Regular Article

Psychotherapy and Psychosomatics

Psychother Psychosom 2002;71:285–297

Psychiatric and Psychosocial Outcome of Orthotopic Liver Transplantation

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Key Words

Liver transplantation · Psychiatric morbidity · Posttraumatic stress disorder · Health-related quality of life · Cognitive performance · Consultation-liaison psychiatry

Abstract

Background: The study aimed to explore the prevalence of psychiatric disorders among orthotopic liver transplantation (OLT) recipients, and to investigate how psychiatric morbidity was linked to health-related quality of life (HRQOL). ***Methods:*** We recruited 75 patients who had undergone OLT a median of 3.8 years previously (range = 5–129 months). Psychiatric morbidity was assessed using the Structural Clinical Interview for the DSM-III-R. Psychometric observer-rating and self-rating scales were administered to evaluate cognitive functioning (SKT), depressive symptomatology ($HAMD_{17}$), posttraumatic stress symptoms (PTSS-10), social support (SSS), and HRQOL (SF-36 Health Status Questionnaire). Treatment characteristics were obtained from medical records. ***Results:*** 22.7% (n = 17) of our sample had a current or probable psychiatric diagnosis according to DSM-III-R: 2.7% full posttraumatic stress disorder (PTSD) (n = 2), 2.7% major depressive disorder (MDD) comorbid to full PTSD (n = 2), 1.3% MDD comorbid to partial PTSD (n = 1), and 16% partial PTSD (n = 12). Patients with PTSD symptoms demonstrated lower cognitive performance, higher severity of depressive symptoms and more unfavorable perception of social support. OLT-related PTSD symptomatology was associated with maximal decrements in HRQOL. The duration of intensive care treatment, the number of medical complications, and the occurrence of acute rejection were positively correlated with the risk of PTSD symptoms subsequent to OLT. ***Conclusion:*** OLT-related PTSD symptomatology impairing HRQOL is a complication for a subgroup of OLT recipients. Health-care providers should be aware of the possible presence of PTSD in OLT survivors.

Introduction

Owing to the introduction of more effective immunosuppressive agents such as cyclosporine (CsA) in 1980 and tacrolimus (FK 506) in 1989, the standardization of the surgical procedure, and the significant advances in intensive care treatment, patient selection, tissue matching and organ preservation, the clinical outcome of liver transplant recipients has tremendously improved over the past

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15 years [1]. Orthotopic liver transplantation (OLT) is now the treatment of choice for end-stage liver disease, with 1-year survival rates in adult transplant recipients of about 85% and 9-year survival rates of 55% in most of the 200 international centers including our Munich Liver Transplantation Group with approximately 40 transplants per annum [2, 3].

As transplantation surgery has dramatically advanced, the success of OLT is no longer judged solely by its effects on morbidity and mortality but by its influence on transplant recipients' psychosocial well-being [4]. In recent years, a number of outcome studies have focused on health-related quality of life (HRQOL) after liver transplantation among adults, showing that OLT is associated with improvement in HRQOL relative to the pretransplant period, but without restoring the health status levels described in the general population [5–7]. This finding has raised concern about *full* psychosocial rehabilitation in OLT. However, factors responsible for the persistent difference remain poorly defined. Several studies emphasized the impact of recurrence of hepatitis C virus (HCV) infection [8–11], CsA neurotoxicity [12–14], and mood symptoms during corticosteroid therapy [15].

From a psychiatric point of view, clinical observations point to psychiatric problems after OLT that may impair HRQOL in liver transplant recipients [16, 17]. One study has examined psychiatric complications of the postoperative period of OLT in 63 adult liver transplant recipients. The investigators found that psychiatric morbidity was 29%. Organic mental disorders were the most prevalent, especially delirium (13%), followed by adjustment disorders (8%), major depression (5%) and organic anxiety disorders (3%) [18]. Surman et al. [19] reported that 20% of 40 adult liver transplant recipients were referred for treatment of depressive disorder typically associated with deterioration of hepatic status, infectious complication or recurrence of cancer. To date, only two studies have focused specifically on psychiatric morbidity and HRQOL in adult intermediate-term survivors of OLT [20, 21]. Commander et al. [20] found that psychiatric morbidity in the 32 liver transplant recipients was associated with significant impairment in some areas of social functioning. The prevalence rate of psychiatric morbidity was 18.8% according to Research Diagnostic Criteria [22], and major depressive disorder (MDD) accounted for two thirds of all psychiatric diagnoses. Investigating 30 liver transplant recipients, Collis et al. [21] also demonstrated that there was a significant association between psychiatric morbidity and impaired HRQOL. They recorded a prevalence figure of 26.7%, using the Clinical Interview Schedule [23]. Mild mixed anxiety and depressive disorders accounted for 50%, severe depressive disorder for 12.5% of all psychiatric diagnoses.

The overall aim of the present outcome study was to examine concurrently psychiatric morbidity including cognitive deficits and psychopathologically relevant dimensions, and quality of life in intermediate-term survivors of OLT, and to investigate how psychiatric morbidity is related to HRQOL. As previous research has documented that anxiety and depressive symptomatology are most commonly present in a substantial portion of liver transplant recipients, we were specifically interested in the prevalence rate of posttraumatic stress disorder (PTSD) in our patient population. In our view, it is conceivable that OLT representing a 'high-tech' medical procedure associated with the risk of a variety of medical complications (e.g. acute rejection, bleeding, infections) during the intensive care unit (ICU) stay might be a traumatic stressor that is capable of producing posttraumatic stress symptoms. We therefore examined variables such as the extent of medical complications during the ICU course subsequent to OLT, length of ICU stay, duration of waiting period for OLT, type of liver failure, history of retransplantation and of recurrence of HBV/HCV, and preexisting trauma that may contribute in some way to the development of posttraumatic stress symptoms in OLT recipients. To our knowledge, this is the first study that has addressed posttraumatic stress responses after OLT in adult liver transplant recipients, and only one previous study has examined this issue in older children [24] to date.

Subjects and Methods

Subjects and Procedure

Between March 1996 and October 1997, the outpatient clinic of the Department of Medicine II at the Klinikum Grosshadern, the tertiary care center of the Ludwig-Maximilians University, Munich, Germany, treated 81 adult liver transplant recipients (age 16 or older) who survived more than 5 months after undergoing OLT at our transplantation center, who had CsA or tacrolimus (FK 506) concentrations in blood within therapeutic range, and who did not receive steroid therapy. These 81 patients were approached by their physicians from our outpatient clinic to participate. The refusal rate for the present sample was 7.4% (n = 6). Respondents were indistinguishable from the few nonrespondents on transplant-related and sociodemographic characteristics. Those agreeing were then contacted by the research assistants, the study was explained, and informed consent was obtained. Consenting patients were interviewed by experienced consultation-liaison psychiatrists (H.-B.R., H.-P.K.), and completed the research battery at the time of a regularly scheduled medical follow-up examination at the Klinikum Gross-

hadern. The battery included a brief author-compiled questionnaire, a structured clinical interview, self-report questionnaires, and psychometric observer-rating scales. The study was approved by the Institutional Review Board of our institution. Data protection met the standard set by German law.

Sociodemographic and Clinical Characteristics

Information about patient and treatment characteristics were obtained from a brief author-compiled questionnaire and from the medical record. Demographic variables included age, gender, race, marital status, and employment status at the time of the psychiatric assessment. Marital status was categorized as married or living with a spouse, single, divorced, or widowed. The patient's employment status was rated with respect to the following criteria: (a) full-time/part-time employment, (b) unemployment, (c) retirement, (d) homemakers in lieu of paid employment, and (e) disabled from work because of health problems. According to WHO [25], disability is the consequence of impairment, in terms of functional performance and activity by the afflicted person. Hence, we classified the OLT recipients as disabled if they met criterion (e). Clinical characteristics included the primary liver disease that led to end-stage liver disease and necessitated OLT, as determined by the results of serologic, biochemical, and histopathologic evaluations prior to the transplant surgery. History of medical complications during ICU treatment following OLT was obtained from the medical record. They comprised acute rejection, gastrointestinal bleeding, acute renal failure, acute respiratory distress syndrome, acute cardiovascular disturbances, delirium, viral, mycotic and/or bacterial infections. Further, the waiting period for OLT, duration of ICU treatment following OLT, history of retransplantation, history of recurrence of HBV or HCV positivity after OLT, and the type of liver failure (acute vs. chronic) were recorded. All medical information regarding treatment characteristics and history of medical complications following OLT was collected by experienced physicians from the outpatient clinic of the Department of Medicine II (R.Z., M.B.).

Psychiatric Diagnosis

Two experienced psychiatrists from the consultation-liaison service (H.-B.R., H.-P.K.) conducted the Structural Clinical Interview for the DSM-III-R (SCID) [26, 27] to assess current and past psychiatric diagnoses according to DSM-III-R criteria [28]. A sample of 15 randomly selected cases assessed by both raters [1 conducting the interview (H.-B.R.) and 1 observing (H.-P.K.)] was used to assess interrater reliability. The kappa for these 15 patients was 0.84, and was considered to be adequate.

While psychiatric disorders other than PTSD were only assigned to the OLT recipients when DSM-III-R criteria were completely met, in the case of PTSD, we differentiated between a full PTSD and a subthreshold or partial PTSD. According to our concept, OLT recipients received a subthreshold disorder of partial PTSD if they failed to meet all the diagnostic criteria B (reexperiencing phenomena), C (symptoms of avoidance and emotional numbing), D (symptoms of increased arousal), but fulfilled two of these three key responses to trauma and, additionally, the criteria A (trauma criterion), E (duration of the disturbance is more than 1 month), and F (the disturbance causes clinically significant distress or psychosocial impairment). The *trauma criterion A* was homogeneously defined as *OLT*. In order to validly assess any pre-OLT relevant trauma or any post-OLT exposure to traditional traumatic experiences other than our defined criterion A stressor event for PTSD itself, we used the PTSD supplement as included in the SCID. Since PTSD symptoms were rearranged, but not changed, between DSM-III-R and DSM-IV [29], we were able to generate DSM-IV diagnoses for PTSD.

Psychometric Tests

After completion of the SCID, pertinent psychometric observer-rating and self-rating scales were administered to assess cognitive functioning, depressive symptomatology, posttraumatic stress symptoms, social support, and HRQOL.

The neuropsychological evaluation was based on the SKT, a short cognitive performance test including 9 subtests for assessing deficits of memory and attention [30, 31]. Norm values range from 0 to 27, and differentiate between profound (24–27), severe (19–23), moderate (14–18), mild (9–13), questionable (5–8) cognitive impairments, and no cognitive deficits (0–4). Published reliability data varied between 0.86 and 0.88 [32]. The German version of the 17-item Hamilton rating scale for depression ($HAMD_{17}$) was used to measure the severity of depressive symptomatology [33, 34]. According to Paykel [35], a score of 18 points or more typically equals major depression, and the range of 13–17 points is generally used to indicate probable major depression. The Posttraumatic Stress Syndrome 10-Questions Inventory (PTSS-10) is a self-rating 10-item scale based on the DSM-III [36] that measures the presence and intensity of posttraumatic stress symptoms [37]. The German version of the PTSS-10 (range: 10–70 points) has been successfully validated in patients with PTSD after prolonged ICU treatment, and has proved to be a reliable scale (Crohnbach's alpha = 0.93). An optimal cut-off score of 35 points of the questionnaire for diagnosis of PTSD has been noted [38]. To evaluate the patients' perception of a range of socially supportive experiences, the Social Support Scale (SSS) [39] was used. The German version of the SSS [40] is a self-report scale with 19 items on a scale from 0 (never) to 4 (always), and a sum score range from 0 to 76 points. Higher scores reflect a more favorable perception of social support. To assess HRQOL after OLT in adult liver transplant recipients, we applied the psychometrically validated German translation of the Medical Outcome Study Short Form (SF-36) [41, 42]. The SF-36 is a 36-item, self-rating questionnaire that covers 8 health-related domains. Each domain yields a score ranging from 0 to 100 (best). Published internal consistency data of the SF-36 exceeded 0.8 in the vast majority of the studies [43, 44].

Control Group for HRQOL Measurement

Control subjects were randomly selected from a large epidemiological database (n = 3,000) used to provide standard values for the SF-36 in a German population. Our HRQOL control group (n = 75) represented age and gender-identical healthy subjects whose sociodemographic characteristics did not differ from the study sample.

Statistical Analyses

This outcome study examines the intermediate-term status in a selected cohort of OLT recipients. The OLT recipients (n = 75) were divided into three subcategories of patients based on whether the criteria for PTSD according to DSM-III-R and DSM-IV were completely met, partially met, or not met at a median time of 3.8 years after OLT. SF-36 data were compared with data from an age and gender-matched control group of 75 healthy subjects. All statistical analyses were performed using SPSS 10.0 for Windows (SPSS Inc., Chicago, Ill., USA). Descriptive statistics were carried out on demographic, treatment-related, and psychometric data (SF-36, PTSS-10, SKT, $HAMD_{17}$, SSS scores), and are presented as median ± SD or mean

Table 1. Sociodemographic characteristics of adult OLT recipients according to the diagnostic status of PTSD at the time of psychiatric assessment

Category	Total sample (n = 75)	No PTSD (n = 58)	Partial PTSD (n = 13)	Full PTSD (n = 4)	p
Gender					
Male/female	43/32	33/25	6/7	4/0	0.162[1]
Age					
Median, years	54	55	51	44.5	
SD	10.9	11.1	9.3	9.9	0.198[2]
Range, years	16–71	16–71	35–70	31–54	
Employment status					
Disabled	27	19	6	2	
Not disabled	48	39	7	2	0.553[1]
Marital status					
Single	11	8	2	1	
Married	59	47	10	2	0.294[1]
Widowed	2	1	1	–	
Divorced	3	2	–	1	

[1] χ^2 tests.
[2] Kruskal-Wallis one-way analysis of variance or ranks.

± SD, and ranges (minimum and maximum values, or 25th and 75th percentiles) when appropriate. Kruskal-Wallis one-way analysis was applied between the three subgroups of OLT recipients with full, partial and no PTSD, and SKT, HAMD, PTSS-10, SF-36 scores, age, time interval between OLT and psychiatric evaluation, ICU days, waiting period for OLT, and number of medical complications during ICU treatment. In this context, pairwise multiple comparison procedures (Bonferroni) were used in order to determine which subgroups were significantly different. In the analysis of significant distribution differences for categorical variables between the three subgroups, we applied χ^2 tests. The nonparametric Wilcoxon signed rank test was used for comparison of SF-36 data between the entire sample of 75 OLT recipients and the age and gender-matched control group of 75 healthy subjects. All tests were two-tailed. Significance was set at p = 0.05 for all analyses.

Results

Clinical Status

A total of 44% (n = 33) of our entire sample (n = 75) met the criteria for any lifetime diagnosis on the SCID: alcohol abuse/dependence (n = 24; 32% of the sample), other drug abuse/dependence (n = 3; 4% of the sample), depressive disorders NOS (n = 3; 4% of the sample), MDD (n = 2; 2.7% of the sample), and bipolar affective disorder (n = 1; 1.3% of the sample). Prior psychiatric history did not reveal any lifetime diagnosis of PTSD in our sample. 2.7% (n = 2) of our sample reported any lifetime exposure to traditional stressors in terms of physical attack.

22.7% (n = 17) of our entire sample (n = 75) had a current or probable psychiatric diagnosis on the SCID: full PTSD (n = 2; 2.7% of the sample), MDD comorbid to partial PTSD (n = 1; 1.3% of the sample), and partial PTSD (n = 12; 16.0% of the sample). Those participants with lifetime histories of alcohol abuse/dependence or other drug abuse/dependence were fully remitted at the time of psychiatric assessment. Of the 13 current cases of partial PTSD, 5 had histories of alcohol abuse/dependence and 3 had histories of depressive disorders NOS. Of the 4 current cases of full PTSD, 2 had histories of MDD. None of the 2 patients reporting lifetime exposure to traditional stressors met the criteria for full or partial PTSD.

Sociodemographic and Treatment Characteristics

Seventy-five out of 81 eligible OLT recipients were enrolled in this psychiatric outcome study. All participants (32 females and 43 males) were Caucasian, and the mean age was 52.2 years (SD = 10.9). The median time interval between OLT and psychiatric assessment was 46 months (SD = 27.9; range 5–129 months). Table 1 summarizes the sociodemographic characteristics, and table 2

Table 2. Treatment characteristics of adult OLT recipients according to the diagnostic status of PTSD at the time of psychiatric assessment

Category	Total sample (n = 75)	No PTSD (I) (n = 58)	Partial PTSD (II) (n = 13)	Full PTSD (III) (n = 4)	p	I+III	I+II	II+III
Time interval								
Median, months	46	45	63	42.5	0.267[1]			
SD	27.9	28.6	27.0	13.9				
Range, months	5–129	5–129	25–120	32–65				
Waiting period								
Median, days	22	28	11	8.5	0.027[1]	–	–	–
SD	38.1	41.0	21.1	4.1				
Range, days	1–205	1–205	1–76	1–10				
ICU days								
Median, days	10	9	14	13	0.011[1]	–	*	–
SD	17.6	14.4	25.4	13.2				
Range, days	4–90	4–65	9–90	7–36				
Number of complications during ICU								
Median	3	3	4	3	0.039[1]	–	*	–
SD	2.0	1.9	1.9	2.6				
Range	0–8	0–6	1–8	0–5				
Primary liver disease								
Alcoholic liver disease	24	19	5	0	0.300[5]			
Infectious hepatitis[2]	17	13	1	3				
PBC/PSC	9	8	1	0				
Malignancy[3]	5	4	1	0				
Miscellaneous[4]	20	14	5	1				
Type of liver failure								
Acute liver failure	13	9	4	0	0.271[5]			
Chronic liver failure	62	49	9	4				
Complications during ICU treatment								
Bleeding	22	16	4	2	0.630[5]			
Infections	41	29	10	2	0.208[5]			
Acute rejection	45	31	12	2	*0.032*[5]			
Cardiovascular	25	17	6	2	0.390[5]			
Acute renal failure	35	25	9	1	0.156[5]			
Delirium	26	17	8	1	0.080[5]			
ARDS	5	3	1	1	0.303[5]			
History of retransplantation								
Yes/No	9/66	5/53	4/9	0/4	0.064[5]			
History of recurrence of HBV/HCV								
Yes/No	16/59	12/46	2/9	2/2	0.325[5]			

SD = Standard deviation; PBC = primary biliary cirrhosis; PSC = primary sclerosing cholangitis; ARDS = acute respiratory distress syndrome. I, II, III: pair-wise multiple comparison procedures (Bonferroni). Statistically significant: * $p < 0.05$.

[1] Kruskal-Wallis one-way analysis of variance or ranks.

[2] Infectious hepatitis encompasses HBV-related and/or HCV-related liver diseases.

[3] Malignancy includes hepatocellular carcinoma and other hepatic malignancies.

[4] Miscellaneous comprises Wilson's disease, Budd-Chiari syndrome, fulminant hepatic failure, and cryptogenic cirrhosis.

[5] χ^2 tests.

Table 3. Test-psychological correlates of adult OLT recipients according to the diagnostic status of PTSD at the time of psychiatric assessment

Category	Total sample (n = 75)	No PTSD (I) (n = 58)	Partial PTSD (II) (n = 13)	Full PTSD (III) (n = 4)	p	I+III	I+II	II+III
SKT	2.0 (0.0–14.0)	1.0 (0.0–8.0)	3.0 (1.0–14.0)	5.5 (4.0–8.0)	++	*	*	–
HAM-D_{17}	4.0 (0.0–31.0)	2.0 (0.0–9.0)	7.0 (3.0–30.0)	22.0 (11.0–31.0)	+++	*	*	*
PTSS-10	18.0 (10.0–52.0)	16.0 (10.0–24.0)	29.0 (25.0–33.0)	47.0 (36.0–52.0)	+++	*	*	*
SSS	69.0 (14.0–76.0)	71.0 (14.0–76.0)	63.0 (28.0–76.0)	33.5 (14.0–62.0)	++	*	–	*

Values are median; scores in parentheses indicate minimum and maximum. +++ $p < 0.001$; ++ $p < 0.01$; + $p < 0.05$ according to Kruskal-Wallis one-way analysis of variance or ranks. I, II, III: pair-wise multiple comparison procedures (Bonferroni). Statistically significant: * $p < 0.05$.

presents information on the treatment characteristics of the whole study sample and according to the diagnostic status of PTSD at the time of psychiatric assessment (see clinical status). The analysis of the employment status of the entire sample showed that 21 of 75 OLT recipients (28%) were full-time or part-time employed, 16 (21.3%) were retired due to age-related reasons, 9 (12%) were homemakers in lieu of paid employment, 2 (2.7%) were unemployed, and 27 (36%) were disabled from work because of health.

Results of Psychological Tests

Test-psychological correlates of our adult OLT recipients are depicted in table 3 for the entire sample and according to the diagnostic status of PTSD at the time of psychiatric assessment.

We found that the mean SKT total score (expressed as norm values) from the whole sample of adult OLT recipients was 2.75 (SD = 2.75; median value = 2.0; range 0.0–14.0) at a median time of 3.8 years after OLT, and lay well under the cut-off point of 5. However, 17.3% (n = 13) of the entire sample showed cognitive impairments as measured on the SKT (mean SKT total score = 7.54, SD = 2.88, range 5.0–14.0). No extreme and severe cognitive deficits were recorded. A significant difference in cognitive functioning between the subgroups was evident (Kruskal-Wallis, H = 13.733, df = 2, $p < 0.01$). Patients without PTSD had significantly lower scores than those with partial or full PTSD on the SKT. On the 17-item HAMD, the entire sample of OLT recipients showed a mean score of 5.33 (SD = 6.47; median value 4.0; range 0.0–31.0). Four patients scored ≥ 18, and 2 patients fell within the range of 13–17 points on the $HAMD_{17}$. However, only 3 out of these 6 patients fulfilled the diagnostic criteria of MDD according to SCID. As illustrated on table 3, a significant difference in the intensity of depressive symptomatology between the three subgroups was noted (Kruskal-Wallis, H = 26.938, df = 2, $p < 0.001$): patients with partial PTSD had significantly higher scores than those without PTSD, and significantly lower scores than those with full PTSD on the $HAMD_{17}$. The results of the PTSS-10 questionnaire in our sample discriminated well with respect to the diagnostic status of PTSD according to SCID (Kruskal-Wallis, H = 39.504, df = 2, $p < 0.001$). Adult OLT recipients with full PTSD scored an average of 45.5 points (SD = 6.95; median value = 47.0; range 36.0–52.0), and lay well above the cut-off score of 35. As shown in table 3, we recorded a significant difference in our subjects' perception of supportive relationships between the three subgroups (Kruskal-Wallis, H = 12.476, df = 2, $p < 0.01$). Patients with full PTSD revealed a marked tendency to perceive supportive relationships less favorably than patients with partial PTSD and patients without PTSD on the SSS.

As shown in figure 1, our 75 participants performed significantly worse on all health-related domains at a median time of 3.8 years after OLT, when compared with 75 age and gender-matched healthy controls [Wilcoxon signed rank test: physical functioning (PF), Z = –7.385, $p < 0.001$; role-physical (RP), Z = –5.420, $p < 0.001$; bodily pain (BP), Z = –5.400, $p < 0.001$; general health (GH), Z = –6.160, $p < 0.001$; vitality (V), Z = –5.131, $p < 0.001$;

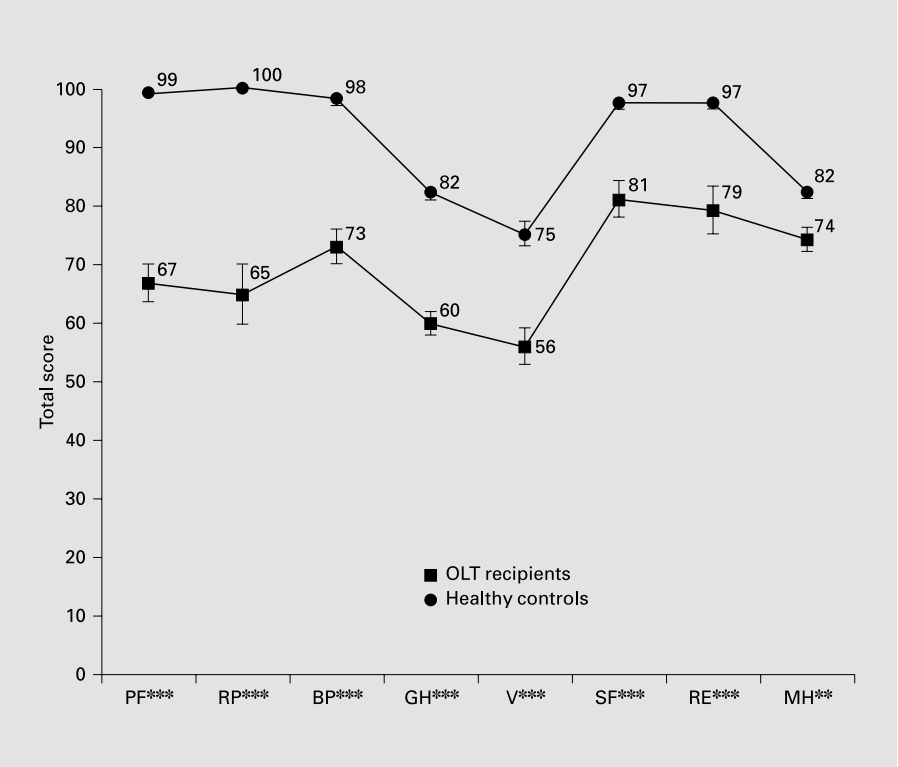

Fig. 1. Mean scores ± standard errors on the SF-36 at the time of psychiatric assessment data (n = 75 OLT recipients) compared with 75 age- and gender-matched healthy controls. Normal score = 100. *** $p < 0.001$ (Wilcoxon signed rank test); ** $p < 0.01$ (Wilcoxon signed rank test).

social functioning (SF), $Z = -4.576$, $p < 0.001$; role-emotional (RE), $Z = -3.869$, $p < 0.001$; mental health (MH), $Z = -2.582$, $p < 0.01$].

Among the studied adult OLT recipients, patients with full PTSD showed the lowest HRQOL, followed by patients with partial PTSD, and patients without PTSD (fig. 2). Significant differences in PF (Kruskal-Wallis, $H = 8.735$, $df = 2$, $p < 0.05$), RP (Kruskal-Wallis, $H = 6.653$, $df = 2$, $p < 0.05$), GH (Kruskal-Wallis, $H = 6.709$, $df = 2$, $p < 0.05$), V (Kruskal-Wallis, $H = 16.774$, $df = 2$, $p < 0.001$), RE (Kruskal-Wallis, $H = 11.260$, $df = 2$, $p < 0.01$), and MH (Kruskal-Wallis, $H = 15.731$, $df = 2$, $p < 0.001$) between the three subgroups were found. No significant differences in BP (Kruskal-Wallis, $H = 4.060$, $df = 2$, $p = 0.131$) and SF (Kruskal-Wallis, $H = 3.397$, $df = 2$, $p = 0.183$) between the three subgroups were evident.

Variables with a Possible Influence on the Risk of PTSD

Variables that may have contributed in some way to the development of posttraumatic stress symptoms in OLT recipients are depicted in tables 1 and 2. The diagnostic status of full or partial PTSD in our cohort of adult OLT recipients was not significantly related to any of the following variables: gender ($\chi^2 = 3.645$, $df = 2$, $p = 0.162$), age (Kruskal-Wallis, $H = 3.244$, $df = 2$, $p = 0.198$), employment status ($\chi^2 = 1.186$, $df = 2$, $p = 0.553$), marital status ($\chi^2 = 7.295$, $df = 6$, $p = 0.294$), number of months from OLT to psychiatric-psychometric assessment (Kruskal-Wallis, $H = 2.642$, $df = 2$, $p = 0.267$), primary liver disease ($\chi^2 = 9.531$, $df = 8$, $p = 0.300$), type of liver failure ($\chi^2 = 2.610$, $df = 2$, $p = 0.271$), history of retransplantation ($\chi^2 = 5.510$, $df = 2$, $p = 0.064$), history of recurrence of HBV/HCV ($\chi^2 = 2.247$, $df = 2$, $p = 0.325$), medical complications during ICU treatment following OLT in terms of gastrointestinal bleeding ($\chi^2 = 0.923$, $df = 2$, $p = 0.630$), viral, mycotic or bacterial infections ($\chi^2 = 3.143$, $df = 2$, $p = 0.208$), acute cardiovascular disturbances ($\chi^2 = 1.884$, $df = 2$, $p = 0.390$), acute renal failure ($\chi^2 = 3.710$, $df = 2$, $p = 0.156$), delirium ($\chi^2 = 5.044$, $df = 2$, $p = 0.080$), and acute respiratory stress syndrome ($\chi^2 = 2.391$, $df = 2$, $p = 0.303$). The duration of ICU treatment following OLT (Kruskal-Wallis, $H = 8.951$, $df = 2$, $p = 0.011$), the total number of medical complications during ICU treatment (Kruskal-Wallis, $H = 6.491$, $df = 2$, $p = 0.039$), and the occurrence of acute rejection during ICU treatment subsequent to OLT ($\chi^2 = 6.858$, $df = 2$, $p = 0.032$), however, were significantly positively correlated with the risk of

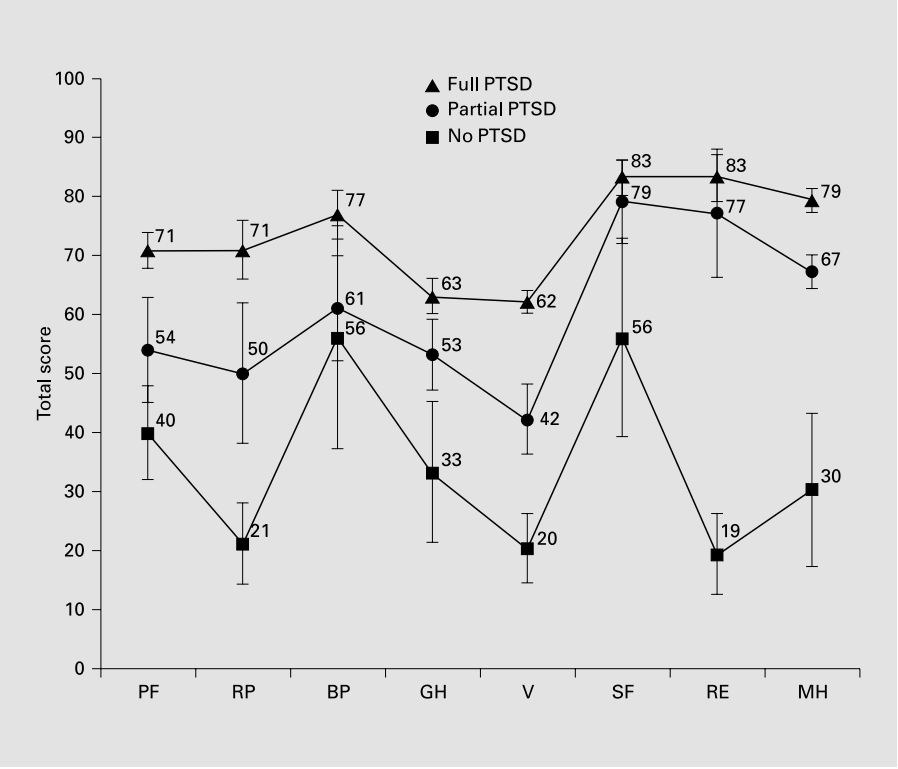

Fig. 2. Comparison of the mean scores ± standard errors of the SF-36 HRQOL questionnaire between the three subgroups of OLT recipients with no PTSD (n = 58), partial PTSD (n = 13), and full PTSD (n = 4) at the time of psychiatric assessment. Normal score = 100. Significant differences between groups were found on all domains but BP and SF.

PTSD symptomatology following liver transplantation. The length of the waiting period for OLT was negatively correlated with the risk of partial and full PTSD (Kruskal-Wallis, H = 7.233, df = 2, p = 0.027; patients with full PTSD: median = 8.5 days; partial PTSD: median = 11 days; no PTSD: median = 28 days); however, Bonferroni correction for pair-wise comparison showed no discrimination reaching statistical significance between the subgroups.

Discussion

Overall, the prevalence of psychiatric morbidity in this sample of adult liver transplant recipients identified by SCID according to DSM-III-R criteria was 22.7%. This prevalence rate fell within the range for psychiatric morbidity in adult intermediate-term survivors of OLT reported in the two previous studies using Research Diagnostic Criteria (18.8%) [20] or Clinical Interview Schedule (26.7%) [21]. It was comparable with the prevalence rate of psychiatric morbidity in the general population, as found in a German epidemiological study [45]. In accordance with Commander et al. [20] and Collis et al. [21], we found that anxiety disorders and depression were the most frequent psychiatric diagnoses in OLT survivors.

17.3% of the OLT recipients displayed mild signs of cognitive impairments at a median time of 3.8 years after liver transplantation; however, none of these patients fulfilled the criteria for any organic mental disorder according to DSM-III-R. This was a main finding in terms of the history of cognitive performance following OLT. As we know from studies targeting organic mental disorders in OLT candidates, the prevalence rate of delirium according to DSM-III ranged from 16.7 to 18.6% [46, 47]. Earlier reports of OLT recipients have even noted a 30–50% prevalence of delirium or encephalopathy [19, 48, 49]. Following OLT, Vieta et al. [18] reported a 13% prevalence of delirium during the postoperative period until discharge, and at a median time of 39 weeks after OLT, Collis et al. [21] found a 3.3% prevalence of organic mental disorder. OLT is obviously effective in reversing delirious states owing to hepatic encephalopathy, and it has been pointed out that improved neuropsychiatric function explained as much as 20% of improvement in quality of life in OLT recipients [50]. However, it has also been stated that cognitive functioning is restored to a large extent, but not completely, subsequent to OLT [51]. This

observation concurs with our results. As we found a positive correlation between severity of PTSD symptoms and cognitive disturbances, it is conceivable that our observed cognitive impairments may be related to psychological distress in terms of PTSD symptoms. At least, Bremner's study [52] has demonstrated that PTSD may be associated with cognitive dysfunction.

The most interesting result of our study resides in the observation that a significant minority of the studied adult OLT survivors developed posttraumatic stress symptoms as a consequence of OLT. We found that 5.3% of the patients met DSM-III-R criteria for a current diagnosis of full PTSD, and 17.3% of the patients for a partial PTSD at a median time of 3.8 years after OLT. Despite the increasing consideration of medically related posttraumatic stress symptoms in a large body of literature over the past 5 years, only three previous studies systematically addressed the issues of posttraumatic stress symptoms related to *solid* organ transplantation [24, 53, 54]. Walker et al. [24] interviewed 18 children aged between 7 and 16 years at a mean time of 16.94 months after liver transplantation by using the Child Posttraumatic Stress Reaction Index (CPTS-RI). The concordance between the CPTS-RI ratings and the DSM-III-R criteria for a diagnosis of PTSD has been found to be high [55]. The study demonstrated that 11% of the studied patients fell within the severe range of posttraumatic stress, 11% fell within the moderate range, and 56% fell within the mild range. These results indicated that the acute life threat involved in the liver transplantation contributed to the development of posttraumatic stress. Using the PTSD module of the Composite International Diagnostic Interview (CIDI) [56] that yields a diagnosis of the disorder based on DSM-III-R criteria, Stukas et al. [53] found that 10.8% of the 158 studied heart transplant recipients met the full criteria for a diagnosis of PTSD, and an additional 5% of the patients were probable cases at 12 months after transplantation. Most recently, Grandi et al. [54] investigated 129 heart transplant recipients who had undergone transplantation 1 month previously. Using the Italian version of the SCID for the DSM-IV, they recorded a 26.3% figure of anxiety disorders in their sample. Full PTSD (7%) and generalized anxiety disorder (7%) constituted the most frequent diagnostic categories in their heart transplant recipients.

There are at least four possible explanations for the observed difference in full and partial PTSD prevalence rates across the studies. First, OLT recipients in the current study were interviewed at a median time of 46 months after OLT, whereas in the other studies, psychiatric assessments were conducted at 1, 16.94 or 12 months after solid organ transplantation. A recent epidemiological study has demonstrated that approximately 26% of PTSD cases remitted by 6 months, and 40% by 12 months, and even from that point on, remission continued, although it tapered off [57]. Reflecting this clinical course of PTSD, we could speculate that a portion of our studied patients suffering from a partial PTSD at the time the evaluation was conducted might have experienced a partial remission from a full PTSD over time. On the other hand, we have to state that our retrospective analysis of lifetime diagnoses by using SCID-I did not reveal a history of full PTSD in those patients meeting the criteria for a current partial PTSD. Second, we investigated adult OLT recipients with a mean age of 52.2 years, whereas Walker et al. [24] studied children with a mean age of 11.8 years. Published studies suggest that younger age represents an important risk factor for PTSD [58, 59]. Third, different types of physical traumata and medical illnesses may produce different rates of full PTSD and partial PTSD. For example, Kapfhammer et al. [60] found that 23.9% of the investigated 46 long-term survivors of the acute respiratory distress syndrome suffered from a full PTSD, and 17.8% from a partial PTSD, as detected by a full diagnostic assessment with the Structured Clinical Interview for DSM-IV, while Green et al. [61] described that only 2.5% of the studied 160 women with an early-stage breast cancer met stringent criteria for cancer-related PTSD according to DSM-III-R. Madianos et al. [62] examining 45 patients with burn injuries reported a 20% prevalence of PTSD according to DSM-III-R criteria. Fourth, our studied sample only included OLT recipients who had CsA or FK 506 concentrations in blood within therapeutic range. Hence, our participants represented a selected cohort of OLT recipients who were highly compliant with medications. One study has recently demonstrated that posttransplant medical compliance and mental health predicted physical morbidity and mortality 1–3 years after heart transplantation, and that the risk of cardiac allograft disease was elevated by anxiety and depressive symptomatology [63]. Considering these results, one could speculate that those OLT recipients showing CsA or FK 506 blood levels not within the target range were noncompliant with immunosuppressive therapy owing to psychological factors such as depressive and anxiety disorders including PTSD. Mayou and Smith [64] emphasized that a partial or full syndrome of PTSD could be associated with avoidance of medical care and poor compliance with treatment. One study investigating the prevalence of noncompliance with immunosuppressive medication in 118

OLT recipients documented a figure of 16% at a mean follow-up time of 53.7 months [65]. Given that OLT recipients with immunosuppressive concentrations in blood not within the target range were enrolled in our study, it is possible that the prevalence of full PTSD in OLT recipients may be similar to that observed in the study by Stukas et al. [53].

It is particularly noteworthy that 50% of our patients meeting DSM-III-R criteria for full PTSD were comorbid with major depression, while only 7.7% of those patients suffering from partial PTSD occurred with major depression. From a point of view of depression, it is worth considering that an additional 15.4% of the patients with partial PTSD scored 13 points or more on the $HAMD_{17}$, indicating major depression. However, the $HAMD_{17}$ scale was not designed to be used for diagnostic purposes and is only used for measuring the severity of symptoms once a diagnosis has been made. Therefore, our comorbidity data only partly concur with the observations made by Kessler et al. [66] in a recent epidemiologic survey. Considering the fact that 50% of our patients with full PTSD had lifetime histories of MDD, and only 23% of our patients with partial PTSD had lifetime histories of depressive disorders NOS, we could raise the hypothesis that patients with a personal psychiatric history of mood disorders might be more susceptible to the development of OLT-related PTSD than those without previous affective disorders. At least, our analysis of possible risk variables for PTSD symptomatology revealed that the length of ICU stay and number of complications during ICU did not significantly differ in our studied OLT recipients with full PTSD from those without PTSD, whereas patients with partial PTSD had been treated significantly longer in the ICU and had experienced significantly more complications during ICU than those without PTSD. We agree with Jacobsen et al. [67] that a longer treatment duration in the ICU is due to the increased incidence of medical complications that may be perceived as life-threatening associated with feelings of fear, helplessness or horror, and therefore may increase the potential for the development of PTSD symptomatology. Other variables that may contribute in some way to the development of PTSD symptoms such as gender, age, waiting period for OLT, primary liver disease, type of liver failure, history of retransplantation, and history of recurrence of HBV/HCV were not significantly different between the studied patients with full, partial, or no PTSD. Regarding the recurrence of HBV/HCV, it is worth discussing that this information is certainly associated with psychological distress for the patients as a rapid progression of the infection cannot be ruled out; however, this stressor is a future-oriented one, since in most cases, prognosis is good and progression of liver disease is relatively slow. The nature of this stressor, therefore, may not fit the PTSD model well. Most interestingly, the occurrence of acute rejection during ICU treatment was a significant predictor of PTSD symptomatology. In fact, experiencing episodes of acute rejections played a major role for the OLT recipients' subjective perception of trauma. According to contemporary immunosuppressive strategies [68], patients with acute rejection were initially treated with pulse intravenous methylprednisolone, up to 1 g/day for 3 consecutive days. As we know from literature [69, 70], transient disruption of sleep, altered perception, and lability of mood often occurs among those receiving 'supraphar-macologic' doses of glucocorticoids as an antirejection therapy. Besides, from a psychobiological perspective, one could speculate that 'pulses' of glucocorticoids might have an influence on the development of PTSD symptomatology. Theoretically, glucocorticoid excess could have neurotoxic effects, particularly in the hippocampus, a primary neural glucocorticoid target site, and it has been hypothesized that hippocampal damage appears to be a correlate of PTSD itself, as decreased hippocampal functioning may cause behavioral disinhibition by promoting the definition of incoming stimuli in the direction of fight/flight responses [71, 72]. However, the role of glucocorticoid pulse therapy in the development of PTSD seems to be very speculative because the role of glucocorticoids in PTSD is controversial, and, generally, the instances of glucocorticoid-induced hippocampal atrophy require *prolonged* or *repeated* bursts of glucocorticoid excess [73].

A major aim of the present study was to explore the relation between psychiatric morbidity in OLT recipients and HRQOL. HRQOL in the entire sample of our patients was characterized by statistically significant decrements in all eight domains of the SF-36 when compared with a German age and gender-matched *healthy* control group. This finding was only partly in accordance with the results reported by Bravata et al. [7] who quantitatively synthesized the complete published English-language literature on HRQOL after liver transplantation. They reported that the SF-36 scores from the studied 468 OLT recipients were not significantly different from those of the *general* US population, except in the pain domain. Besides, we found 64% employed at the time the evaluation was performed. This figure was quite similar to the average overall employment rates in other recent studies [74]. In accordance with the other two previous studies investigating the relation between psychiatric morbidity

and HRQOL [20, 21], our study demonstrates that there was a significant association between psychiatric morbidity and impaired HRQOL. In detail, OLT recipients fulfilling DSM-III-R criteria for PTSD, either comorbid with MDD or not, manifested the most impaired mental and physical health status and perceived supportive relationships most unfavorably, followed by those with subthreshold expressions of PTSD, whereas OLT recipients without current or probable psychiatric disorders showed the most favorable health status. The finding regarding mental health subscales suggests that PTSD symptomatology subsequent to OLT is a clinically relevant phenomenon. So far as the physical health subscales are concerned, one could argue that either the presence of PTSD symptomatology had adverse health effects that made them less able to cope with activities in daily living, or that their physical health was worse and reminded them of traumatic aspects of their ICU treatment following OLT.

Finally, there are several limitations of this study to be respected. First, the varying time intervals between OLT and psychiatric evaluation. Second, the study was retrospective in design. A recall bias might have significantly lowered the report on any psychiatric disorder and traumatic experiences prior to and following OLT. Third, no pretransplant measures of psychiatric symptomatology and other psychosocial variables including SF-36 baseline data were available with which to compare our findings. Fourth, the sample was a selected cohort of OLT recipients. Although our decision to consider OLT recipients only eligible for enrollment if they had CsA or FK 506 concentrations in blood within therapeutic range certainly helped to avoid confounding present cognitive deficits, mood and anxiety phenomena with cyclosporine-associated or tacrolimus-associated organic mental disturbances; it is possible that the prevalence rate of PTSD symptomatology would have been higher if we had included patients who were not compliant with immunosuppressive medication. Fifth, the conduction of brain magnetic resonance imaging examining the hippocampus, psychophysiologic and endocrinological evaluations should be proposed in future studies in order to measure presumed neurobiological correlates of PTSD itself that could add objectivity to the assessment of PTSD. Sixth, the inclusion of appropriate control groups (e.g. heart transplant recipients) needs to be considered in forthcoming studies, and future research should also include longitudinal study designs. Seventh, the Diagnostic Criteria for Psychosomatic Research, as proposed by Fava et al. [75], should be used in future studies in order to improve the identification of psychological factors which could result in a worsening of HRQOL in OLT recipients [54, 76–78].

In conclusion, our study demonstrated that a subgroup of intermediate-term survivors of OLT exhibited PTSD symptomatology that was related to impaired HRQOL. This finding highlights the need to be aware of the possible presence of PTSD in OLT survivors who present to health-care providers with a variety of common psychiatric symptoms such as sleep difficulties and poor concentration. HRQOL may be improved in affected OLT recipients by attenuating posttraumatic stress symptoms. Definitive psychotherapeutical and pharmacotherapeutical treatment approaches for PTSD exist.

Acknowledgments

The authors wish to thank Prof. Dr. Monika Bullinger and Matthias Morfeld, MA, from the Institute of Medical Psychology, University Hospital Eppendorf, Hamburg, Germany, for providing control group data of the SF-36 health survey.

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