Transplant International

Transplant International ISSN 0934-0874

ORIGINAL ARTICLE

Health-related quality of life in adult transplant recipients more than 15 years after orthotopic liver transplantation

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Keywords
health-related quality of life, long-term outcomes, orthotopic liver transplantation, SF-36.

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Received: 11 February 2008
Revision requested: 11 March 2008
Accepted: 19 June 2008

doi:10.1111/j.1432-2277.2008.00733.x

Summary

With continuously rising survival rates following orthotopic liver transplantation (OLT), health-related quality of life (HRQOL) of transplant recipients becomes increasingly important. Recipients more than 15 years after OLT were studied retrospectively. HRQOL in 104 adult liver transplant recipients surviving more than 15 years after OLT was assessed using the German Version of the 36-Item Health Survey (SF-36). Liver transplant recipients surviving more than 15 years after OLT scored lower in all categories of SF-36 revealing a poor HRQOL in comparison to the German reference population. A statistical significance was reached in almost all SF-36 categories with the exceptions of mental health and bodily pain, where our study population scored similarly to the reference population. Job rehabilitation after OLT had a positive effect on HRQOL. Patients who returned to their job during the first year after OLT scored significantly higher in the SF-36 categories of physical functioning and role physical. Marital status and the immunosuppression used didn't affect HRQOL as there was no statistical significance reached in any of the comparisons performed. More than 15 years after OLT, long-term survivors present a poor HRQOL comparable to the reference population. Occupational rehabilitation was the only factor shown to positively influence long-term HRQOL.

Introduction

Over the last decades, orthotopic liver transplantation (OLT) has become the treatment of choice not only for acute and chronic liver failure but also for special cases of metabolic diseases and liver tumors [1–3].

Although the procedure of OLT was first described in 1960 [4], the first liver transplantation considered to be successful, with a recipient survival of about 400 days, was performed 7 years later by Starzl *et al.* [5]. The following years were characterized by a small number of surgical procedures and poor clinical outcomes with 1-year patient survival of about 30% even in large and experienced liver transplantation centers in Europe and the United States [6].

The latest developments in liver transplantation and especially the introduction of new immunosuppressive agents [7,8], the better selection of recipients and grafts, innovations in surgical techniques [9,10] and perioperative care of patients have led to continuously improved patient and graft survival rates. The 2006 annual report of the United Network for Organ Sharing (UNOs) demonstrated an impressive 1-year survival rate of 83.7% and 88.2% for deceased and living donor liver transplant recipients, respectively.

Health-related quality of life (HRQOL) following OLT is a subject of increasing importance. Numerous studies have demonstrated that HRQOL improves significantly after OLT and that liver transplant recipients report gains mostly in the aspects of HRQOL affected by physical health in contrast to smaller improvements in areas affected by psychological functioning [11,12]. However, the number of studies focusing on long-term HRQOL is limited, with only a single study evaluating quality of life in patients

15 years after OLT. Specifically, de Kroon *et al.* [13] reports that patients surviving longer than 15 years after OLT are generally satisfied with their present health status, although some limitations in the domains of mobility, usual activities and bodily pain are reported. According to de Kroon *et al.*, HRQOL improves after OLT but remains always lower than that of the general population. The findings of de Kroon *et al.* are supported by the results presented by Lewis and Howdle[14], according to whom, patients surviving more than 10 years after OLT have significant cognitive dysfunction and poor HRQOL. On the other hand, according to Kizilisik *et al.* [15], recipients surviving longer than 10 years after liver transplantation report all aspects of their lives to be just as good, if not better, than their age-matched peers. The findings of Kizilisik *et al.* are in agreement with the results presented by Karam *et al.* [16], according to whom HRQOL beyond 10 years after OLT is quite similar to the general population.

The goal of this study was to assess long-term HRQOL after OLT and compare it to the German reference population. With rising survival rates after liver transplantation we decided to evaluate HRQOL of patients surviving for more than 15 years, as this time point was considered appropriate to define long-term HRQOL.

The second part of the survey was focused on the effect of immunosuppression and socioeconomic factors, especially of professional life and marital status, on long-term HRQOL. According to Hellgren *et al.* [17], employed liver transplant recipients presented significant differences in all health areas with the exception of vitality and social functioning. Aadahl *et al.* [18] reported that working status of liver transplant recipients had significant effects on postoperative physical function and fatigue. Another interesting study is that of Saab *et al.* [19] from California, according to whom physical functioning and role physical were significantly associated with post-transplantation employment. Regarding the effect of marital status on HRQOL, Neipp *et al.* [20] showed that married or cohabiting long-term survivors after kidney transplantation experienced a better life quality in all of the SF-36 dimensions. The findings of Neipp *et al.* on kidney transplant recipients correlate with the results presented from Sainz-Barriga *et al.* [12] according to whom cohabitant liver transplant recipients presented a better HRQOL.

Materials and methods

From the total of 2500 liver transplantations performed in the Hanover Medical School from the beginning of our transplantation program in 1972 by Rudolf Pichlmayr, we focused on 623 patients (117 children defined as under 16 years of age and 506 adults, representing 18.7% and 81.2% of the recipients, respectively) who received a liver graft between January 1, 1972 and December 31, 1991. The decision to focus on these 623 patients transplanted in the period mentioned above and to exclude the remaining 1877 patients transplanted from 1992 up to the time point of our study was based on the fact that only patients surviving longer than 15 years after OLT were considered eligible for our study; therefore, patients transplanted after 1991 were excluded. From the total of the 623 recipients transplanted between 1972 and 1991, 231 patients survived at least 15 years after the OLT giving an overall 15-year survival for the entire cohort of 37%. More specifically, the 15-year survival for adult recipients was 33% ($n = 167$) and for pediatric recipients 54% ($n = 64$). The pediatric recipients ($n = 64$) were excluded from the study because they are a distinct population not only with respect to the principal diagnosis and the post-transplantation complications but also regarding socioeconomic factors, which of course influence HRQOL to a different degree in comparison to adult transplant recipients [21–23].

After the exclusion of the 64 pediatric recipients from the total of 231 patients surviving more than 15 years after OLT, 167 patients remained. One-hundred thirty-seven liver graft adult recipients qualified for this study. Thirty patients were excluded for the following reasons: three had received a combined liver–kidney transplant, 14 lived in foreign countries and were not under continuous care in our outpatient clinic and 13 were reported dead at the time of our study but having survived for more than 15 years after OLT.

Out of the 137 patients who took part in our study, 104 recipients returned the German Version of the 36-Item Health Survey (SF-36) fully completed (response rate of 75.9%).

The average age of the study population at the time point of OLT was 38 years and ranged from 17 to 63 years of age. At the time of our study, 77.8% of the recipients were married or lived in a close relationship, whereas 18.2% of the patients lived alone. One year after the liver transplantation, 40.3% ($n = 42$) of the recipients were employed, whereas 57.6% ($n = 60$) were unemployed. Regarding the occupational status at the time point of our study, 60.5% of the recipients were retired and 25.9% were employed, of which 14.4% had a full-time employment and 11.5% a part-time employment (Table 1).

The etiology of liver disease in the 104 patients assessed in our study is presented in Table 2.

The issue of immunosuppression was examined at two different time points: one at the time point immediately after the OLT and the other during the actual time of our study, taking into consideration the pharmacological developments and the various combinations of immunosuppressive regimens used by the clinicians, while trying to minimize long-term complications of immunosuppres-

Table 1. Characteristics of the 104 adult liver transplant recipients assessed in our study.

No. patients	104
Gender (male/female)	40/64 (38%/62%)
Age at OLT (years)	38.26 (17–63)
Actual age (years)	57.36 (32–82)
Actual family status (%)	
Married/cohabiting	81 (77.8)
Living alone	19 (18.2)
No data	4 (3.8)
Actual professional life (%)	
Retired	63 (60.5)
Full-time employment	15 (14.4)
Part-time employment	12 (11.5)
Never employed	9 (8.6)
Job-seeking	3 (2.8)
No data	2 (1.9)
Professional life 1-year after OLT (%)	
Employed	42 (40.3)
Unemployed	60 (57.6)
No data	2 (1.9)

Table 2. Etiology of liver disease in 104 adult liver transplant recipients assessed in our study.

Cryptogenic cirrhosis	17 (16.3%)
Budd-Chiari syndrome	16 (15.3%)
Virus B cirrhosis	10 (9.6%)
Primary biliary cirrhosis	8 (7.6%)
Primary sclerosing cholangitis	7 (6.7%)
Virus C cirrhosis	7 (6.7%)
Alcoholic cirrhosis	4 (3.8%)
HCC and cirrhosis	4 (3.8%)
Others	31 (29.8%)
Malignant liver tumors	9
Polycystic liver disease	8
Metabolic disease	8
Virus BD cirrhosis	3
Benign liver tumors	3

Table 3. Immunosuppressive therapy 15 years after liver transplantation.

Immunosuppressive regimens	No. patients (*n*)
Calcineurin-inhibitor-free protocol	19 (18.2%)
Mycophenolate mofetil monotherapy	7
Steroids + azathioprin	5
Steroids + mycophenolate mofetil	5
Azathioprin monotherapy	1
Rapamycin monotherapy	1
Calcineurin-inhibitor-based protocol	85 (81.7%)
Cyclosporine/tacrolimus monotherapy	44
CNI-based triple therapy	15
CNI + steroids	12
CNI + mycophenolate mofetil	10
CNI + azathioprin	3
CNI + rapamycin	1

Table 4. Immunosuppressive therapy immediately after OLT.

Immunosuppressive regimens	No. patients (*n*)
Calcineurin-inhibitor-free protocoll	10 (9.6%)
Steroids + azathioprin	6
Azathioprin monotherapy	4
Calcineurin-inhibitor-based protocoll	94 (90.3%)
Cyclosporine/tacrolimus monotherapy	41
CNI + steroids	30
CNI + azathioprin	13
CNI-based triple therapy	10

sive agents and in particular nephrotoxicity of calcineurin-inhibitors (CNIs) (Tables 3 and 4). From the total of the 104 patients who took part in this study, 10 (9.6%) received a CNI-free protocol immediately after OLT, whereas the number of patients under CNI-free immunosuppression increased to 19 (18.2%) at the actual time of our study, clearly showing a trend to avoid CNIs to minimize specific side effects such as nephrotoxicity. At the time point of our study, 81.7% of the patients ($n = 85$) received a CNI-based protocol in contrast to 90.3% of patients with CNI-based immunosuppression immediately after the OLT. More specifically, out of the 85 patients mentioned above, 44 received cyclosporine ($n = 37$) or tacrolimus ($n = 7$) as monotherapy, 15 CNI-based triple therapy and 12 patients a combination of CNIs with corticosteroids. The current practice is to aim for a reduced dose of cyclosporine or tacrolimuns and a minimum dose of corticosteroids to minimize the risk of long-term complications.

Health-related quality of life after OLT was assessed between August and September 2006 for all liver graft recipients who qualified for our study. The Standard German Version of the 36-Item Health Survey, a validated quality-of-life survey [24,25] was sent to each individual recipient. The SF-36 survey contains 36 questions for the assessment of HRQOL, grouped into eight different health concepts: physical functioning (PF), role physical (RP), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), role emotional (RE), and mental health (MH). The number of questions directed to each health concept ranges from 2 (for social functioning and physical pain) to 10 questions (for physical functioning). An average score is produced for each health concept, ranging from 0 to 100, with higher scores indicating a better outcome. The results of our study population were compared with mean score values of the German reference population as reported in Bullinger and Kirchberger [26].

To test the effect of the socioeconomic factors mentioned above on HRQOL, we separated our study population in groups based on the marital status at the time point of our study and on the occupational status during

the first year after OLT. The data regarding the socioeconomic factors were collected from our outpatient clinic.

The study was reviewed by the local ethic committee and was performed in accordance with the Declaration of Helsinki.

Statistical analysis

The follow-up of liver transplant recipients until September 2006 was studied based on data collected in our transplant outpatient clinic. The AMIS/WINDOWS Version 1.0 software package was utilized (AMIS/WIMDOWS; Hanover Medical School, Hanover, Germany). For statistical analyses, the SPSS software package (SPSS; Chicago, IL, USA) was used. Differences in the mean score values of SF-36 among subgroups were analyzed by two-tailed, unpaired *t*-test as indicated. Because of the multiple comparisons the Bonferroni correction was used.

Results

In the comparison between our study population of the 104 patients and the German reference population, as reported in Bullinger and Kirchberger, it is obvious that our study population scored lower in all categories of SF-36 (Table 5). A statistical significance ($P < 0.001$) was reached in the categories of physical functioning, role physical, general health, vitality, social functioning, and role emotional. Long-term liver transplant recipients scored similarly to the control population and without statistical significance only in the categories of bodily pain and mental health.

In the first subgroup analysis between married patients or patients living in a close relationship and patients living alone, there was no statistically significant difference in any of the SF-36 categories (Table 6).

Regarding the professional life of the recipients, patients who returned to their job during the first year after OLT revealed higher average score values in all categories of SF-36 compared to unemployed recipients, but a statistical significance ($P < 0.05$) was reached only in the categories of physical functioning and role physical (Table 7).

The third subgroup analysis was focused on the immunosuppression protocols used and more specifically on the effect of CNIs on HRQOL not only immediately after the OLT but also at the time point of our survey. In this

Table 5. Results of SF-36 (mean score ± SD) for liver graft recipients surviving more than 15 years after OLT.

	n	PF	RP	BP	GH	VT	SF	RE	MH
German reference population		85 ± 22	83 ± 31	79 ± 27	68 ± 20	63 ± 18	88 ± 18	90 ± 25	73 ± 16
Study population	104	67 ± 26	55 ± 43	72 ± 29	56 ± 21	53 ± 20	78 ± 26	72 ± 41	69 ± 19
P-value (Bonferroni correction)		<0.001	<0.001	0.128	<0.001	<0.001	<0.001	<0.001	0.272

PF, physical functioning; RP, role physical; BP, bodily pain; GH, general health; VT, vitality; SF, social functioning; RE, role emotional; MH, mental health.

Table 6. Results of SF-36 (mean score ± SD) for liver graft recipients surviving more than 15 years after OLT based on marital status of the recipients.

	n	PF	RP	BP	GH	VT	SF	RE	MH
Married or cohabiting	81	70 ± 25	60 ± 42	75 ± 29	57 ± 21	56 ± 20	80 ± 24	77 ± 38	71 ± 18
Living alone	19	57 ± 31	31 ± 41	60 ± 26	50 ± 22	45 ± 17	68 ± 31	53 ± 46	63 ± 20
P-value (Bonferroni correction)		0.44	0.064	0.328	1	0.232	0.536	0.152	0.728

PF, physical functioning; RP, role physical; BP, bodily pain; GH, general health; VT, vitality; SF, social functioning; RE, role emotional; MH, mental health.

Table 7. Results of SF-36 (mean score ± SD) for liver graft recipients surviving more than 15 years after OLT based on occupational status during the first year after OLT.

	n	PF	RP	BP	GH	VT	SF	RE	MH
Employed recipients	42	76 ± 23	68 ± 38	72 ± 28	58 ± 21	56 ± 22	79 ± 25	78 ± 36	71 ± 19
Unemployed recipients	60	60 ± 27	44 ± 45	71 ± 31	53 ± 21	51 ± 18	76 ± 27	67 ± 44	68 ± 18
P-value (Bonferroni correction)		0.016	0.048	1	1	1	1	1	1

PF, physical functioning; RP, role physical; BP, bodily pain; GH, general health; VT, vitality; SF, social functioning; RE, role emotional; MH, mental health.

Table 8. Results of SF-36 (mean score ± SD) for liver graft recipients surviving more than 15 years after OLT based on (a) immunosuppressive protocols used immediately after the liver transplantation and (b) immunosuppressive regimens used at the actual time of our study.

	n	PF	RP	BP	GH	VT	SF	RE	MH
(a)									
CNI-based IS after OLT	94	70 ± 25	59 ± 42	74 ± 28	56 ± 21	55 ± 20	79 ± 26	73 ± 40	70 ± 19
CNI-free IS after OLT	10	47 ± 32	22 ± 41	58 ± 40	55 ± 24	51 ± 19	69 ± 30	63 ± 48	66 ± 15
P-value (Bonferroni correction)		0.064	0.072	0.824	1	1	1	1	1
(b)									
CNI-based IS after 15 years	82	69 ± 24	57 ± 42	73 ± 28	55 ± 21	52 ± 19	80 ± 26	74 ± 39	70 ± 19
CNI-free IS after 15 years	18	59 ± 36	41 ± 48	63 ± 34	58 ± 24	62 ± 23	73 ± 30	62 ± 47	68 ± 18
P-value (Bonferroni correction)		1	1	1	1	0.44	1	1	1

PF, physical functioning; RP, role physical; BP, bodily pain; GH, general health; VT, vitality; SF, social functioning; RE, role emotional; MH, mental health; CNI, calcineurin inhibitor; IS, immunosuppressive therapy; OLT, orthotopic liver transplantation.

analysis, there were no statistically significant differences in any of the SF-36 categories between CNI-based and CNI-free immunosuppression protocols (Table 8).

Discussion

The aim of the study was to focus on HRQOL of patients who have survived for more than 15 years after OLT. As the transplant community managed over the years to overcome the initial obstacles which did not allow the transplant recipients to have a good long-term prognosis, the assessment of HRQOL in long-term survivors is important in order to assess overall OLT success.

This single-center study presented a 15-year survival rate of 37% for the entire cohort of the 623 patients transplanted between 1972 and 1991, and more specifically a 15-year survival rate of 33% for the 506 adult recipients transplanted in the same period. The survival rates mentioned above are inferior to figures reported by Busuttil *et al.* [27] from California or by Jain *et al.* [6] from Pittsburgh, who present a 15-year survival rate of 64% and 50%, respectively, but the major difference of our study is that it focuses on the first years of OLT, as 12% of our patients were transplanted between 1972 and 1983, when patient and organ survival were inferior.

In the comparison of our study population to the German reference population, our patients scored lower in all categories of SF-36, showing that although HRQOL improves after OLT [11,12], it remains lower than that of the general reference population. A statistical significance was reached in almost all SF-36 categories with the exceptions of bodily pain and mental health where our study population scored similarly to the German reference population. Long-term survivors after OLT presented, as mentioned above, a mental HRQOL comparable to that of the control population, probably as a result of coping with their disease [28], or of having managed to overcome the factor of bodily pain, which during the initial period after OLT causes great anxiety to the patient [29]. On the other hand, long-term immunosuppressive therapy, nephrotoxicity of CNIs, cardiovascular and metabolic complications of corticosteroids and disease recurrence, especially in primary sclerosing cholangitis and primary biliary cirrhosis [30], hepatitis C [31], hepatocellular carcinoma [32] and alcoholic liver disease [33] might be some of the factors to blame for the lower scores of our study population in the above mentioned SF-36 categories [13].

Employment after OLT was particularly revealing regarding HRQOL. Patients who returned to their job during the first year after the liver transplantation scored higher in all SF-36 categories, but statistical significance was reached only in the categories of physical functioning and role physical. Our findings correlate with the results presented by Saab *et al.* [19] from California, according to whom, lower mean values in physical functioning and role physical correlate with significantly reduced employment rates after OLT. However, there are certain points that need to be made regarding the correlation between occupational status during the first 12 months after OLT and HRQOL. Although the protective effect of job-related rehabilitation on HRQOL is demonstrated in many studies [18], we must take into consideration the fact that patients returning to work during the first year after OLT are the patients who probably presented few and of course minor complications and who were able to be discharged from the hospital in a short period of time after OLT. These factors may be the ones directly affecting HRQOL, giving at the same time the opportunity to the patients to return to their jobs shortly after OLT.

Regarding the effect of marital status on HRQOL the comparison between married or cohabiting recipients and recipients living alone showed no statistical significance in any of the SF-36 categories. The results of our study do not correlate with the ones presented by Sainz-Barriga *et al.* [12] regarding liver transplant recipients or with the results presented by Neipp *et al.* [20] regarding kidney transplant recipients, where a positive effect of marital status on HRQOL was presented. The absence of statisti-

cally significant difference could be attributed to the fact that the presence of a stable familial environment might be more important during the first months after OLT, as in this point of time the need for psychological support from the recipients is of course increased. In this way, marital status of long-term survivors after OLT does not seem to have an effect on HRQOL.

Another issue evaluated in this study was that of immunosuppression and especially the effect of CNIs on HRQOL. CNIs and corticosteroids remain until today the mainstay of immunosuppression after OLT, although their long-term complications significantly contribute to morbidity and mortality of transplant recipients. Nephrotoxicity of CNIs remains the major complication leading about 25% of nonrenal solid organ recipients to chronic renal failure and dialysis [34–36]. Moreover, diabetes mellitus, cardiovascular disease, and osteoporosis are some of the other most commonly encountered adverse effects of immunosuppression [37–39]. Based on the facts mentioned above, CNI-free protocols and the quick reduction to a minimum dose for corticosteroids is currently the mainstay of immunosuppressive therapy leading to a significant improvement in renal function and to a better patient and graft survival [40,41]. Moreover, new immunosuppressive regimens and especially rapamycin and mycophenolate mofetil, as monotherapy or combination therapy, reduce CNI-related side effects and offer a stable therapeutic concept especially in long-term liver transplant recipients [42,43].

Although, as mentioned above, the use of CNIs significantly contributes to morbidity and mortality of liver transplant recipients, this seems to have no effect on long-term HRQOL. In the two comparisons performed between patients on CNI-based and CNI-free immunosuppression, there was no statistical significance reached in any of the SF-36 categories neither immediately after the OLT nor at the time point of our study. The above mentioned results could be attributed to the fact that patients surviving more than 15 years after OLT are the ones presenting a stable graft function and of course fewer long-term complications attributed to immunosuppression. This way, immunosuppressive regimens did not seem to have as much influence on HRQOL.

Our study has some potential limitations. First of all, wanting to assess long-term HRQOL we had to focus only on the 623 patients transplanted between 1972 and 1991 and to exclude the rest of the patients, about 1800, transplanted from the beginning of our transplantation program up to 2006. Considering inclusion and exclusion criteria, we finally selected only 137 patients who qualified for our study. This selection may be a source of bias resulting in an underestimation of HRQOL or of the factors affecting HRQOL. It also has to be mentioned that the statistical power of our analyses, especially regarding the effect of immunosuppression and marital status on HRQOL, is limited as the sample size in the comparisons mentioned above is relatively small. This could be a possible reason why no statistical significance was reached in these comparisons. Moreover, our study included a number of patients, 12% of the study population, transplanted between 1972 and 1983 when patient and organ survival were inferior in all transplantation centers in Europe and the United States. The inclusion of these patients, although important to estimate correctly long-term HRQOL, might be to blame for the lower survival rates presented in our study. At last, it has to be mentioned that patients surviving more than 15 years after OLT are of course the fittest ones presenting a stable graft function and fewer complications. Therefore, it has to be questioned whether HRQOL of this group of patients reflects HRQOL of the whole liver transplant population, as critically ill patients who presented severe complications are more likely to have already died at the time point of our study.

To conclude, our study showed that long-term survivors after OLT present a HRQOL that remains lower in almost all categories of SF-36 in comparison to the German reference population. Employment during the first year after OLT had a positive effect on HRQOL and was correlated with significantly higher mean values in the categories of physical functioning and role physical. Marital status of the recipients and the use of CNIs had no effect on HRQOL of long-term liver transplant recipients.

Authorship

LK: collected the data, performed the study, and wrote the paper. MN: designed the study. HB-H: collected the data. SJ: analyzed the data. CPS, JK, and TB: designed the study.

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