the cross-sectional part of the PATx-study regarding the prevalence rates of psychological problems among liver transplant recipients and their associated transplant-related risk factors at different time periods after transplantation are described. 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. Symptoms of anxiety and depression were more prevalent in the first two years and in the long term (>10 years) after transplantation. PTS symptoms were more prevalent in the first five years after transplantation. However, these prevalence rates did not differ significantly between time periods. Regarding risk factors, we found that viral hepatitis as the primary disease and the number of side-effects of the immunosuppressive medication were significantly associated with all psychological problems at all time periods after transplantation. Besides this, the length of the hospital stay after the transplant surgery and the number of transplant-related complications in the year before the study were significantly associated with symptoms of depression and PTS. Alcoholic liver disease as the primary disease and the number of transplant related medical problems after the transplant surgery were significantly associated with symptoms of anxiety in the short term after transplantation.
This study showed that a significant subset of transplant recipients experiences psychological problems especially at the short term and the long term after transplantation, and that these problems were often associated with the perceived side-effects of the immunosuppressive medication and medical complications.

The data of the cross-sectional study of the PATx-study were also used to validate the Transplant Effects Questionnaire (TxEQ) for the use in Dutch liver transplant recipients (Chapter 3). The TxEQ measures the emotional response to the receipt of a transplanted organ on five subscales: worry about the transplant, feelings of guilt towards the donor, disclosure about the transplant, medication adherence, and feelings of responsibility towards others. The TxEQ was translated into Dutch (TxEQ-NL) using the backward-forward translation method. In this study, we evaluated the psychometric properties of the TxEQ-NL. Confirmatory factor analyses of the TxEQ-NL revealed an adequate fit with the original version, although four items showed low factor loadings (<40). Internal consistency was acceptable (.66-.79). The small correlations between the TxEQ-NL and generic measures of psychological functioning indicated that the constructs measured are related but distinguishable. Therefore, the TxEQ-NL adds a new dimension, not covered by commonly used research instruments, to the measurement of psychological functioning of transplant recipients.

Chapter 4 & 5 discussed the results of the “Communication about Donation”-study. In Chapter 4, the results regarding opinions of transplant recipients on anonymity of organ donation and their wish for direct contact with the family of the deceased donor were described. Fifty-three percent of the transplant recipients (n = 177) agreed with the principle of anonymity of organ donation, mainly out of respect for the donor. Whereas transplant recipients (17%) who disagreed with the principle of anonymity of organ donation found that this should be their own decision and should not be imposed by law. Transplant recipients who lived alone and those who were younger than 40 years or older than 60 years of age were more in favor of anonymity of organ donation, whereas transplant recipients with a higher level of positive affect disagreed

more often with anonymity of organ donation. The majority of the transplant recipients (65%) indicated that they would like to receive some information about their donor, like age, sex, and health status. Only 19% of the transplant recipients favored direct contact with the donor's family, mainly to express their gratitude personally. Recipients transplanted for alcoholic cirrhosis were less in favor of direct contact, whereas transplant recipients with more feelings of guilt doubted more about direct contact.
Based on these results, we concluded that there is no need to change the current legislation on anonymity of organ donation. However, because most liver transplant recipients would like to receive some general information about their donor, clear guidelines on the sharing of donor data with recipients need to be established.

In Chapter 5, the results regarding the wish for information of liver transplant patients about donor-related risks, such as disease transmission and increased risk of graft failure, and involvement in the decision making process of accepting an organ offer are described. We found that the majority of patients wanted to be informed about donor-related risks, respectively 59.8% of the transplant recipients and 74.8% of the transplant candidates. The preferred timing for being informed about donor-related risks was at the time of the organ offer for 53.3% of the patients. Among these patients, 79.8% wished to be involved in making the decision to accept or not to accept a liver for transplantation, 10.6% wished to make the final decision alone, and only 9.6% did not want to be involved in the decision-making process.

Therefore patient preferences regarding the provision of information on donor-related risk and their wish for shared decision making needs to be assessed. However, to enable transplant patients to make informed decisions, education and decision aid tools need to be provided

In the studies described in the Chapters 6 to 8, data of the prospective part of the PATx-study were used.
In Chapter 6, we examined if distinct trajectories of symptoms of anxiety and depression were present among liver transplant candidates (n = 216) during the waiting-list period, and which demographic, clinical, and individual variables were associated with these distinct trajectories. Three stable trajectories of symptoms of anxiety during the waiting-list period were identified: 1) a trajectory of symptoms of anxiety below clinical level, 2) a trajectory of symptoms of anxiety slightly above clinical level, and 3) a trajectory of symptoms of anxiety high above clinical level. These trajectories comprised respectively 51%, 34%, and 15% of the transplant candidates. Regarding symptoms of depression four stable trajectories were identified: 1) a trajectory of depressive symptoms below clinical level, 2) a trajectory of depressive symptoms slightly below clinical level, 3) a trajectory of depressive symptoms slightly above clinical level, and 4) a trajectory of depressive symptoms high above clinical level. Comprising respectively 23%, 34%, 28%, and 6% of the transplant candidates. For anxiety as well as for depression, experiencing more liver disease symptoms, a lower level of personal control, making more use of emotional coping, and making less use of task-oriented coping increased the likelihood of membership in those trajectories with higher symptom levels.

This study showed that distinct trajectories of symptoms of anxiety and depression are present in liver transplant candidates, and that especially clinical and individual factors were significantly associated with the trajectories of higher symptom levels. However, the symptom level at baseline seems to be indicative of the symptom level during the waiting-list period. Therefore, screening of psychological symptoms and associated variables is warranted early in the transplant process. Subsequently, appropriate interventions should be undertaken to optimize psychological wellbeing in liver transplant candidates.

Chapter 7 describes on posttraumatic stress disorder (PTSD) in liver transplant patients (n = 95), by describing the prevalence and course of PTSD from the waiting-list period up until the first year after transplantation, by exploring which symptoms of PTSD contribute the most to a diagnosis of PTSD in liver transplant patients, by examining the overlap of PTSD with anxiety and depression, and by examining the nature of re-experiencing symptoms in liver transplant patients. Before transplantation, 32% of the respondents showed clinically relevant symptom levels of PTS. Of the transplant candidates, 10.5% fulfilled the criteria of full PTSD and 6.3% fulfilled the criteria of partial PTSD. In all cases, co-morbid conditions of anxiety and/or depression were present. After transplantation, ~15% showed clinically relevant symptoms of PTSD, but no new onset of full PTSD was found, while new onset of partial PTSD was found in six respondents. Arousal symptoms were the most frequently reported symptoms both before and after transplantation, but these symptoms were found not to be distinctive for PTSD in transplant patients because of the overlap with disease- and treatment-related symptoms. Re-experiencing symptoms before transplantation were mostly related to waiting for a donor organ and the upcoming surgery. After transplantation, re-experiencing symptoms were mainly related to aspects of the hospital stay.
Based on these results, we concluded that that clinically relevant symptoms of PTS were more present in liver transplant patients than caseness for full or partial PTSD, and that both PTSD symptomatology and caseness is more prevalent in liver transplant candidates than in liver transplant recipients during the first year after transplantation. Therefore, being diagnosed with a life-threatening disease seems to be the main stressor for PTS(D) in liver transplant patients. However, because of the overlap with disease and treatment-related factors and with other psychological disorders, it is difficult to disentangle differences between those problems. Therefore, when a diagnosis of PTSD is suspected, referral to a psychiatrically oriented clinician is warranted.

In Chapter 8, we examined if distinct trajectories of anxiety and depression were present among liver transplant recipients (n = 153) from the waiting-list period up until two years after transplantation. Besides this, demographic, clinical, and individual variables associated with these trajectories, and the impact of the distinct trajectories on outcomes regarding medication adherence and health-related quality of life were examined. For both symptoms of anxiety and depression, three distinct trajectories were identified: 1) a trajectory in which respondents showed no clinically relevant symptom levels before and after the transplantation (“no symptoms”), 2) a trajectory in which

respondents showed clinically relevant symptom levels before transplantation, but not after transplantation ("resolved symptoms"), and 3) a trajectory in which respondents showed clinically relevant symptom levels both before and after transplantation ("persistent symptoms"). The trajectories regarding symptoms of anxiety comprised respectively 39%, 39%, and 23% of the transplant recipients. The trajectories regarding depressive symptoms comprised respectively 23%, 48%, and 29% of the transplant recipients. Experiencing more side-effects from the immunosuppressive medication, being re-hospitalized for a prolonged period of time, making more use of emotional coping, and the presence of other stressful life events were found to contribute to trajectories of persistent anxiety and depression. Having had biliary complications, a higher level of personal control, making more use of task-oriented coping, and disclosure about having had a transplant seemed to have a beneficial effect. With respect to outcomes, transplant recipients within the trajectories of "persistent symptoms" reported worse medication adherence and lower scores in all domains of health-related quality of life at two years after transplantation.
This study showed that a significant subset of liver transplant recipients showed unresolved symptoms of anxiety (23%) or depression (29%) after transplantation, with a negative effect on medication adherence and health-related quality of life. The trajectories of "persistent symptoms" were influenced by clinical variables, especially side-effects of the immunosuppressive medication, as well as individual variables, such as coping, personal control, and disclosure about the transplant. These finding emphasize the importance of psychosocial evaluation and psychosocial support in the care of transplant patients.

In general, the "Psychological Aspect of Transplantation"-study showed that a significant subset of transplant candidates and recipients encounter psychological problems, especially during the waiting-list period, but also on the short term and long term after transplantation. Individual variables, such as coping style and personal control, and clinical variables, such as the perceived severity of disease symptoms or medication side-effects, were identified as important risk factors in relation to the psychological well-being of transplant candidates and recipients. Besides this, transplant recipients who showed persistent symptoms of anxiety and depression reported worse outcomes regarding medication adherence and health related quality of life.
In the "Communication about Donation"-study, transplant recipients were found to have different opinions on topics of interest to them. Therefore, integration of preferences and opinions of transplant candidates and recipients into the care and policies seems warranted to make patients a partner in care.

Our results emphasize the importance of psychosocial evaluation and psychosocial support in the routine care of transplant recipients throughout the transplant process and warrant greater patient involvement in the transplant care process. Assessment of psychological problems and associated risk factors should start early in the transplant process during the screening phase for transplantation, followed by continuous monitoring of psychological problems throughout the transplant process. Based on

these assessments, psychosocial interventions to optimize the psychological well-being of transplant candidates and recipients can be undertaken. However, psychosocial interventions for transplant patients still need to be developed and examined for their effectiveness. Furthermore, the incorporation of a psychologically- or psychiatrically-oriented healthcare professional in the transplant team is recommended. However, to fully integrate psychosocial care into the routine care of transplant candidates and recipients and to enhance the involvement of patients in the care process, a re-design of the current clinical practice, primarily based on a biomedical acute care model, to a biopsychosocial model of care, based on the principles of the Chronic Illness Management, may be needed. The integration of psychosocial care into the care for transplant candidates and recipients may offer a valuable contribution to the healthy ageing of the transplant population.

NEDERLANDSE SAMENVATTING

Het ondergaan van een levertransplantatie is een ingrijpende gebeurtenis in iemands leven. Alhoewel een transplantatie, in het algemeen, een positieve invloed heeft op de algehele gezondheid en de kwaliteit van leven van een patiënt, gaat het transplantatieproces ook gepaard met diverse stressfactoren. Deze omvatten onder meer: het hebben van een levensbedreigende ziekte, het wachten op een geschikt donororgaan, het ondergaan van een grote operatie, het aan moeten passen aan een leven met strikte richtlijnen, het levenslang in moeten nemen van immunosuppressieve medicatie, en de kans op verschillende medische complicaties. Gezien deze stressoren, is het niet onwaarschijnlijk dat een deel van de levertransplantatiepatiënten psychologische problemen ervaart gedurende het transplantatieproces, zoals symptomen van angst, depressie en/of posttraumatische stress (PTS). Tot nu toe is relatief weinig bekend over deze psychologische problemen onder Nederlandse levertransplantatiepatiënten. Om de psychosociale zorg voor levertransplantatiepatiënten, zowel voor als na de transplantatie, te kunnen optimaliseren is het noodzakelijk meer inzicht te verkrijgen in het psychologisch functioneren van deze patiëntenpopulatie. Daarnaast is het van belang de mening van transplantatiepatiënten te weten over transplantatie-gerelateerde onderwerpen die van invloed kunnen zijn op het beleid rondom of de zorg voor deze patiëntenpopulatie.

In dit proefschrift worden de resultaten beschreven van twee studies naar emoties en percepties van levertransplantatiekandidaten en -ontvangers. De eerste studie betreft de 'Psychologische Aspecten van Transplantatie'-studie (PATx-studie), gericht op het onderzoeken van psychologische problemen onder volwassen levertransplantatiepatienten in Nederland door: 1) inzicht te verkrijgen in de prevalentie van symptomen van angst, depressie, en posttraumatische stress, 2) demografische, klinische en individuele kenmerken die geassocieerd worden met deze psychologische problemen te identificeren, en 3) de invloed van deze psychologische problemen op resultaten na transplantatie na te gaan. De PATx-studie bestond uit een cross-sectioneel onderzoek onder 281 patiënten die, tussen 1979 en 2009, een levertransplantatie ondergaan hebben in het Universitair Medisch Centrum Groningen (UMCG) en een prospectief cohort onderzoek onder 260 levertransplantatiepatiënten van alle drie de levertransplantatiecentra in Nederland. In het prospectief onderzoek werden patiënten gevolgd gedurende de wachtlijstperiode tot en met twee jaar na hun transplantatie.

Het doel van de tweede studie, de 'Communicatie over Donatie'-studie, was inzicht te verkrijgen in de mening van levertransplantatiepatiënten in Nederland over vier transplantatie-gerelateerde onderwerpen: 1) het principe van de anonimiteit van orgaandonatie, 2) direct contact met de familie van de donor, 3) gezamenlijke besluitvorming over het accepteren van een donoraanbod, en 4) de informatievoorziening over donorgerelateerde risico's. Dit cross-sectionele onderzoek werd uitgevoerd onder volwassen

levertransplantatiepatiënten die onder behandeling waren bij het UMCG. Patiënten die getransplanteerd zijn tussen 2000 en 2010 en levertransplantatiekandidaten die in februari 2013 actief op de wachtlijst voor een levertransplantatie stonden, werden uitgenodigd om deel te nemen aan dit onderzoek.

In hoofdstuk 2 zijn de resultaten van het cross-sectionele deel van de PATx-studie beschreven. In dit onderzoek is gekeken naar de prevalentie van psychologische problemen onder levertransplantatiepatiënten in verschillende tijdsperioden na transplantatie en transplantatie-gerelateerde risicofactoren die van invloed zijn op deze problemen. In de gehele groep (n = 281) had 33,4% van de levertransplantatiepatiënten klinisch relevante symptomen van één of meerdere psychologische problemen. Hiervan had 28,7% klinisch relevante symptomen van angst, 16,5% klinisch relevante symptomen van depressie en 10,0% klinisch relevante symptomen van PTS. Klinisch relevante symptomen van angst en depressie waren met name in de eerste twee jaar en op de lange termijn (>10 jaar) na de transplantatie aanwezig. PTS-symptomen werden vaker in de eerste vijf jaar na de transplantatie gezien. De prevalentiecijfers verschilden echter niet significant tussen de verschillende tijdsperioden. Wat betreft de risicofactoren waren het hebben van virale hepatitis als primaire leverziekte en het aantal bijwerkingen van de immunosuppressieve medicatie significant geassocieerd met alle psychologische problemen, ongeacht de tijdsperiode na transplantatie. Tevens waren de opnameduur in het ziekenhuis na de transplantatie en het aantal transplantatie-gerelateerde complicaties in het jaar voorafgaand aan het onderzoek significant geassocieerd met klinisch relevante symptomen van depressie en PTS. Het hebben van alcoholische levercirrose als primaire leverziekte en het aantal transplantatie-gerelateerde complicaties na de transplantatie waren op de korte termijn na de transplantatie significant geassocieerd met klinisch relevante symptomen van angst.
Dit onderzoek toont aan dat een substantieel deel van de volwassen levertransplantatiepatiënten in Nederland psychologische problemen ervaart, vooral op de korte en de lange termijn na de transplantatie. Deze problemen werden met name beïnvloed door de ervaren bijwerkingen van de immunosuppressieve medicatie en medische complicaties.

De data van de cross-sectionele studie van de PATx-studie zijn ook gebruikt om de 'Transplant Effects Questionnaire' (TxEQ) te valideren voor gebruik bij Nederlandstalige levertransplantatiepatiënten (Hoofdstuk 3). De TxEQ meet de emotionele reactie van een patiënt op het ontvangen van een getransplanteerd orgaan op vijf dimensies: zorgen maken over het donororgaan, schuldgevoelens naar de donor, openheid over de transplantatie, therapietrouw ten aanzien van medicatie en verantwoordelijkheidsgevoel ten opzichte van anderen. Voor dit onderzoek werd de TxEQ vertaald in het Nederlands (TxEQ-NL) met behulp van de 'backward-forward' vertaalmethode. Vervolgens werden de psychometrische eigenschappen van de TxEQ-NL geëvalueerd. Uit de confirmatieve factoranalyse bleek dat TxEQ-NL voldoende overeenkomt met de oorspronkelijke versie, alhoewel vier items een lage factorlading (<.40) toonden. De interne consistentie was redelijk (.66-.79). De lage correlaties tussen de TxEQ-NL en generieke meetinstrumenten op het gebied van psychologische functioneren gaven aan

dat de gemeten constructen verwant zijn, maar wel van elkaar te onderscheiden. De TxEQ-NL voegt daarmee een nieuwe, niet door gangbare generieke meetinstrumenten toegedekte, dimensie toe aan het meten van het psychologische functioneren van transplantatiepatiënten.

In hoofdstuk 4 en 5 worden de resultaten van de "Communicatie over Donatie"-studie beschreven. In hoofdstuk 4 zijn de resultaten beschreven wat betreft de mening van levertransplantatiepatiënten over anonimiteit van orgaandonatie en hun wens voor direct contact met de familie van de overleden donor. Drieënvijftig procent van de transplantatiepatiënten (n = 177) was het eens met het principe van anonimiteit van orgaandonatie, voornamelijk uit respect voor de donor. Transplantatiepatiënten (17%) die het niet eens waren met het principe van de anonimiteit van orgaandonatie vonden dat dit hun eigen beslissing zou moeten zijn en niet door een wet kan worden opgelegd. Transplantatiepatiënten die geen partner hadden en degenen die jonger dan 40 jaar of ouder dan 60 jaar oud waren, waren meer voor het principe van anonimiteit van orgaandonatie, terwijl transplantatiepatiënten die een hogere mate van positieve affect hadden het vaker oneens waren met het principe van anonimiteit van orgaandonatie.
De meerderheid van de transplantatiepatiënten (65%) gaf aan dat ze graag algemene informatie over hun donor zouden willen ontvangen, zoals leeftijd, geslacht en gezondheidstoestand. Negentien procent van de transplantatiepatiënten gaf aan direct contact met de familie van de donor te willen hebben, voornamelijk om hun dankbaarheid persoonlijk te kunnen uiten. Patiënten die getransplanteerd waren in verband met alcoholische levercirrose hadden minder behoefte aan rechtstreeks contact. Transplantatiepatiënten die meer schuldgevoelens naar de donor toe hadden, twijfelden hier meer over.
Op basis van deze resultaten is geconcludeerd dat er op dit moment geen noodzaak is om de huidige wetgeving ten aanzien van anonimiteit van orgaandonatie te veranderen. Echter, omdat de meeste levertransplantatiepatiënten graag enige algemene informatie over hun donor zouden willen ontvangen is het van belang richtlijnen te ontwikkelen over het delen van donorgegevens met transplantatiepatiënten.

In hoofdstuk 5 zijn de resultaten beschreven ten aanzien van de behoefte onder levertransplantatiepatiënten aan informatie over donor-gerelateerde risico's, zoals ziekteoverdracht en verhoogde kans op transplantaatfalen, en hun behoefte aan betrokkenheid bij de besluitvorming over het accepteren van een donoraanbod. De meerderheid van de patiënten, respectievelijk 59,8% van de getransplanteerde patiënten en 74,8% van de wachtlijstpatiënten, gaf aan geïnformeerd te willen worden over donor-gerelateerde risico's. Het tijdstip waarop men hierover geïnformeerd wilde worden was voor 53,3% van de patiënten ten tijde van het donoraanbod. Van deze patiënten wenste 79,8% te worden betrokken bij de besluitvorming over het al dan niet aanvaarden van een donororgaan voor transplantatie, 10,6% wilde de uiteindelijke beslissing alleen maken en 9,6% wilde niet betrokken worden bij het besluitvormingsproces.
Het is daarom van belang de voorkeuren van patiënten te inventariseren met betrekking tot de verstrekking van informatie over donor-gerelateerde risico's en hun wens

voor gezamenlijke besluitvorming. Echter, alvorens transplantatiepatiënten geïnformeerde beslissingen kunnen nemen, is het noodzakelijk hen hiervoor educatie en besluitvorming ondersteunende instrumenten aan te bieden.

In de studies beschreven in de hoofdstukken 6 tot 8, zijn data van het prospectieve deel van de PATx-studie gebruikt. In hoofdstuk 6, is onderzocht of in de wachtlijstperiode verschillende trajecten van symptomen van angst en depressie aanwezig zijn onder patiënten (n = 216) die op de wachtlijst staan voor een levertransplantatie en welke demografische, klinische en individuele variabelen van invloed zijn op de afzonderlijke trajecten. Wat betreft symptomen van angst werden drie verschillende, maar stabiele, trajecten vastgesteld: 1) een traject met geen klinisch relevante symptomen van angst, 2) een traject met matig ernstige klinisch relevante symptomen van angst, en 3) een traject met ernstige klinisch relevante symptomen van angst. Deze trajecten omvatten respectievelijk 51%, 34% en 15% van de transplantatiekandidaten. Voor symptomen van depressie werden vier afzonderlijke, eveneens stabiele, trajecten geïdentificeerd: 1) een traject met geen klinisch relevante symptomen van depressie, 2) een traject met milde klinisch relevante symptomen van depressie, 3) een traject met matig ernstige klinisch relevante symptomen van depressie, en 4) een traject met ernstige klinisch relevante symptomen van depressie. Deze trajecten omvatten respectievelijk 23%, 34%, 28% en 6% van de transplantatiekandidaten. Voor zowel de trajecten van angst als voor depressie geldt dat patiënten die meer symptomen ervoeren van hun leverziekte, een lager niveau van persoonlijke controle hadden, meer gebruik maakten van emotionele coping en minder gebruik maakten van taakgeoriënteerde coping een verhoogde kans hadden om deel uit te maken van de trajecten met een hogere mate van symptomen. Dit onderzoek toont aan dat verschillende trajecten van symptomen van angst en depressie aanwezig zijn onder levertransplantatiekandidaten. Deze trajecten werden met name beïnvloed door klinische en individuele risicofactoren. Echter, de mate van symptomen op het eerste meetmoment lijkt indicatief te zijn voor de mate van symptomen gedurende de wachtlijstperiode. Daarom is het van belang om vroegtijdig in het transplantatieproces te screenen op psychologische problemen en risicofactoren. Vervolgens kunnen passende interventies ondernomen worden om het psychologisch welzijn van levertransplantatiekandidaten te optimaliseren.

Hoofdstuk 7 gaat in op posttraumatische stress stoornis (PTSS) onder levertransplantatiepatiënten (n = 95). In dit onderzoek is gekeken naar de prevalentie en het beloop van PTSS in de wachtlijstperiode en het eerste jaar na de transplantatie te beschrijven, welke symptomen van PTSS het meest bijdragen aan de diagnose van PTSS en de overlap van PTSS met angst en depressie. Tevens is de aard van de herbelevingssymptomen geanalyseerd. Voor transplantatie rapporteerde 32% van de respondenten klinisch relevante symptomen van PTSS. Van deze patiënten voldeed 10,5% aan de criteria voor de diagnose 'full' PTSS en 6,3% aan de criteria voor 'partial' PTSS. In alle gevallen was sprake van co-morbiditeit met angst en/of depressie. Na de transplantatie rapporteerde circa 15% van de patiënten klinisch relevante symptomen van PTSS. Onder deze patiënten werden geen nieuwe gevallen van 'full' PTSS en zes nieuwe gevallen van 'partial' PTSS gevonden.

'Arousal'-symptomen werden, zowel voor als na transplantatie, het meest gerapporteerd maar bleken niet onderscheidend te zijn voor PTSS bij transplantatiepatiënten vanwege de overlap met ziekte- en behandeling-gerelateerde symptomen, zoals cognitieve problemen en slaapproblemen.
Symptomen van herbeleving waren voor de transplantatie vooral gerelateerd aan het wachten op een donororgaan en de transplantatieoperatie. Na de transplantatie hadden de symptomen van herbeleving voornamelijk betrekking op aspecten van het ziekenhuisverblijf.
Uit dit onderzoek blijkt dat onder levertransplantatiepatiënten klinisch relevante symptomen van PTSS meer aanwezig zijn dan diagnoses van 'full' dan wel 'partial' PTSS en dat zowel de diagnose PTSS als klinisch relevante symptomen van PTSS vaker voorkomen onder levertransplantatiekandidaten dan onder getransplanteerde patiënten tijdens het eerste jaar na de transplantatie. Gediagnosticeerd worden met een levensbedreigende ziekte lijkt de belangrijkste stresserende factor voor PTSS onder levertransplantatiepatiënten te zijn. Vanwege de overlap met ziekte- en behandeling-gerelateerde factoren en met andere psychische stoornissen is het echter moeilijk verschillen tussen PTSS en andere problematiek te onderscheiden. Daarom is bij het vermoeden van PTSS een doorverwijzing naar een psycholoog of psychiater aan te bevelen.

In hoofdstuk 8, is onderzocht of verschillende trajecten van angst en depressie te onderscheiden zijn onder levertransplantatiepatiënten (n = 153) vanaf de wachtlijstperiode tot aan twee jaar na transplantatie, welke demografische, klinische en individuele variabelen van invloed zijn op deze trajecten en de impact van de verschillende trajecten op uitkomsten na transplantatie wat betreft medicatietherapietrouw en kwaliteit van leven. Voor zowel symptomen van angst als depressie werden drie verschillende trajecten vastgesteld: 1) een traject waarin zowel voor als na de transplantatie geen klinisch relevante symptomen aanwezig waren (geen symptomen), 2) een traject waarin voor transplantatie wel klinisch relevante symptomen aanwezig waren, maar niet na de transplantatie (opgeloste symptomen) en 3) een traject waarbij zowel voor als na de transplantatie klinisch relevante symptomen aanwezig waren (aanhoudende symptomen). Wat betreft angst omvatten de trajecten respectievelijk 39%, 39% en 23% van de transplantatiepatiënten. De trajecten aangaande depressieve symptomen omvatten respectievelijk 23%, 48% en 29% van de transplantatiepatiënten.
Het ervaren van meer bijwerkingen van de immunosuppressieve medicatie, langdurig heropgenomen geweest zijn in het ziekenhuis, meer gebruik maken van een emotionele copingstijl en de aanwezigheid van meerdere stressvolle levensgebeurtenissen waren gerelateerd aan de trajecten met aanhoudende symptomen van zowel angst als depressie. Daarentegen bleken het hebben van galwegcomplicaties, een hogere mate van persoonlijke controle, meer gebruik maken van taak-georiënteerde coping en openheid over het hebben ondergaan van een transplantatie een positief effect te hebben. Met betrekking tot uitkomsten rapporteerden transplantatiepatiënten binnen de trajecten van 'aanhoudende symptomen' twee jaar na de transplantatie een lagere medicatietherapietrouw en lagere scores op alle domeinen van kwaliteit van leven. Uit dit onderzoek blijkt dat een significant deel van de levertransplantatiepatiënten aan-

houdende symptomen van angst (23%) of depressie (29%) heeft na de transplantatie, met een negatief effect op medicatietherapietrouw en kwaliteit van leven. De trajecten met aanhoudende symptomen van angst en depressie werden met name beïnvloed door de ervaren bijwerkingen van de immunosuppressieve medicatie, de gebruikte copingstijl, de mate van persoonlijke controle en de openheid over het hebben ondergaan van een transplantatie.

Concluderend kunnen we zeggen dat uit de 'Psychologische Aspecten van Transplantatie'-studie blijkt dat een significant deel van de transplantatiepatiënten psychologische problemen ervaart, met name tijdens de wachtlijstperiode, maar ook op de korte- en lange termijn na transplantatie. Verschillende individuele variabelen, zoals copingstijl en persoonlijke controle, en klinische variabelen, zoals de ervaren ernst van de ziektesymptomen en bijwerkingen van de immunosuppressieve medicatie, werden geïdentificeerd als belangrijke risicofactoren voor psychologische problemen bij transplantatiepatiënten. Tevens bleek dat patiënten die klinisch relevante symptomen van angst en depressie blijven houden slechtere uitkomsten rapporteerden wat betreft therapietrouw en kwaliteit van leven. Deze resultaten benadrukken het belang van psychosociale evaluatie en ondersteuning in de zorg voor transplantatiepatiënten gedurende het gehele transplantatieproces. Het screenen op psychologische problemen en gerelateerde risicofactoren zou vroegtijdig in het transplantatieproces plaats moeten vinden, gevolgd door continue monitoring van psychologische problemen tijdens het gehele transplantatietraject. Op basis van deze evaluaties, kunnen psychosociale interventies ondernomen worden om het psychologische welzijn van transplantatiepatiënten te optimaliseren. Echter, psychosociale interventies voor transplantatiepatiënten moeten worden ontwikkeld en onderzocht op hun effectiviteit. Ook het toevoegen van een psychologisch of psychiatrisch georiënteerde hulpverlener aan het transplantatieteam wordt aanbevolen.

Uit de 'Communicatie over Donatie'-studie, bleek dat transplantatiepatiënten verschillende meningen hebben over onderwerpen die zijn gerelateerd aan het transplantatieproces, zoals anonimiteit van orgaandonatie en gezamenlijke besluitvorming. Het integreren van deze voorkeuren en meningen van transplantatiepatiënten in de transplantatie-zorg lijkt dan ook een voorwaarde om de patiënten een volwaardige partner in de zorg te laten zijn.

Echter, het volledig integreren van de psychosociale zorg in de transplantatiezorg en het vergroten van de betrokkenheid van transplantatiepatiënten in het zorgproces, vragen om een herontwerp van de huidige klinische praktijk van een op acute zorg gestoelde biomedische zorgverleningsmodel naar een biopsychosociaal zorgverleningsmodel gebaseerd op de principes van het Chronic Illness Management. De integratie van psychosociale zorg in de zorg voor transplantatiepatiënten zou tevens een waardevolle bijdrage kunnen leveren aan de 'Healthy ageing of the transplant population'.

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LIST OF PRESENTATIONS

April 2010	Oral presentation 'Psychological consequences of organ transplantation: design of a prospective cohort study. ELPAT conference, Rotterdam.
April 2011	Oral presentation 'The emotional response to the receipt of a transplanted organ of liver transplant recipients'. Congress The Netherlands Transplantation Society, Amsterdam.
Sept. 2011	Oral presentation 'The emotional response to the receipt of a transplanted organ of liver transplant recipients'. Symposium of the International Transplant Nurses Society, Goteborg, Sweden.
Sept. 2013	Oral presentation 'The opinion of liver transplant recipients on anonymity of organ donation and their wish for direct contact with the donor's family. European Society of Organ Transplantation conference, Vienna, Austria.
Sept. 2013	Oral presentation. 'The opinion of liver transplant recipients on anonymity of organ donation and their wish for direct contact with the donor's family. Symposium of the International Transplant Nurses Society, Washington, USA.
Feb. 2014	Poster presentation 'Psychological health of liver transplant recipients at different time frames after transplantation'. Symposium Association of Researcher in the Psychology of Health, Groningen. (Best poster award)
March 2014	Oral presentation. 'Psychological health of liver transplant recipients at different time frames after transplantation'. Congress The Netherlands Transplantation Society, Leiden. (Best abstract award)
March 2014	Oral presentation. 'The opinion of liver transplant recipients on anonymity of organ donation and their wish for direct contact with the donor's family. Congress The Netherlands Transplantation Society, Leiden
Aug. 2014	Poster presentation 'Psychological health of liver transplant recipients at different time frames after transplantation'. International Conference of Behavioral Medicine, Groningen.
Sept. 2014	Oral presentation. 'Psychological health of liver transplant recipients at different time frames after transplantation'. European Conference Doctoral students in Nursing Science, Maastricht.
Sept. 2014	Poster presentation 'The opinion of liver transplant recipients on anonymity of organ donation and their wish for direct contact with the donor's family. European Conference Doctoral students in Nursing Science, Maastricht.
Oct. 2014	Invited speaker: Workshop Anonymity of organ donation. First meeting European Transplant Allied Health Professionals, Budapest, Hungary.
March 2015	Oral presentation. 'Trajectories of anxiety and depression of liver transplant candidates during the waitlist period. Congress The Netherlands Transplantation Society/British Transplantation Society. Bournemouth, England.
Sept. 2015	Oral presentation. 'Trajectories of anxiety and depression of liver transplant candidates during the waitlist period. Congress Europeans Society of Organ Transplantation. Brussels, Belgium.
March 2016	Invited speaker. Shared Decision making in organ Transplantation. Congress The Netherlands Transplantation Society, Groningen.

DANKWOORD

Alhoewel kunst en wetenschap, oftewel emotie versus verstand, op het eerste gezicht ver uit elkaar lijken te liggen, realiseerde ik mij tijdens dit promotietraject dat beide juist veel met elkaar gemeen hebben. Voor beide is een creatieve geest en een kritische en analytische blik nodig. Ook heeft het schrijven van een onderzoeksartikel veel overeenkomsten met het maken van een schilderij. Eerst verzamel je de juiste materialen, waarna je begint met het opzetten van de ruwe schets. Daarna begint het uitwerken, neerzetten en weer weghalen, steeds gedetailleerder tot het gewenste resultaat bereikt is. Maar waar bij het maken van een schilderij een goedkeurend oog van de meester vaak volstaat, was het volbrengen van mijn promotieonderzoek en het schrijven van de daarbij behorende onderzoeksartikelen niet mogelijk geweest zonder de hulp en begeleiding van velen. Ik wil dan ook iedereen bedanken die mij hierin gesteund heeft. Een aantal personen wil ik in het bijzonder noemen.

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ABOUT THE AUTHOR

Coby (Jacoba Henny) Annema-de Jong was born on November 18, 1966, in Bedum, the Netherlands. After graduating from high school (Wessel Gansfort College, VWO) in Groningen in 1985, she began her studies in Nursing at the Hanze University of Applied Sciences in Groningen. In 1989, Coby obtained her Bachelor of Nursing degree. In 1991, she commenced a Masters in Nursing Science at the University of Maastricht/Groningen. She successfully completed her Masters in 1995 with a study on nursing diagnoses in liver transplant recipients.

From 1989 to 2000, Coby held different nursing positions at the Department of Surgery of the University Medical Center Groningen (UMCG). During this period, she became interested in the care for transplant patients. Improving the quality of nursing care for liver transplant recipients was one of her points of interest. In addition, she was involved in setting up the Working Group for Transplantation Nursing at the UMCG, the National Working Group for Transplant Nurses, and an educational program for Transplant Nursing. She worked as a tutor for the latter program from 2000 to 2001. Coby was also a member of the Protocol Working Group of the Department of Surgery and led the project 'Nursing diagnosis, Interventions and Outcomes' on behalf of the Department of Gynecology and Obstetrics of the UMCG from 1995 to 1998.

After working as a nurse for a good ten years, Coby turned her focus to research. From 2000 to 2008, she worked as a researcher at the Department of Integrated Care and the Coordination Center Chronic Illnesses of the UMCG. In this function, she conducted evaluation studies on the effects of care improvement projects on quality of care and quality of life in different patient groups. In addition, Coby supervised the research of several students of the Master study Nursing Science and she worked on the COACH-study, a study on the effects of nursing care on the health of heart failure patients, which was initiated by the Department of Cardiology of the UMCG. In 2009, Coby began her PhD research on the psychological aspects of transplantation.

Coby has been a board member of the National Working Group for Transplant Nurses since 2011, with a specific focus on research and development. In 2013, she became Chairwoman of the Social Scientific Research Working Group of the UMC Groningen Transplant Center. In this capacity, she was involved in setting up TransplantLines, a longitudinal cohort study aimed at identifying variables related to healthy ageing in the transplant population.

Coby currently works as a researcher at the School of Nursing & Health of the UMCG, research coordinator for TransplantLines and as a staff member at the Department of Gastroenterology and Hepatology of the UMCG. In this capacity, Coby participates in multiple projects aimed at improving the psychosocial care for transplant patients and in a study on of the effects of Mindfulness Based Stress Reduction.

Coby is married to Duco Annema. They have two children, Laura (1996) and Sander (1998)

OVER DE AUTEUR

Coby (Jacoba Henny) Annema-de Jong werd geboren op 18 november 1966 te Bedum. Na het behalen van haar VWO-diploma aan het Wessel Gansfort College te Groningen in 1985, begon zij met de studie Verpleegkunde aan de Academie voor Gezondheidszorg Noord-Nederland, thans Hanzehogeschool, te Groningen. In 1989 behaalde Coby haar bachelor diploma Verpleegkunde. Na enige jaren werkervaring, startte Coby in 1991 met de studie Verplegingswetenschap aan de Universiteit van Maastricht (deeltijdopleiding te Groningen). Deze master-studie werd in 1995 succesvol afgerond met een onderzoek naar verpleegkundige diagnoses bij levertransplantatiepatiënten.
Vanaf 1989 tot 2000 was Coby werkzaam in verschillende verpleegkundige functies op de afdeling Chirurgie van het Universitair Medisch Centrum Groningen (UMCG). In deze periode is haar interesse in de zorg voor transplantatiepatiënten ontstaan. Op de verpleegafdeling was het verbeteren van kwaliteit van de verpleegkundige zorg na levertransplantatie één van haar aandachtspunten. Coby was betrokken bij het opzetten van de Werkgroep Transplantatie Verpleegkunde (WTV) in het UMCG, de Landelijke Werkgroep Transplantatie Verpleegkundigen (LWTV) en de vervolgopleiding Transplantatieverpleegkunde, waarvan zij van 2000-2001 kerndocent was. Daarnaast maakte Coby deel uit van de protocollen werkgroep van de afdeling Chirurgie en leidde zij van 1995 tot 1998 het project 'Verpleegkundige diagnostiek, interventies en uitkomsten' voor de afdeling Gynaecologie & Obstetrie van het UMCG.
Na meer dan tien jaar als verpleegkundige gewerkt te hebben, verlegde Coby haar focus naar het doen van onderzoek. Van 2000 tot 2008 was Coby als onderzoeker werkzaam voor de sectie Transmurale Zorg & Coördinatie Centrum Chronisch Zieken van het UMCG. In deze functie verrichtte Coby onderzoek naar de effecten van zorgverbeteringsprojecten op kwaliteit van zorg en kwaliteit van leven bij verschillende patiëntengroepen. Daarnaast begeleidde Coby meerdere studenten Verplegingswetenschap bij hun afstudeeronderzoek. Na een jaar werkzaam te zijn geweest voor de COACH-studie, een studie naar de effecten van verpleegkundige zorg bij hartfalen, vanuit de afdeling Cardiologie van het UMCG, startte Coby in 2009 met haar promotieonderzoek 'Psychologische Aspecten van Transplantatie'.
Sinds 2011 is Coby bestuurslid van de LWTV met als aandachtsgebied 'Onderzoek en ontwikkeling'. Tevens is zij sinds 2013 voorzitter van de werkgroep Sociaal Wetenschappelijk Onderzoek van het UMC Groningen Transplantatie Centrum. In deze hoedanigheid was zij ook betrokken bij het opzetten van TransplantLines, een langlopend cohortonderzoek naar het gezond ouder worden met een donororgaan.
Momenteel is Coby werkzaam als zorgonderzoeker voor de School of Nursing & Health van het UMCG, researchcoördinator voor TransplantLines en is vanuit de afdeling Maag-, Darm-, Leverziekten van het UMCG als projectleider betrokken bij meerdere projecten ter verbetering van de psychosociale zorg voor transplantatiepatiënten en bij een onderzoek naar de effecten van Mindfulness Based Stress Reduction.
Coby is getrouwd met Duco Annema. Samen hebben zij twee kinderen, Laura (1996) en Sander (1998).

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