The impact of osteoporosis on health-related quality of life in patients after liver transplantation – a pilot study

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Abstract

Introduction: Liver transplantation (LT) is now a well-established procedure with 5-year survival rates over 70%, and one of its ultimate goals is the improvement of patient health-related quality of life (HRQOL). Osteoporosis remains a serious potential complication of LT, leading to fragility fractures, pain, and functional impairment.

Aim: To assess the degree of osteoporosis and the impact of fragility fractures on HRQOL in patients with chronic liver diseases treated with LT.

Material and methods: Twenty-seven patients (14 female, 13 male) at a median period of 3.5 years post LT participated in the study. HRQOL was assessed by Short Form-36 and PBC-40 instruments. Bone mineral density (BMD) in the lumbar spine and hip neck were measured by dual-energy X-ray absorptiometry. Physical activity was assessed by questionnaire. Data on the duration of the liver disease, time from LT, and fragility fractures were also collected.

Results: As many as 74.1% of the patients had reduced BMD (t-score < –1.0 SD) in the hip. Mean values of the spine and hip BMD z-scores were –1.1 and –0.9 SD, respectively. Time after LT, percentage of lean tissue, and physical activity were positively associated with BMD. The prevalence of fractures was 48%. We did not find significant differences in age, gender, body composition parameters, physical activity, BMD, and HRQOL scores between the subjects with and without fractures.

Conclusions: We found a high prevalence of fragility fractures and a decreased BMD in LT recipients. Patients with a history of fractures had similar HRQOL scores to those without fractures.

Introduction

Liver transplantation (LT) is the treatment of choice for patients with decompensated cirrhosis, acute liver failure, and advanced hepatocellular carcinoma. The success of LT has resulted in a growing cohort of LT recipients. However, the long-term survivors are at risk of morbidity, mainly due to cardiovascular disease, metabolic syndromes, renal failure, recurrence of the underlying disease, and malignancy. Moreover, osteoporosis, characterised by reduced bone mass and disruption of bone architecture leading to decreased bone strength and the increased risk of fragility fractures [1], is a common feature in both the pre- and post-transplant period.

Osteoporosis has long been recognised mainly as a complication of cirrhosis, especially in patients with chronic cholestatic liver disease [2]. In addition, in the early months after LT, patients suffer from rapid bone loss that leads to a high incidence of fragility fractures of the vertebral bodies, distal forearm, ribs, and hip [3]. This may cause significant functional impairment leading to prolonged immobilisation, muscular atrophy, and restrictions in activities of daily living and, as a result, in impairment of health-related quality of life (HRQOL).

HRQOL, as a quantitative estimation of a patient's self-assessment of physical, functional, social, and psychological dimensions of life [4], has become integrated into the measurement of LT outcomes. In LT recipients it may be measured with either generic or disease-specific tools. The Short Form-36 (SF-36) questionnaire was designed to measure HRQOL in various populations with a wide variety of medical conditions, making it possible to compare several health states [5]. PBC-40 is nowadays the most popular disease-specific questionnaire used for the assessment of HRQOL in patients with chronic cholestatic disorders such as primary biliary cirrhosis (PBC) and primary sclerosing cholangitis (PSC) [6, 7]. Both measures were also validated in patients after LT [8, 9]. Several studies identified fatigue, physical function, psychosocial stress, medical complications, cognitive function, employment status, and sexual dysfunction [4] as well as socioeconomic and demographic factors [6] that may affect both short- and long-term HRQOL outcomes in LT recipients. However, much less is known about the impact of osteoporosis on HRQOL in these patients. Moreover, there have been no previous reports on the prevalence of osteoporosis and fragility fractures in Polish LT recipients.

Aim

Therefore, in this study, we assessed the frequency of reduced bone mineral density and osteoporotic fractures in Polish liver graft recipients. We also sought associations between prior fractures, duration of liver disease, time since LT, actual physical activity, and the HRQOL outcomes in these patients.

Material and methods

Study population

The study involved 27 patients (14 female, 13 male) aged from 23 to 66 years, who underwent LT due to autoimmune hepatitis (AIH), PBC, and PSC. The median time since LT was 3.5 years (range: 0.5 to 20.0 years). We included only those patients who had no other medical conditions than the primary study condition that required the pharmacological treatment, and who showed no apparent abnormalities on physical examination. We excluded patients with a history of malignancy, poorly-controlled diabetes, and rapid weight change in the previous 12 months. In all subjects we measured weight and height.

Informed consent was obtained from each patient included in the study. The study protocol was approved by the Ethics Committee of the Pomeranian Medical University in Szczecin and conformed to the ethical guidelines of the 1975 Declaration of Helsinki.

Assessment of HRQOL

The SF-36 and PBC-40 questionnaires were undertaken by each of the study participants. SF-36 measures quality of life across eight domains, which are both physically and emotionally based. These domains refer to physical functioning, role limitations due to physical health, role limitations due to emotional problems, energy and fatigue, emotional well-being, social functioning, bodily pain, and general health. Two summary scores: the Physical Component Summary (PCS) and Mental Component Summary (MCS), were also calculated. Scale scores ranged between 0 (the most impaired HRQOL) and 100 (ideal well-being) [5].

The PBC-40 questionnaire is a specific tool to assess HRQOL in PBC [7]. The six domains of the questionnaire relate to fatigue, emotional, social, and cognitive functions, general symptoms, and itching. Answers are marked on a five-point Likert-like scale (from 1 = never to 5 = always), with higher scores denoting the greater impact of symptoms and poorer HRQOL. The possible ranges of each domain were: symptom domain 7–35, itch 3–15, fatigue 11–55, cognitive 6–30, and social and emotional 13–65 points [10].

Assessment of physical activity

The International Physical Activity Questionnaire (IPAQ) is a comparable and standardised self-report measure of habitual physical activity of populations from different countries and socio-cultural contexts, with a 7-day recall of physical activity within a month. The IPAQ consists of 27 questions related to four life domains: physical activity associated with the patient's occupation, work at home, and around the house, moving around various places, and mobility during free time devoted to recreation, playing games, sports, tourism, or other muscular work, and additional time spent in the sitting position. Only physical activity lasting longer than 10 min without any rest break is recorded. IPAQ (both long and brief versions) have been validated in many countries world wide, including Poland [11]. Based on IPAQ, total physical activity can be categorised as low (below 600 MET min/week), moderate (600–3000 MET min/week), or vigorous (above 3000 MET min/week).

Bone mineral density measurements

Bone mineral density (BMD) was measured in the lumbar spine (L1–L4) and total hip by dual-energy X-ray absorptiometry (GE Lunar Prodigy; Madison, WI; software enCORE version 14.1) using automatic scan modes. Osteopenia and osteoporosis were defined according to World Health Organization diagnostic criteria [1].

Bone mineral density values were expressed in g/cm^2 along with z-scores (standard deviation from the mean BMD for normal, age-matched, gender-specific subjects) and t-scores (standard deviation from the mean BMD for normal young individuals). Additionally, we measured body fat (BF) and lean mass from the total body scan. The coefficients of variation (CV%) of lumbar spine, total hip, and total body measurements were below 1.5%.

Assessment of fragility fractures

Based on anamneses and available medical reports, we collected the following data on past fragility fractures: location of the fracture and its severity, time from LT, X-ray imaging (if available), and type of trauma. Fragility fractures were defined as a traumatic fractures of the distal forearm, neck of the femur, rib, lower leg, shoulder, and vertebral body, or resulting from a minimal trauma, such as a fall from standing height or lower [1].

Statistical analysis

Descriptive analyses are presented as means and standard deviation (SD) or numbers (proportion). Differences between groups were evaluated by Welch's t-test for continuous variables and by χ^2 test for categorical variables. Spearman's rank correlation coefficient and regression or non-parametric regression analyses were used to determine the relationships between BMD, body composition, anthropometric measurements, and the HRQOL scores. Statistical tests were two-sided at a level of significance of 0.05. Statistical analysis was conducted using Statistica 10.0 (StatSoft; Poland).

Results

The baseline characteristics of study participants are given in Table I. Using the WHO definition based on femur BMD t-score values [1], one patient had osteoporosis (a 34-year-old male with PSC) and 19 patients (7 men, 12 women) had osteopaenia. Overall, 74.1% of patients had a hip BMD t-score below –1.0 SD. Mean values of the spine and hip BMD z-scores were lower (–1.11 SD and –0.91 SD, respectively).

The fracture rate was 70% in patients with PBC, 50% for AIH, and 27% for PSC. Overall, fractures occurred in nearly 50% of cases (8 women and 5 men). Twelve fractures, including 7 forearm, 3 hip, and 2 lower leg fractures, occurred after diagnosis of chronic liver disease but before LT. Only one fracture (of the shoulder) was diagnosed after LT. All cases had a single fracture, and none of them reported vertebral fracture. The majority of subjects declared moderate to vigorous physical activity, and as many as 48% performed physical activity above 3000 MET min per week.

We did not find significant differences in age, gender distribution, body composition parameters, physical activity, and BMD values between the subjects with and without fractures. Similarly, the HRQOL outcomes measured by SF-36 and PBC-40 were comparable in both groups. Although the mean scores in the SF-36 role-physical domain were lower in subjects with a fracture compared to those without fractures, the observed difference did not reach statistical significance.

In the regression analysis, several SF-36 domain scores, adjusted for age, physical activity, and prior fractures, were strongly associated with female gender: physical functioning ($p = 0.0016$), role–physical ($p = 0.0014$), role–emotional ($p = 0.0068$), mental health ($p = 0.0045$), and physical component ($p = 0.0262$). In PBC-40, similar gender-specific associations related to itching ($p = 0.0085$), fatigue ($p = 0.0353$), cognitive ($p = 0.02$), and symptoms ($p = 0.0417$) were found. However, prior fractures adjusted for gender were not associated with PCS ($p = 0.129$) or MCS ($p = 0.318$).

Lumbar BMD positively correlated with the length of time since LT and IPAQ score. Hip BMD was correlated with lean tissue mass but not with BF (Table II).

Discussion

In this study we evaluated a middle-aged population of LT recipients and found a high incidence of fragility fractures that had occurred since the beginning of the underlying disease (with a high predominance of patients with PBC) and a reduced BMD measured in the spine and hip. This is in line with earlier studies, which demonstrated a high rate of fractures after LT, ranging from 24% to 65%, mainly within the first years after surgery [12, 13]. It has been shown that bone mass decreases rapidly during the early months after LT [3, 14], especially in patients with persistent cholestasis [14]. In some studies [4], including our series, and in contrast to other reports [15, 16], this rapid bone loss was independent of gender and BMI. However, in the general population, BMD is not the only factor contributing to bone strength and fracture risk. Additionally, in patients with chronic liver disease, other disease-specific factors may affect bone strength and susceptibility to fractures. Thus, advanced age, the type and severity of liver disease, a history of previous fractures, low vitamin D level, lack of physical activity, inadequate nutrition status, and deterioration of vitamin K metabolism, in addition to low bone mass, have been considered the most important pre-transplant risk factors for bone fractures after LT [15, 17, 18]. In the post-transplant period, immunosuppressive drugs, especially glucocorticoids, and immobilisation have been identified as important contributors of a traumatic fracturing [14, 17, 19, 20].

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Table I. Baseline characteristics of study participants

Parameter	All (*n* = 27)	Fractures (*n* = 13)	No fractures (*n* = 14)	Value of *p*
Gender (F/M)	14/27	8/5	6/8	0.558
Age [years]	49.90 ±12.70	52.98 ±11.11	47.42 ±13.42	0.250
Duration since transplantation [years]	4.70 ±4.70	6.29 ±5.49	3.21 ±3.39	0.097
Body mass index (BMI) [kg/m^2]	24.72 ±4.17	25.05 ±4.45	24.99 ±4.73	0.975
Lean mass [kg]	48.06 ±11.57	47.972 ±12.46	48.143 ±11.15	0.970
Body fat [kg]	20.89 ±8.55	24.121 ±8.60	17.88 ±7.59	0.057
Body fat [%]	30.25 ±10.08	33.31 ±8.65	27.4 ±10.76	0.127
Indication for transplantation, *n* (%):				
Autoimmune hepatitis	6 (22)	3 (50)	3 (50)	1
Primary biliary cirrhosis	10 (37)	7 (70)	3 (30)	0.179
Primary sclerosing hepatitis	11 (41)	3 (27)	8 (73)	0.159
Bone mineral density:				
Lumbar spine [g/cm^2]	0.993 ±0.14	0.997 ±0.14	0.991 ±0.14	0.913
Lumbar spine (*z*-score)	−1.11 ±1.15	−1.161 ±1.07	−1.064 ±1.26	0.829
Lumbar spine (*t*-score)	−1.66 ±1.12	−1.654 ±1.09	−1.665 ±1.19	0.98
Femoral neck [g/cm^2]	0.875 ±0.13	0.914 ±0.36	0.870 ±0.13	0.678
Femoral neck (*z*-score)	−0.904 ±0.71	−1.075 ±0.53	−0.75 ±0.83	0.240
Femoral neck (*t*-score)	−1.392 ±0.83	−1.29 ±0.93	−1.50 ±0.71	0.527
Osteoporosis (*t*-score ≤ 2.5 SD), *n* (%)	1 (4)	0	1 (7)	1
Osteopaenia (*t*-score −1.0 to −2.5), *n* (%)	19 (70)	−1.72 ±0.54	−1.61 ±0.52	0.663
Health-related quality of life				
SF-36:				
Physical functioning	65.87 ±23.39	68.00 ±19.89	64.23 ±34.27	0.744
Role – physical	55.24 ±38.72	47.29 ±36.09	62.05 ±40.91	0.338
Bodily pain	64.81 ±25.06	59.25 ±24.0	69.57 ±25.84	0.302
General health	56.15 ±22.56	61.67 ±23.48	51.43 ±21.45	0.260
Vitality	53.12 ±19.00	53.54 ±20.44	52.77 ±18.46	0.920
Social functioning	69.71 ±23.16	68.54 ±22.17	70.71 ±24.76	0.815
Role – emotional	58.01 ±41.08	53.81 ±38.9	61.61 ±43.98	0.636
Mental health	66.30 ±20.34	67.66 ±21.62	65.12 ±19.92	0.759
Physical component	54.91 ±20.67	53.89 ±19.39	55.79 ±22.40	0.817
Mental component	53.24 ±21.78	52.43 ±21.36	53.94 ±22.97	0.864
PBC-40:				
Symptoms	13.83 ±6.05	15.36 ±5.85	12.42 ±6.13	0.251
Itching	2.52 ±2.54	2.27 ±3.17	2.75 ±1.91	0.670
Fatigue	25.61 ±10.84	27.36 ±12.04	24.0 ±9.87	0.474
Cognitive	12.22 ±5.45	13.82 ±5.12	10.75 ±5.55	0.182
Social and emotional	25.39 ±9.00	25.91 ±9.62	24.92 ±8.81	0.799
Physical activity:				
Total [MET min/week]	3773.1 ±2102	3411.2 ±1788	3953.3 ±2302	0.533
Above 3000 MET min/week, *n* (%)	13 (48)	6 (54)	7 (58)	0.422

Value of p refers to comparison between subjects with and without fractures.

Table II. Correlations between bone mineral density, age, BMI, duration of time since transplantation, physical activity, and body composition

Parameter	Spine BMD [g/cm²]	Value of *p*	Hip BMD [g/cm²]	Value of *p*
Age [years]	−0.251	0.203	−0.120	0.572
Body mass index [kg/m²]	−0.013	0.947	0.232	0.251
Duration of liver disease [years]	−0.231	0.089	−0.204	0.091
Time from liver transplantation [years]	0.403	0.034	0.161	0.436
Lean mass [kg]	0.304	0.125	0.410	0.041
Body fat [kg]	0.093	0.649	0.081	0.682
Physical activity [MET min/week]	0.422	0.048	0.393	0.481

Numbers in each cell refer to Spearman's rank correlation coefficient.

We found that BMD in the lumbar spine, but not in the hip, was positively correlated with time from LT, suggesting a possible gain in bone mass after successful treatment of the underlying liver disease with LT. Indeed, some previous studies have demonstrated a slight increase in spine BMD during the first 2 years following LT [14], or even recovery of spine BMD to pre-transplant levels after 36 months and 85 months post LT [12, 15].

We also found a positive correlation between hip BMD and lean tissue mass. Similarly, Wang *et al.* [16] reported that although in the general population both lean tissue and fat mass were positively correlated with BMD at all skeletal sites, lean tissue had a greater effect on bone density in younger subjects. Lean tissue, composed predominantly of muscles, stimulates the skeleton by providing mechanical stress, while muscle wasting is a frequent feature of chronic liver disease [14]. Muscle mass is maintained by sex hormones and physical activity, both of which are commonly decreased before transplantation. However, the majority of subjects in our study declared moderate to high physical activity after LT. This finding, together with the positive correlation between physical activity and spine BMD found in our subjects, and similar associations found in the general population [18], strongly suggest that regular exercise is essential to maintain or even gain spine BMD in the post-transplant period.

Nowadays, the goal of LT is not only survival but also the state of health and quality of life that patients enjoyed prior to the liver disease, as well as to achieve a balance between the functional efficacy of the graft and mental and physical well-being. The majority of studies reported overall satisfactory short-term [21–23] and long-term [24, 25] effects of LT on HRQOL. On the other hand, others reported impairments in different domains of HRQOL [4, 26, 27] suggesting that an age above 60 years at transplantation, employment and marital status, education level and post-LT complications, significantly influence the HRQOL scores [4, 8, 28–33]. We addressed this issue to osteoporosis-related fractures, which potentially also might have an impact on some aspects of quality of life. However, we could not demonstrate the differences between patients who did and did not experience fractures in any of the HRQOL domains measured by SF-36 and PBC-40. In contrast to our results, and to our best knowledge, only one study in this research area by Desai *et al.* [34] has found severe osteoporosis to be correlated with a reduced physical functioning if age and gender were excluded from the analysis. However, in their study severe osteoporosis was defined as severe bone pain (with or without associated bone fractures) and prior treatment for osteoporosis, which does not meet the WHO criteria [1].

Another remarkable result of our study refers to associations between several SF-36 domain scores and female gender. Gender-associated differences in HRQOL after LT have been shown in earlier studies [31–35] and were explained mostly by psychological factors, bodily structure of females, metabolic changes after menopause, and the prevalence of cholestatic and autoimmune liver disease [31–33]. Moreover, after transplantation, female patients are expected by their families to care not only about themselves, but also other family members as well as domestic duties [31, 36, 37], which may influence their self-evaluation of physical functioning, mental health, and role physical and emotional components.

Our study has several possible limitations. First, this was a pilot study performed on a relatively modest population with a wide age range and duration since LT and BMI, which along with the menopause status might influence the outcomes measured in this study. Second, our cases had not sustained any vertebral fractures, so we had not evaluated any vertebral fractures

by lateral X-ray of the thoracic and lumbar spine. Vertebral fractures are the most common in osteoporosis and may significantly worsen quality of life due to chronic back pain. Therefore, we may speculate that some of these fractures, as clinically asymptomatic or poorly symptomatic, were not detected in the earlier evaluation. Finally, because no disease-specific tool shave been developed to evaluate HRQOL after LT, we used a combination of generic and PBC-specific instruments, which may not be fully specific to the LT recipients. Albeit, Saab *et al.* [38] have recently developed and tested a new post-transplant quality of life instrument (pLTQ) on graft recipients in the U.S., this tool has not yet been validated.

Conclusions

In this pilot study we found a high prevalence of fragility fractures and a decreased BMD in LT recipients. However, prior non-vertebral fractures did not influence HRQOL in these patients.

Conflict of interest

The authors declare no conflict of interest.

References

1. Consensus development conference: diagnosis, prophylaxis, and treatment of osteoporosis. Am J Med 1993; 94: 646-50.
2. Trautwein C, Possienke M, Schlitt HJ, et al. Bone density and metabolism in patients with viral hepatitis and cholestatic liver diseases before and after liver transplantation. Am J Gastroenterol 2000; 95: 2343-51.
3. Leidig-Bruckner G, Hosch S, Dodidou P, et al. Frequency and predictors of osteoporotic fractures after cardiac or liver transplantation: a follow-up study. Lancet 2001; 357: 342-7.
4. Guichelaar MM, Kendall R, Malinchoc M, Hay JE. Bone mineral density before and after OLT: long-term follow-up and predictive factors. Liver Transpl 2006; 12: 1390-402.
5. The World Health Organization Quality of Life Assessment (WHOQOL): development and general psychometric properties. Soc Sci Med 1998; 46: 1569-85.
6. Jacoby A, Rannard A, Buck D, et al. Development, validation, and evaluation of the PBC-40, a disease specific health related quality of life measure for primary biliary cirrhosis. Gut 2005; 54: 1622-9.
7. Al-Harthy N, Kumagi T, Parasar S, et al. High prevalence of fatigue in patients with sclerosing cholangitis. J Hepatol 2009; 50 (Suppl. 1): S241.
8. Bownik H, Saab S. Health-related quality of life after liver transplantation for adult recipients. Liver Transpl 2009; 15 Suppl 2: S42-9.
9. Ware JE Jr, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care 1992; 30: 473-83.
10. Baranyi A, Krauseneck T, Rothenhausler HB. Overall mental distress and health-related quality of life after solid-organ transplantation: results from a retrospective follow-up study. Health Qual Life Outcomes 2013; 11: 15.
11. Carbone M, Bufton S, Monaco A, et al. The effect of liver transplantation on fatigue in patients with primary biliary cirrhosis: a prospective study. J Hepatol 2013; 59: 490-4.
12. Lips P, van Schoor NM. Quality of life in patients with osteoporosis. Osteoporos Int 2005; 16: 447-55.
13. Saab S, Bownik H, Ayoub N, et al. Differences in health-related quality of life scores after orthotopic liver transplantation with respect to selected socioeconomic factors. Liver Transpl 2011; 17: 580-90.
14. Al-Harthy N, Kumagi T, Coltescu C, Hirschfield GM. The specificity of fatigue in primary biliary cirrhosis: evaluation of a large clinic practice. Hepatology 2010; 52: 562-70.
15. Baccaro LF, Boin IF, Pedro AO, et al. Decrease in bone mass in women after liver transplantation: associated factors. Transplant Proc 2011; 43: 1351-6.
16. Ninkovic M, Love SA, Tom B, et al. High prevalence of osteoporosis in patients with chronic liver disease prior to liver transplantation. Calcif Tissue Int 2001; 69: 321-6.
17. Monegal A, Navasa M, Guanabens N, et al. Bone disease after liver transplantation: a long-term prospective study of bone mass changes, hormonal status and histomorphometric characteristics. Osteoporos Int 2001; 12: 484-92.
18. Compston JE. Osteoporosis after liver transplantation. Liver Transpl 2003; 9: 321-30.
19. Craig CL, Marshall AL, Sjostrom M, et al. International physical activity questionnaire: 12-country reliability and validity. Med Sci Sports Exerc 2003; 35: 1381-95.
20. Ninkovic M, Skingle SJ, Bearcroft PW, et al. Incidence of vertebral fractures in the first three months after orthotopic liver transplantation. Eur J Gastroenterol Hepatol 2000; 12: 931-5.
21. Premaor MO, Das TK, Debiram I, et al. Fracture incidence after liver transplantation: results of a 10-year audit. QJM 2011; 104: 599-606.
22. Feller RB, McDonald JA, Sherbon KJ, McCaughan GW. Evidence of continuing bone recovery at a mean of 7 years after liver transplantation. Liver Transpl Surg 1999; 5: 407-13.
23. Wang MC, Bachrach LK, Van LM, et al. The relative contributions of lean tissue mass and fat mass to bone density in young women. Bone 2005; 37: 474-81.
24. Pigozzi F, Rizzo M, Giombini A, et al. Bone mineral density and sport: effect of physical activity. J Sports Med Phys Fitness 2009; 49: 177-83.
25. Krasnoff JB, Vintro AQ, Ascher NL, et al. Objective measures of health-related quality of life over 24 months post-liver transplantation. Clin Transplant 2005; 19: 1-9.
26. Santos JR, Miyazaki MC, Domingos NA, et al. Patients undergoing liver transplantation: psychosocial characteristics, depressive symptoms, and quality of life. Transplant Proc 2008; 40: 802-4.
27. Telles-Correia D, Barbosa A, Mega I, et al. When does quality of life improve after liver transplantation? A longitudinal prospective study. Transplant Proc 2009; 41: 904-5.
28. Chen PX, Yan LN, Wang WT. Health-related quality of life of 256 recipients after liver transplantation. World J Gastroenterol 2012; 18: 5114-21.

29. Duffy JP, Kao K, Ko CY, et al. Long-term patient outcome and quality of life after liver transplantation: analysis of 20-year survivors. Ann Surg 2010; 252: 652-61.

30. Kugler C, Gottlieb J, Warnecke G, et al. Health-related quality of life after solid organ transplantation: a prospective, multiorgan cohort study. Transplantation 2013; 96: 316-23.

31. Tome S, Wells JT, Said A, Lucey MR. Quality of life after liver transplantation. A systematic review. J Hepatol 2008; 48: 567-77.

32. Saab S, Wiese C, Ibrahim AB, et al. Employment and quality of life in liver transplant recipients. Liver Transpl 2007; 13: 1330-8.

33. Walter M, Bronner E, Pascher A, et al. Psychosocial outcome of living donors after living donor liver transplantation: a pilot study. Clin Transplant 2002; 16: 339-44.

34. Desai R, Jamieson NV, Gimson AE, et al. Quality of life up to 30 years following liver transplantation. Liver Transpl 2008; 14: 1473-9.

35. Blanch J, Sureda B, Flavia M, et al. Psychosocial adjustment to orthotopic liver transplantation in 266 recipients. Liver Transpl 2004; 10: 228-34.

36. Cowling T, Jennings LW, Goldstein RM, et al. Liver transplantation and health-related quality of life: scoring differences between men and women. Liver Transpl 2004; 10: 88-96.

37. Burra P, De ME, Gitto S, Villa E. Influence of age and gender before and after liver transplantation. Liver Transpl 2013; 19: 122-34.

38. Saab S, Ng V, Landaverde C, et al. Development of a disease-specific questionnaire to measure health-related quality of life in liver transplant recipients. Liver Transpl 2011; 17: 567-79.