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The effect of recurrence of HCV infection of life after liver transplantation

M. De Bona
G. Rupolo
P. Ponton
R. M. Iemmolo
P. Boccagni
C. Destro
M. Ermani
R. Naccarato
P. Burra

M. De Bona · P. Burra · R. Naccarato
Department of Gastroenterology,
University of Padova, via Giustiniani, 2,
35128 Padova, Italy

G. Rupolo · P. Ponton
Department of Psychiatry,
University of Padova, via Giustiniani, 2,
35128 Padova, Italy

R. M. Iemmolo · C. Destro
Department of Internal Medicine,
University of Padova, via Giustiniani, 2,
35128 Padova, Italy

P. Boccagni
Department of Surgery,
University of Padova, via Giustiniani, 2,
35128 Padova, Italy

M. Ermani
Department of Neurology,
University of Padova, via Giustiniani, 2,
35128 Padova, Italy

P. Burra (✉)
Cattedra Malattie Apparato Digerente,
Monoblocco Ospedale, via Giustiniani 2,
35128 Padova, Italy,
Tel. + 39.49.8212892; Fax + 39.49.8760820

Abstract The present study evaluated the quality of life (QOL) of adult cirrhotic patients before orthotopic liver transplantation (OLT), the effect of OLT on QOL in the long-term and the effect of HCV recurrence within medical complications on QOL. Three groups of patients were studied: 19 pre-OLT, 33 during the first year post-OLT and 41 1 to 5 years post-OLT. The patients completed questionnaires on QOL and underwent liver function tests, immunosuppressive drug blood level determinations and medical complications evaluation. Somatization and depression and anxiety scores improved significantly during the first year post-OLT compared with pre-OLT, but they worsened again during the 1–5-year period post-OLT. Physical functioning and life satisfaction scores improved significantly during the first year post-OLT compared with pre-OLT and the improvement persisted 1–5-year during the period post-OLT. Patients with HCV recurrence compared with patients without HCV recurrence during the first year post-OLT showed a significant worsening of most of the domains of QOL. In conclusion, OLT improved most of the domains of QOL by the end of the first post-transplant year, though the improvements did not all persist in the long-term. Recurrence of HCV infection plays a major role in the impairment of QOL after OLT.

Key words Liver transplantation · Quality of life · HCV infection recurrence

Introduction

Orthotopic liver transplantation (OLT) is an effective treatment for patients with liver failure resulting from acute and chronic liver disease and should be offered to selected patients with end-stage liver disease refractory to medical measures. Both graft and patient survival rates have been increasing continuously and now exceed 70% at 5 years in most centers [1]. Despite the encouraging results, however, both risks and untoward outcomes are such that not all patients do well, mostly because of occurrence of postsurgical complications in the short term and a new set of medical problems emerging in relation to lifelong immunosuppressive treatment in the long term.

The assessment of the quality of life (QOL) is increasingly used as an outcome measure when evaluating medical procedures [2] and a marked improvement has been reported in health-related QOL after OLT, particularly in relation to the physical, psychological and so-

Table 1 Demographic characteristics and etiology of liver disease of the study population

	Group A (pre-OLT) ($n = 19$)	Group B (< 1 year post-OLT) ($n = 33$)	Group C (1–5 years post-OLT) ($n = 41$)
Age (years)			
Mean	49	44	48
Range	26–61	22–65	26–64
Gender			
Male	14	26	27
Female	5	7	14
Primary liver disease			
Cholestatic			
Primary biliary cirrhosis	0	1	1
Primary sclerosing cholangitis	0	1	7
Chronic			
Alcoholic liver disease (ALD)	2	5	4
Hepatitis C	5	9	16
ALD + hepatitis C	1	2	2
Autoimmune hepatitis	0	0	1
Hepatitis B	3	6	4
Hepatitis B and C	3	1	3
Hepatitis B and D	2	2	0
Cryptogenetic hepatitis	0	1	1
Malignancy	3	1	1
Miscellaneous	0	4	1

cial domains of health, as perceived by patients [3–10]. However, the perception of OLT outcome may be disturbed by side effects of immunosuppressive treatment such as hirsutism, hypertension, tremor or weight gain, and the interference of these medical complications with QOL is generally reported [4–11]. However, little information is available on the effect on QOL of recurrence of previous liver disease.

Recurrent liver disease is mainly seen in patients with hepatitis B virus (HBV) [12, 13] or HCV infection [14–17] prior to transplantation. The selection of HBV DNA-negative candidates and long-term passive immunoprophylaxis have dramatically reduced HBV reinfection after OLT [12], whereas the incidence of recurrent histological HCV hepatitis varies widely, ranging between 14% to 72% [18–21]. It is probable that the recurrence of HCV infection contributes negatively to the QOL even in patients who may have experienced a phase of postoperative euphoria [22].

Therefore, the aims of this cross-sectional prospective study were: (1) to evaluate the QOL of adult cirrhotic patients before OLT, (2) to assess the effect of OLT on QOL in the long term, and (3) to evaluate the effect on QOL of the recurrence of HCV infection within medical complications.

Patients and methods

Patients

A total of 93 patients were evaluated, divided into three groups: *group A* 19 patients listed for OLT (14 males, 5 females, mean age 49 years, range 26–61 years); *group B* 33 patients during the first year post-OLT (26 males, 7 females, mean age 44 years, range 22–65 years); *group C* 41 patients from 1 to 5 years post-OLT (27 males, 14 females, mean age 48 years, range 26–64 years). Table 1 shows the demographic characteristics and indications for OLT of each group.

Quality of life

Because of the multidimensionality of QOL, it was evaluated by standardized autoadministered questionnaires, including measures for physical, psychological and work-performance domains. The Brief Symptoms Inventory (BSI) [23] and the LEIPAD Quality of Life Scale [24] were used.

BSI

The BSI is a self-report symptom inventory designed to assess the psychological symptom status of psychiatric and medical patients as well as healthy individuals. The BSI is essentially the brief form of the SCL-90-R, a self-report inventory that has been developed for use in a wide variety of settings and applications [25].

The instrument comprises 53 items selected to reflect best the nine primary symptom dimensions of the SCL-90-R in a brief measurement. These nine dimensions are: (1) *Somatization (SOM)* reflects psychological distress arising from perception of bodily dysfunction; (2) *obsessive-compulsive (O-C)* focuses on thoughts and actions that are experienced as unremitting and irresistible by the

patients but are of an ego-alien or unwanted nature; (3) *interpersonal sensitivity (I-S)* focuses on feelings of personal inadequacy and inferiority; *depression (DEP)* reflects a broad range of signs and symptoms of the clinical depressive syndromes; (5) *anxiety (ANX)* subsumes a set of symptoms usually associated clinically with high manifest anxiety; (6) *hostility (HOS)* is organized around three categories of hostile behavior: thoughts, feelings and actions; (7) *phobic anxiety (PHOB)* comprises phobic fears oriented toward travel, open spaces, crowds and public places; (8) *paranoid ideation (PAR)* is a mode of thinking characterized by projection, hostility, suspiciousness, centrality and fear of loss of autonomy; (9) *psychoticism (PSY)* represents a continuum, progressing from a mildly alien life-style at one extreme to a floridly psychotic state at the other.

LEIPAD

The LEIPAD has been specifically designed to assess QOL with the sensitivity to identify modifications attributable to any kind of intervention (medical, surgical, social). In the LEIPAD the psysical dimensions includes health status and health perception and basic activities of daily living assessment. The mental or psychological dimensions include an assessment of psychopathology. Subjective aspects of mental functioning are considered as reflected by feelings of self-esteem and optimism representing the positive side, and by anxiety, depression and mood disturbances representing the negative side. Socioeconomic aspects are assessed by means of questions regarding income, housing, and leisure activities.

The LEIPAD comprises the following six scales.
(1) *physical functioning (PHY)* consists of five items covering different areas of physical functioning. The scores range from "no complaints" to "extreme complaints". (2) *self care (S-C)* consists of seven items pertaining to the ability to take care of oneself independently from others. The scores range from "no problem" to "unable to care for oneself". (3) *Depression and anxiety (D-A)* consists of four items measuring the level of anxiety and depression from "no anxiety or depression" to "extreme anxiety and depression". (4) *Cognitive functioning (C-F)* concerns problems with cognitive functioning and consists of five items ranging from "no problems" to "extreme problems". (5) *Social functioning (S-F)* consists of three items dealing with social integration and satisfaction, ranging from "high satisfaction" to "extreme dissatisfaction". (6) *Life satisfaction (L-S)* reflects satisfaction with different aspects of living, measuring the attitude with regard to one's present situation and anticipated future. The scale consists of six items and the scores range from "high satisfaction" to "extreme dissatisfaction".

Cirrhotic patients completed tests when placed on the waiting list for OLT (group A); transplanted patients had a QOL evaluation according to the follow-up visit protocol, at 3, 6 and 12 months (group B) and then yearly after OLT (group C).

Medical complications

All patients at the time of QOL assessment underwent a clinical evaluation and blood tests. Liver function and kidney function tests were carried out, (AST, ALT, gGT, ALP, total bilirubin, albumin, prothrombin time, urea, creatinine, Na^+, K^+). Hepatitis B, C and D virus markers were also assessed.

In cirrhotic patients, the severity of liver disease was classified using the Child-Pugh score. Medical complications (gastrointestinal hemorrhage, infections, osteoporosis, diabetes, ascites, peripheral edema, pruritus, jaundice and renal failure) were evaluated semiquantitatively as follows: 0 = absent, 1 = mild, 2 = moderate, 3 = severe. In transplanted patients, immunosuppressive drug blood levels (cyclosporine, or FK506) were measured. Medical complications (infections, hypertension, renal failure, osteoporosis, gingival hyperplasia, headache and tremors) were evaluated semiquantitatively as follows: 0 = absent, 1 = mild, 2 = moderate, 3 = severe.

Recurrence of HCV infection

Recurrence of HCV infection and/or liver disease was investigated by means of HCV RNA (primer 5'UTR, genomic amplification) and liver biopsy, performed whenever clinically indicated or at 6 and 12 months and then yearly after OLT. Histological features were classified according to the recommendations of Ishak et al. [26].

Statistical analysis

For both BSI and LEIPAD, numerical scores were assigned to each question and answer scores were then added to obtain global scores for each category which were then expressed as means ± SD. Comparison between scores at different time-points were made using the Mann-Whitney *U*-test. Correlations between demographic, physical and biochemical variables and QOL were assessed using Spearman's Rho test. A *P*-value of 0.05 or less was considered significant.

Results

Quality of life

BSI

Somatization scores improved significantly during the first year post-OLT compared with pre-OLT (group B versus group A: 2.7 ± 3.2 versus 6.1 ± 5.4, $P = 0.029$), but they worsened again betwen 1 and 5 years after the operation (group C 3.7 ± 2.9 versus group B, $P = 0.043$; Fig. 1).

LEIPAD

Physical functioning (group B versus group A 4.3 ± 2.4 versus 7.4 ± 3.9, $P = 0.004$) and life satisfaction (group B versus group A 2.9 ± 1.4 versus 5.5 ± 2.7, $P = 0.0006$) scores improved significantly during the first year post-OLT compared with pre-OLT and persisted during 1 to 5 years after the operation (physical functioning, group C 5.3 ± 2.3 versus group A, $P = 0.036$; life satisfaction, group C 3.6 ± 1.9 versus group A, $P = 0.01$). Depression and anxiety improved significantly during the first year post-OLT compared with pre-OLT (group B versus group A 3.6 ± 2.5 versus 2.0 ± 2.3, $P = 0.01$), but worsened between 1 and 5 years after the operation (group C 2.8 ± 2.2 versus group B, $P = 0.05$; Fig. 2).

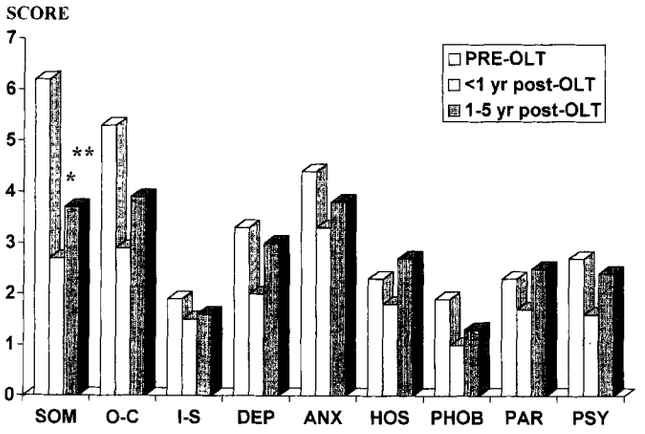

Fig. 1 BSI evaluation of QOL before and after OLT (*PRE-OLT* group A, *< 1 year post-OLT* group B, *1–5 years post-OLT* group C). *$P < 0.05$ group B and group C vs group A, **$P < 0.05$ group C versus group B

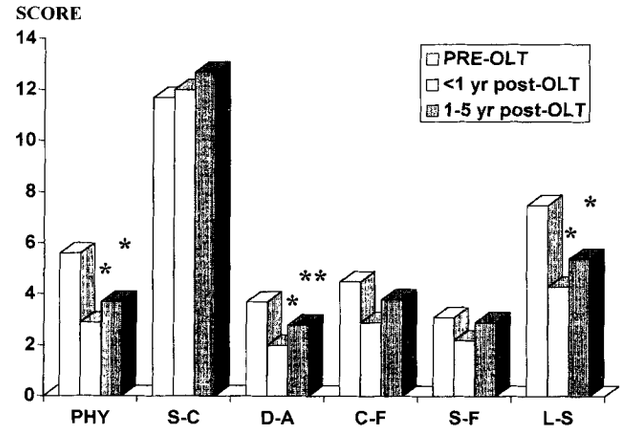

Fig. 2 LEIPAD evaluation of QOL before and after OLT (*PRE-OLT* group A, *< 1 year post-OLT* group B, *1–5 years post-OLT* group C). *$P < 0.05$ group B and group C versus group A, **$P < 0.05$ group C versus group B

Medical complications

Cirrhotic patients were classified as follows: Child-Pugh A, four patients; B, eight patients; C, seven patients. Liver function and kidney function tests, as well as medical complication scores did not correlate with any areas of QOL either in the BSI or the LEIPAD evaluation.

In transplanted patients liver function and kidney function tests, cyclosporine and FK506 blood levels and medical complication scores did not correlate at any time-point with any areas of QOL either in the BSI or the LEIPAD evaluation.

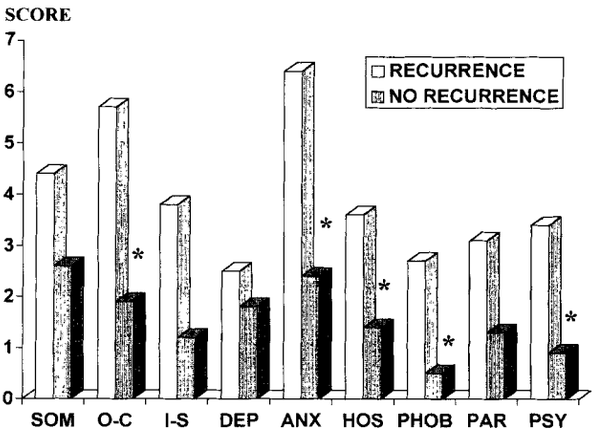

Fig. 3 QOL and HCV recurrence after OLT: BSI evaluation. *$P < 0.05$ patients with HCV recurrence vs patients with no recurrence

Recurrence of HCV

Of 33 patients, 27 had HCV recurrence post-OLT (6 patients during the first year, and 21 patients during 1 to 5 years post-OLT). Mild changes on histology were seen in 16 of the 27 patients (59.3%), chronic hepatitis in 9 (33.3%), cirrhosis in 2 (7.4%).

Patients with HCV recurrence compared with patients without HCV recurrence during the first year post-OLT showed significantly higher scores for anxiety (6.4 ± 5.3 versus 2.3 ± 2.2, $P = 0.025$), hostility (3.6 ± 3.0 versus 1.4 ± 1.8, $P = 0.028$), phobic anxiety (2.7 ± 2.5 versus 0.5 ± 1.1, $P = 0.009$), psychoticism (3.4 ± 2.8 versus 0.9 ± 1.2, $P = 0.01$) and obsessive-compulsive (5.7 ± 3.4 versus 1.9 ± 2.3, $P = 0.01$) in the BSI evaluation (Fig. 3), and for depression and anxiety (4.0 ± 2.6 versus 1.6 ± 2.0, $P = 0.024$) in the LEIPAD evaluation (Fig. 4). No differences in QOL in either the BSI or the LEIPAD scores were seen between patients with and those without HCV recurrence during 1 to 5 years post-OLT.

Discussion

The results of this study confirm that most of the domains related to QOL do better after transplantation. The pretransplant state in patients with cirrhosis is characterized by many physical disorders and a low level of experienced wellbeing. These patients also experience the fear of being on the waiting list with the awareness that there are not enough donations in our country to enable all of them to be transplanted before clinical deterioration can cause exclusion from the list.

One year after transplantation patients showed a considerable rise in QOL, but this did not appear to per-

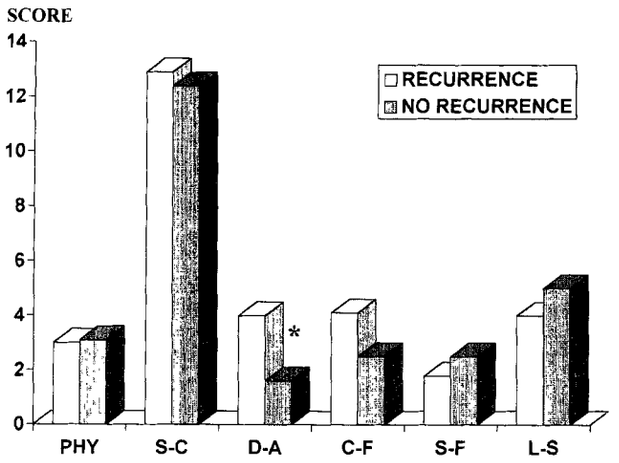

Fig. 4 QOL and HCV recurrence after OLT: LEIPAD evaluation. *$P < 0.05$ patients with HCV recurrence vs patients with no recurrence

sist in the long term. The immunosuppression-related medical complications (commonly seen in transplant recipients) probably interfered with the perception of good health even in patients with otherwise successful OLT.

Somatization reflects psychological distress arising from perception of bodily dysfunction. Complaints which focus on cardiovascular, gastrointestinal, respiratory and other systems, were undoubtedly mitigated after transplantation, as is expected in such patients. However, it seemed that patients complained of discomfort again later, and it was not easy to distinguish real pain from somatization resulting from anxiety. The same trend was also seen for depression and anxiety levels, which improved with OLT but then tended to worsen.

The high rate of recurrent HCV infection post-OLT in patients viremic prior to OLT confirmes the findings of several studies [14, 27]. We believe that, in this setting, the fear of falling ill because of viral reinfection of the new graft is the main problem, rather than the general medical complications, that influences the level of anxiety and depression in the long-term. This is confirmed by the fact that no correlations were found between QOL and medical complications, whereas, when patients were divided according to HCV reinfection, the ones with recurrent HCV did worse in most of the domains of QOL. It was also evident that many symptoms of discomfort that could have been due to immunosuppressive drugs were unassociated in the present study with either cyclosporine or FK506 blood levels.

Despite the nearly universal recurrence of HCV viremia, histological hepatitis was not found in all patients. The reported incidence of recurrent histological hepatitis varies widely, ranging from 14% to 72% [18–21]. Reduced graft and patient survival has been seen in the past in patients with pretransplant HBV infection, before the candidate selection protocol and long-term passive immunoprophylaxis were introduced [12], whereas HCV behaves differently. Nearly 95% of patients transplanted for HCV experience virological recurrence [17], but prognosis is usually good, even in the face of liver disease. However, the awareness of being HCV-positive again, sometimes soon after the operation, always has a negative psychological impact. Patients know that HCV infection can cause liver disease and the possible onset of cirrhosis would waste the new organ. Moreover, their recollection of their pretransplant status undoubtedly alters their perception of good health.

We therefore believe that these findings support the theory that a specific pretransplant assessment should be defined for HCV-positive candidates for OLT in order to better inform patients and relatives on the risk of reinfection and possible development of liver disease. They should also be assured that the progression of liver disease is usually slow, cirrhosis being reported in 5–10% of patients at 2 years after OLT [13]. It is also necessary during the post-OLT follow-up to offer psychological support to patients with recurrent severe liver disease. Despite the good prognosis in the majority of recipients, a rapid progression of the infection with liver failure cannot be ruled out, and retransplantation is still a controversial matter in these cases.

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