CHAPTER 6

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


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. 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. 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. 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. Although the prospect of a transplantation offers new hope for the future, transplant candidates often feel that their life is on hold.

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 and of 17%-60% regarding depression have been described. Psychological problems before transplantation have been associated with poor psychological health after transplantation, which in turn has been associated with poorer outcomes after transplantation regarding adherence, quality of life, and mortality. 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. 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. 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; clinical characteristics, such as the Model for
End-stage Liver Disease (MELD) score, time on the waiting list, and perceived health status;\textsuperscript{12,15,28} and individual characteristics, such as coping style, personal control, social support, and self-efficacy.\textsuperscript{10,12,29} However, other studies have shown contradictory results regarding these factors.\textsuperscript{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).\textsuperscript{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,\textsuperscript{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. 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). 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. 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. Moreover, it has been found to be applicable in a transplant population.

- The Liver Disease Symptom Index 2.0 (LDSI) 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 LDSI has shown good feasibility and good test-retest reliability. 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. 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. 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). 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). 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. 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 ($\eta^2_p$) was used. Partial eta squared describes the proportion of the total variability attributable to a factor. GLM repeated measures ANOVA with time as a factor was used to calculate $\eta^2_p$. 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;
Patients on liver transplant waiting list between October 2009 and April 2013
N=474

Invitation to participate n=350

Not invited to participate N=124 (26.1%)
• n=56 excluded (11.8%) not able to fill out a questionnaire
  - n=28 due to language
  - n=6 physical functioning
  - n=17 cognitive functioning
  - n=5 psychological functioning

N=68 other reasons (14.3%)
• n=53 transplantation within one week after enlisting
• n=10 deceased
• n=4 re-transplantation during study period
• n=1 removed from waiting list within one week

N=56 excluded (11.8%)
• n=28 due to language
• n=6 physical functioning
• n=17 cognitive functioning
• n=5 psychological functioning

N=68 other reasons (14.3%)
• n=53 transplantation within one week after enlisting
• n=10 deceased
• n=4 re-transplantation during study period
• n=1 removed from waiting list within one week

Informed Consent n=241

Baseline (T0) measurement n=216

No T0 measurement n=25
• n=18 transplantation before questionnaire was filled out
• n=6 withdrawal informed consent
• n=1 deceased

• n=72 transplanted
• n=6 removed from waiting list
• n=10 deceased
• n=6 end of study after T0

T1 (6 months after T0) n=122

T2 (12 months after T0) n=69

T3 (18 months after T0) n=47

T4 (24 months after T0) n=26

T5 (30 months after T0) n=14

T6 (36 months after T0) n=7

T7 (42 months after T0) n=6

Figure 1. Study inclusion flow diagram.
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,
the effect sizes ($\eta^2_p$) 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, and 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.

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 ($\geq 12$) 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.
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

<table>
<thead>
<tr>
<th>Variable</th>
<th>Estimate</th>
<th>P value</th>
<th>Odds ratio</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low educational level</td>
<td>0.14</td>
<td>0.73</td>
<td>1.15</td>
<td>0.51 - 2.64</td>
</tr>
<tr>
<td>Middle educational level</td>
<td>-0.68</td>
<td>0.09</td>
<td>0.51</td>
<td>0.23 - 1.11</td>
</tr>
<tr>
<td>High educational level</td>
<td>reference</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDSI score</td>
<td>0.14</td>
<td>&lt;0.01</td>
<td>1.16</td>
<td>1.09 - 1.23</td>
</tr>
<tr>
<td>Personal control</td>
<td>-0.11</td>
<td>&lt;0.01</td>
<td>0.89</td>
<td>0.84 - 0.95</td>
</tr>
<tr>
<td>Emotional coping style</td>
<td>0.12</td>
<td>&lt;0.01</td>
<td>0.89</td>
<td>0.82 - 0.96</td>
</tr>
<tr>
<td>Task-oriented coping style</td>
<td>0.12</td>
<td>&lt;0.01</td>
<td>0.89</td>
<td>0.82 - 0.96</td>
</tr>
<tr>
<td>Number of life events</td>
<td>0.19</td>
<td>0.11</td>
<td>1.21</td>
<td>0.96 - 1.53</td>
</tr>
</tbody>
</table>

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
To = baseline measurement, T1 = 6 months after To, T2 = 12 months after To, T3 = 18 months after To,
T4 = 24 months after To, T5 = 30 months after To, T6 = 36 months after To, T7 = 42 months after To.
### Table 4. Demographic, clinical, and individual characteristics of respondents within the distinct trajectories of depression

<table>
<thead>
<tr>
<th></th>
<th>Trajectory 1 Depression below clinical level n = 36</th>
<th>Trajectory 2 Depression slightly below clinical level n = 104</th>
<th>Trajectory 3 Depression slightly above clinical level n = 66</th>
<th>Trajectory 4 Depression high above clinical level n = 10</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Gender: Male</strong></td>
<td>21 (58.3)</td>
<td>71 (68.3)</td>
<td>45 (68.2)</td>
<td>7 (70.0)</td>
<td>0.71</td>
</tr>
<tr>
<td><strong>Marital status: Partner</strong></td>
<td>28 (77.8)</td>
<td>81 (77.9)</td>
<td>52 (78.8)</td>
<td>7 (70.0)</td>
<td>0.94</td>
</tr>
<tr>
<td><strong>Educational level</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>9 (25.0)</td>
<td>17 (16.3)</td>
<td>16 (24.2)</td>
<td>5 (50.0)</td>
<td>0.14</td>
</tr>
<tr>
<td>Moderate</td>
<td>16 (44.4)</td>
<td>52 (50.0)</td>
<td>24 (36.4)</td>
<td>4 (40.0)</td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>11 (30.6)</td>
<td>35 (33.7)</td>
<td>26 (39.4)</td>
<td>1 (10.0)</td>
<td></td>
</tr>
<tr>
<td><strong>Employment status: Paid job</strong></td>
<td>16 (44.4)</td>
<td>35 (33.7)</td>
<td>13 (19.7)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td><strong>Primary disease</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Biliary cirrhosis</td>
<td>15 (41.7)</td>
<td>37 (35.6)</td>
<td>24 (36.4)</td>
<td>2 (20.0)</td>
<td></td>
</tr>
<tr>
<td>Alcoholic cirrhosis</td>
<td>9 (25.0)</td>
<td>23 (22.1)</td>
<td>16 (24.2)</td>
<td>3 (30.0)</td>
<td></td>
</tr>
<tr>
<td>Metabolic disorder</td>
<td>5 (13.9)</td>
<td>10 (9.6)</td>
<td>5 (7.6)</td>
<td>4 (40.0)</td>
<td></td>
</tr>
<tr>
<td>Viral hepatitis</td>
<td>3 (8.3)</td>
<td>14 (13.5)</td>
<td>10 (15.7)</td>
<td>1 (10.0)</td>
<td></td>
</tr>
<tr>
<td>Cirrhosis of unknown origin</td>
<td>1 (2.8)</td>
<td>10 (9.6)</td>
<td>7 (10.6)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>3 (8.3)</td>
<td>10 (9.6)</td>
<td>4 (6.1)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Hepatocellular Carcinoma</td>
<td>9 (25.0)</td>
<td>20 (19.2)</td>
<td>4 (6.1)</td>
<td>1 (10.0)</td>
<td></td>
</tr>
<tr>
<td><strong>Mean (SD)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (in years)</td>
<td>50.6 (11.2)</td>
<td>52.2 (12.0)</td>
<td>50.9 (11.1)</td>
<td>54.2 (5.7)</td>
<td>0.71</td>
</tr>
<tr>
<td>Number of co-morbidities</td>
<td>1.4 (1.1)</td>
<td>1.9 (1.6)</td>
<td>1.9 (1.7)</td>
<td>3.6 (1.6)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Time since diagnosis (in years)</td>
<td>6.0 (6.0)</td>
<td>6.2 (6.7)</td>
<td>5.3 (5.7)</td>
<td>4.1 (6.5)</td>
<td>0.65</td>
</tr>
<tr>
<td>Time on waiting list (in months)</td>
<td>9.4 (16.2)</td>
<td>9.7 (11.7)</td>
<td>9.5 (16.1)</td>
<td>8.4 (7.3)</td>
<td>0.29</td>
</tr>
<tr>
<td>MELD score</td>
<td>11.1 (4.9)</td>
<td>13.5 (5.6)</td>
<td>14.3 (4.9)</td>
<td>13.7 (5.4)</td>
<td>0.04</td>
</tr>
<tr>
<td>LDSI score</td>
<td>4.8 (3.9)</td>
<td>8.5 (4.2)</td>
<td>13.0 (5.3)</td>
<td>13.1 (4.0)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Personal control</td>
<td>28.1 (4.2)</td>
<td>25.1 (4.5)</td>
<td>20.9 (4.6)</td>
<td>15.5 (4.7)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td><strong>Coping style</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Emotional coping</td>
<td>16.3 (4.8)</td>
<td>17.5 (5.5)</td>
<td>22.3 (6.4)</td>
<td>27.4 (7.2)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Task-oriented coping</td>
<td>26.8 (3.9)</td>
<td>25.4 (4.2)</td>
<td>24.3 (4.3)</td>
<td>21.9 (4.6)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Avoidance coping</td>
<td>17.5 (5.6)</td>
<td>17.0 (5.1)</td>
<td>17.1 (4.6)</td>
<td>15.7 (5.0)</td>
<td>0.80</td>
</tr>
<tr>
<td>Number of life events</td>
<td>1.3 (1.1)</td>
<td>1.5 (1.2)</td>
<td>1.8 (1.4)</td>
<td>1.5 (1.4)</td>
<td>0.27</td>
</tr>
</tbody>
</table>

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 ($\eta^2_p$) 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>
<thead>
<tr>
<th>Variable</th>
<th>Estimate</th>
<th>P value</th>
<th>Odds Ratio</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Lower</td>
<td>Upper</td>
</tr>
<tr>
<td>Number of comorbidities</td>
<td>0.01</td>
<td>0.90</td>
<td>1.01</td>
<td>0.84 - 1.21</td>
</tr>
<tr>
<td>MELD score</td>
<td>0.03</td>
<td>0.34</td>
<td>1.03</td>
<td>0.97 - 1.08</td>
</tr>
<tr>
<td>LDSI score</td>
<td>0.22</td>
<td>0.00</td>
<td>1.24</td>
<td>1.16 - 1.33</td>
</tr>
<tr>
<td>Personal control</td>
<td>-0.18</td>
<td>0.00</td>
<td>0.84</td>
<td>0.78 - 0.90</td>
</tr>
<tr>
<td>Emotional coping style</td>
<td>0.12</td>
<td>0.01</td>
<td>1.13</td>
<td>1.07 - 1.18</td>
</tr>
<tr>
<td>Task-oriented coping style</td>
<td>-0.09</td>
<td>0.01</td>
<td>0.91</td>
<td>0.85 - 0.98</td>
</tr>
</tbody>
</table>

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, 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.\textsuperscript{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.\textsuperscript{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,\textsuperscript{52} common practice may vary between transplant centers, and psychosocial screening is a less standardized procedure.\textsuperscript{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 psycho-social interventions in organ transplant candidates is lacking and needs to be studied in future research.
REFERENCES


