Effect of living donor liver transplantation on depressive symptoms in hepatitis C virus patients

Reem E.L.S. Hashem[a], Walaa Sabry[a], Tamer W. ELSaid[b], Iman F. Montasser[c], Eman El Gendy[c] and Peter William[c]

Departments of [a]Psychiatry, [b]Internal Medicine and [c]Tropical Medicine, Ain Shams University, Cairo, Egypt

Correspondence to Reem E.L.S. Hashem, MD, MRCPsych, Department of Psychiatry, Institute of Psychiatry, Ain Shams University, Abbassia street, 11657 Cairo, Egypt
Tel: + 20 122 590 3031; fax: + 20 222 608 283;
e-mail: r.hashem@med.asu.edu.eg

Background
The number of liver transplantations has shown a steady increase over time, with increasing emphasis on psychosocial assessment. The goal of liver transplantation is not only to promote patient survival but also to enhance their quality of life and mental well-being. Pretransplant psychiatric evaluation is used to identify psychiatric illnesses and psychological problems in transplant candidates in order to improve patient outcome. This study aimed at exploring the impact of living donor liver transplantation on depressive symptoms reported by hepatitis C virus (HCV) recipients during their preoperative psychological assessment.

Materials and methods
Thirty-five recipients with HCV-related liver cirrhosis who had undergone living donor liver transplantation were prospectively assessed using a self-rating scale – the Beck Depression Inventory – for the evaluation of depressive symptoms. The evaluation was carried out three times: before transplantation, 1 month after transplantation, and 6 months after transplantation.

Results
The preoperative depression scores were found to be significantly higher with a mean of 21.80 ± 3.36 as compared with the postoperative scores at 1 (11.74 ± 2.24) and 6 months (7.6 ± 2.43) ($P < 0.0005$). In addition, no statistically significant differences were found on comparing the baseline Beck Depression Inventory scores of patients with hepatocellular carcinoma along with HCV versus those with only HCV disease, nor for Child class B versus class C patients.

Conclusion
Self-reported depression scores for recipients with HCV-related liver diseases showed a greater improvement after living donor liver transplantation surgery. Hence, transplantation has a favorable outcome on the psychological burden experienced by transplant recipients, thereby contributing toward their well-being.

Keywords:
depressive, hepatitis C virus, liver transplantation, living donor

Introduction

Chronic liver disease is associated with many health issues, psychiatric morbidity, and impaired quality of life [1]. Liver transplantation (LT) is considered the standard treatment for patients with irreversible advanced liver disease, thus providing patients with better survival outcome. However, only a limited number of deceased organ donors are available for transplantation [2]. This has led to the emergence of living donor liver transplantation (LDLT). LDLT has gained acceptance as an effective treatment for patients with terminal liver diseases [3]. In Egypt, LDLT has been performed more frequently during the past few years, driven by the absence of a legislation that permits the use of deceased donor organs in the country [4].

Hepatitis C is the leading cause of chronic liver disease in Egypt. About 14.7% of Egypt's population is affected by hepatitis C [5,6]. Hepatitis C-related end-stage liver disease (ESLD) is the main indication for LT in Egypt and accounts for 89.8% of cases [5].

Patients with ESLD caused by hepatitis C virus (HCV) are more likely to develop psychiatric disorders, with depression being the most frequent and clinically important symptom [7]. Other studies have reported that during the preliver transplantation there is a marked decline in physical functioning together with adjustment-related anxiety and depression in the patients [8,9].

Although it is known that mental health disorders are common among ESLD patients, there is limited research on their prevalence during the pretransplantation period, and on how transplantation affects the mental health of those receiving LT.

Measuring the change in mental health after transplant helps to determine the impact of LT.

Aim of the study

The purpose of this prospective study was to (a) identify the prevalence of depressive symptoms in LDLT candidates during their evaluation for hepatic transplantation by using the Beck Depression Inventory (BDI); (b) compare between depressive symptoms before transplant and after transplant at 1 and 6 months; (c) assess the effect of hepatocellular carcinoma (HCC) and severity of liver disease on BDI scores in our recipients before transplantation.

Hypothesis

We hypothesized that the patients undergoing LDLT with pretransplant depressive symptoms would have favorable post-transplant mental health outcomes.

Materials and methods

Study design and population

This was a prospective study conducted on patients with ESLD referred to Ain Shams Center for Organ Transplantation, Cairo, Egypt, from January 2013 to January 2014 for LT evaluation. The study was approved by the Ethics Committee of Ain Shams University Hospitals in accordance with local research governance requirements. Informed written consent was obtained from each participant before enrollment in the study. Inclusion criteria were as follows: (a) presence of HCV-related liver cirrhosis diagnosed by detection of HCV antibody by means of ELISA assay and PCR; and (b) age 18–60 years. Exclusion criteria were as follows: (a) having other etiologies of liver disease; (b) having encephalopathy with inability to complete the study scale; (c) being on antidepressant therapy; (d) having other comorbid psychiatric illnesses; (e) being on interferon therapy; (f) not giving consent to participate in study.

Methods

Basic demographic and clinical assessment data were obtained from hospital records and included age, sex, marital status, education, employment, disease severity as indicated by Child–Pugh and model for end-stage liver disease (MELD) scores, presence of HCC in addition to HCV-related cirrhosis, and associated comorbidities such as diabetes mellitus and hypertension.

Disease severity assessment

The Child–Pugh score is a scoring system to measure the severity of chronic liver disease. The intention is to provide a system with which clinicians can objectively communicate about liver function, and is based on several categories:

(1) Total bilirubin, μmol/l (mg/dl)
   (a) <34: 1 point
   (b) 34–50: 2 points
   (c) >50: 3 points
(2) Serum albumin, g/l
   (a) >35: 1 point
   (b) 28–35: 2 points
   (c) <28: 3 points

(3) International normalized ratio
   (a) <1.7: 1 point
   (b) 1.7–2.3: 2 points
   (c) >2.3: 3 points
(4) Presence of ascites
   (a) None: 1 point
   (b) Mild: 2 points
   (c) Moderate to severe: 3 points
(5) Presence of hepatic encephalopathy
   (a) None: 1 point
   (b) Grades I–II (or suppressed with medication): 2 points
   (c) Grades III–IV (or refractory): 3 points
(6) According to the sum of these points, patients can be categorized into Child–Pugh grades A (5–6 points), B (7–9 points), or C (10–15 points) [10]

The MELD score uses a patient's laboratory values for serum bilirubin, serum creatinine, and international normalized ratio for prothrombin time in a log-transformed equation to estimate the likelihood of 3-month survival. Higher MELD scores have been associated with decreased survival rates [11].

Psychological assessment

All recipients were subject to three psychiatric evaluations – (a) before transplantation; (b) 1 month after transplantation; and (c) 6 months after transplantation – using: the BDI, which was performed to assess the severity of depression. It consists of 21 items, each of which has four responses of increasing severity. Numerical values from 0 to 3 were assigned to each statement to indicate the degree of severity. Scores from 0 to 9 were considered normal, scores from 10 to 16 were considered mild, scores from 17 to 29 were considered moderate, and scores of 30 and above were considered severe depressive symptoms [12]. The Arabic version was used for the study.

Statistical analysis

Statistical analysis was performed using SPSS, version 20.0 for windows (IBM, Armonk, New York, USA). Categorical variables were presented as counts and percentages. Continuous variables were presented as mean ± SD unless otherwise stated. One-way repeated-measures analysis of variance and an independent-sample t-test were used as indicated. A two-sided P value less than 0.05 was considered statistically significant.

Results

Thirty-five (32 men and three women) LDLT candidates who fulfilled the inclusion criteria were included in the study and were assessed at our unit. Mean age was 46.88 ± 15.6 years. Baseline sociodemographic and clinical characteristics are listed in Table 1.

Depression

The mean BDI score was 21.80 ± 3.36, and all recipients (100%) had moderate depressive symptoms in the

Table 1 Basic demographics of the study population

	N = 35 [n (%)]
Age (years) (mean ± SD)	46.88 ± 15.6
Sex	
Male	32 (91.43)
Female	3 (8.57)
Marital status	
Single	0 (0)
Married	35 (100)
Education	
Primary	4 (11.43)
Secondary	14 (40)
University	17 (48.57)
Employed status	
Employed	24 (68.57)
Unemployed	11 (31.43)
Hepatopathalogy	
HCV	26 (65.71)
HCC on top HCV	9 (25.71)
Disease severity	
MELD (mean ± SD)	
< 18	24 (68.5)
> 18	11 (31.42)
Child–Pugh	
B	21 (60)
C	14 (40)
Previous encephalopathy	12 (34.29)
Ascites	13 (37.14)
DM	9 (25.71)
HTN	4 (11.43)

DM, diabetes mellitus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HTN, hypertension; MELD, model for end-stage liver disease.
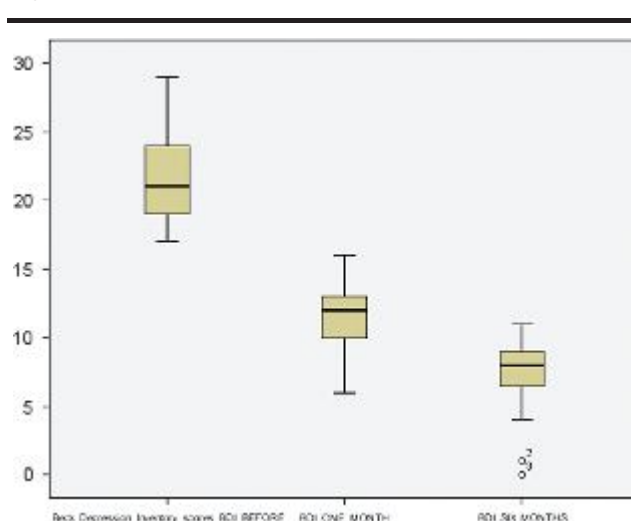
Table 2 BDI scores across visits before and after transplant

BDI	n (%)		
	Before transplant	One month after transplant	Six months after transplant
Normal	0 (0)	4 (11.4)	29 (84.9)
Mild depression	0 (0)	31 (88.6)	6 (17.1)
Moderate depression	35 (100)	0 (0)	0 (0)
Severe depression	0 (0)	0 (0)	0 (0)

BDI, Beck Depression Inventory.

Figure 1

Boxplot showing BDI scores decreasing from 21.80 ± 3.36 before liver transplant surgery to 11.74 ± 2.24 at 1 month and to 7.34 ± 2.43 at 6 months after surgery. BDI, Beck Depression Inventory.

pretransplant visit. Follow-up visits showed notable decline in the prevalence of depressive symptoms (Table 2).

A one-way repeated-measures analysis of variance was conducted to determine whether there were statistically significant differences in BDI scores for symptoms of depression among patients with HCV-related liver cirrhosis undergoing LT over the course of 6 months. There were no outliers, and the data for baseline BDI and BDI at 1 month after surgery were normally distributed, as assessed by boxplots and the Shapiro–Wilk test ($P > 0.05$), respectively. However, there were two outliers observed in the data for 6 months after surgery, as assessed by boxplots along with a statistically significant Shapiro–Wilk test ($P = 0.003$); however, the violation for assumption of normality did not have a major effect on the results of the analysis. The assumption of sphericity was violated, as assessed by Mauchly's test of sphericity $[\chi^2(2) = 6.632, P = 0.036]$. Therefore, a Greenhouse–Geisser correction was applied ($\epsilon = 0.846$). LT elicited statistically significant changes in BDI scores over time $[F(1.69, 67.53) = 327.596, P < 0.0005, \text{partial } \eta^2 = 0.906]$, with BDI score decreasing from 21.80 ± 3.36 before liver transplant surgery to 11.74 ± 2.24 at 1 month and to 7.34 ± 2.43 at 6 months after surgery. Post-hoc analysis with a Bonferroni adjustment revealed that BDI scores underwent a statistically significant decrease from before surgery to 1 month after surgery [10.06, 95% confidence interval (CI): 8.50–11.61), $P < 0.0005$), and from before surgery to 6 months after surgery [14.46 (95% CI: 12.80–16.11)], $P < 0.0005$), and from 1 month to 6 months after surgery [4.40 (95% CI: 3.29–5.51), $P < 0.0005$], as seen in Fig. 1.

Further subgroup analysis was performed to test for the possible effect of malignancy as an associated comorbidity on baseline BDI scores in the study subjects. There were nine patients who had an associated HCC as compared with 26 patients with no associated malignancy. An independent-samples *t*-test was run to determine whether there were differences in baseline BDI scores between the two groups of patients. There were no outliers in the data, as assessed by inspection of a boxplot. BDI scores for each group were normally distributed, as assessed by Shapiro–Wilk's test ($P > 0.05$), and there was homogeneity of variances, as assessed by Levene's test for equality of variances ($P = 0.878$). Patients who had associated HCC had a slightly higher mean baseline BDI score (23.6 ± 3.24) than did patients with no associated malignancy (21.1 ± 3.22), although a borderline nonstatistically significant difference was observed [$t(33) = 2.014, P = 0.052$].

Finally, another subgroup analysis was performed to test for possible effect of disease severity (as indicated by Child–Pugh and MELD scores) on baseline BDI scores in the study subjects. There were 15 patients who were

Child B as compared with 20 patients who were Child C, and there were 11 patients with MELD scores greater than 18 as compared with 24 patients with MELD scores less than 18. An independent-samples t-test was run to determine whether there were differences in baseline BDI scores between the two groups of patients. There were no outliers in the data, as assessed by inspection of a boxplot. BDI scores for each group were normally distributed, as assessed by Shapiro–Wilk's test ($P > 0.05$), and there was homogeneity of variances, as assessed by Levene's test for equality of variances ($P = 0.912$ and 0.060), respectively). In both comparisons a nonstatistically significant difference was observed [$t(33) = 0.200$, $P = 0.843$, and $t(33) = -1.76$, $P = 0.088$, respectively].

Discussion

Depression has been regarded as a common clinical manifestation in patients enlisted to different kinds of transplants. The transplantation process is perceived as a period of uncertainty, with the patient believing that his disease is worsening and there is no other possible cure, a feeling of having no control over the availability of organs and hence the timing of transplantation, and apprehension about the events surrounding the transplantation [13].

A few studies have focused on the psychiatric status of LDLT candidates before and after transplantation. Assessment of the impact of LDLT on mental health is considered one of the important outcome of transplantation to emphasis it's efficacy, as it finally aimed to improve the recipient's well-being.

The present study aimed at investigating depressive symptoms in LDLT recipients. To our knowledge, there are no studies correlating depression, HCV, and LDLT in Egypt.

In our study, the BDI scores before LDLT indicated that all of our patients (100%) suffered from moderate depressive symptoms. This was similar to a study conducted by Singh *et al*. [14], in which 42 patients with HCV showed higher depression scores on BDI with a mean score of 15.9, compared with other patients. The results of Qureshi and colleagues revealed that patients with hepatitis C had greater depression (72.6%) on the hospital anxiety scale [14]. Our results are in agreement with Bianchi *et al*. [15], who reported BDI scores to be indicative of depressed mood in 57% of patients, in relation to the presence of clinical symptoms. There were matching reports about the rates of depression in patients with hepatitis C that ranged from 22 to 59% [16,17].

However, the depression level in our study was higher in comparison with the results of a study by Guimaro *et al*. [18] in which 73 patients (17%) listed for transplantation had symptoms of depression. The depression level was also higher than the findings of another study exploring neuropsychiatric symptoms in patients with chronic HCV infection, in which the depression rate ranged from 2 to 30% [19]. It has to be considered that in our study we included only HCV patients who were more vulnerable to depression owing to their younger age (46.88 ± 15.6 years), social life restrictions, and the presence of more medical complications from their disease progression, as 34.29% of patients previously experienced encephalopathy and 37.14% suffered from ascites. The different measures and methodologies for assessing depression can account for this variance in the prevalence of depression.

After transplantation, we compared the pretransplant BDI scores of our patients with their scores obtained 1 and 6 months after transplantation. The results indicated a high statistically significant improvement after the liver transplant surgery as only 17% of the patients suffered from mild depressive symptoms 6 months after transplant, which may be due to the feeling of relief from psychological distress after the LT. The patients perceived life from a different perspective and became more optimistic. There was also an improvement in their quality of life, as confirmed by multiple studies [20–22], as most of them started participating in life activities that they had enjoyed before their diagnosis. Another important factor contributing to the improved quality of life is the family support obtained during the perioperative and postoperative periods as all of our patients (100%) were married.

These findings were confirmed by multiple studies that reported significantly improved depression scores during the 6 months after transplantation [20–23]. However, some studies showed high levels of depression after transplantation [24,25]. Singh *et al*. [14] reported that patients with HCV exhibited significant depression at 6 months after transplantation, and they attributed this to HCV recurrence. Comparatively, in our center, we performed a routine liver biopsy at 6 months to detect the early stages of HCV recurrence, and, accordingly, patients were administered antiviral treatment, which resulted in a high cure rate.

When we compared pretransplant BDI scores with the scores in HCC patients, we could not detect any statistically significant difference in BDI scores between patients with only HCV disease and those with associated HCC. This finding was obtained despite the circumstances associated with HCC recipients, the risk of tumor progression, and the sense of impending death, which are strong reasons for having more depressive symptoms. This contributed to the small sample size as only nine patients were detected with HCC. Meanwhile, three of our patients were not aware of having HCC, and other patients considered the transplantation the curative treatment. This corresponded to a study that reported neuropsychological symptoms to be unrelated to HCC [26]. On the other hand, another study observed an increased risk of depressive disorders among HCC survivors with HCV [27]. Similarly, other studies have shown higher depression scores in HCC subjects who were evaluated by the Hamilton Depression Rating Scale [28,29].

Connor and Leonard [30] reported that the severity of liver disease was the most important independent predictor of the severity of psychiatric disorders. They suggested that ESLD might produce changes in immune functions that may lead to depressive symptoms. However, we found no statistically significant difference in BDI scores within the degrees of severity of liver disease using Child–Turcotte–Pugh (CTP) and MELD classifications. This might be related to the inability of our patients to discriminate between the degrees of severity as both B and C groups felt the same physical impairment. This result was congruent with the studies carried out by Martin *et al.* [13] and Ko *et al.* [31], who suggested that individual biochemical data may be more sensitive than CTP scores in reflecting the psychological burden of liver cirrhosis.

This finding did not support the results of Rocca *et al.* [32], who had shown that CTP and previous psychiatric history were independent predictors of depression in LT candidates, or the results of Bianchi *et al.* [15], who detected a correlation between CTP scores and BDI ratings.

Our study was limited by the small sample size and that there was no control group. In addition, the findings of our study were from a single transplant center. We also did not evaluate the effects of other post-transplant conditions, such as surgical complications and immunosuppressant medications, on the psychological outcome.

The psychological burden and benefits of LDLT are important aspects of its legitimacy. The aim of LDLT is not only to ensure survival but also to restore an optimal post-transplantation quality of life. Our study demonstrated that LDLT had a positive impact on depressive symptoms in our recipients, thus improving their psychological well-being. Meanwhile it showed that HCV patients were more susceptible to depression. Armed with this knowledge, we can be proactive in our management strategy, by giving special psychiatric attention to them with early detection and adequate intervention.

References

1 Shah SA, Levy GA, Greig PD, Smith R, McGilvray ID, Lilly LB, *et al.* Reduced mortality with right-lobe living donor compared to deceased-donor liver transplantation when analyzed from the time of listing. Am J Transplant 2007; 7:998–1002.

2 Krahn LE, DiMartini A. Psychiatric and psychosocial aspects of liver transplantation. Liver Transpl 2005; 11:1157–1168.

3 Walter M, Walter OB, Fliege H, Klapp BF, Danzer G. Personality and donor-recipient relationships of potential donors before living donor liver transplantation – diagnostics with the repertory-grid technique. Psychother Psychosom Med Psychol 2003; 53:275–280.

4 Abdeldayem HM, Allam NA, Salah E, Mostafa Aziz A, Kashkoush S, Adawy NM, *et al.* Moral and ethical issues in living-donor liver transplant in Egypt. Exp Clin Transplant 2009; 7:18–24.

5 Yosry M, Abdel-Rahman G, Esmat G, El-Serafy M, Omar A, Doss W, *et al.* Recurrence of hepatitis C virus (genotype 4) infection after living-donor liver transplant in Egyptian patients. Exp Clin Transplant 2009; 7:157–163.

6 El-Zanaty F, Way A. *Egypt demographic and health survey 2008 Egyptian: Ministry of Health*. Cairo: El-Zanaty and Associates, and Macro International; 2009.

7 Singh N, Gayowski T, Wagener MM, Marino IR. Quality of life, functional status, and depression in male liver transplant recipients with recurrent viral hepatitis C. Transplantation 1999; 67:69–72.

8 Surman OS. Psychiatric aspects of organ transplantation. Am J Psychiatry 1989; 146:972–982.

9 Collis I, Lloyd G. Psychiatric aspects of liver disease. Br J Psychiatry 1992; 161:12–22.

10 Pugh RN, Murray-Lyon IM, Dawson JL, Pietroni MC, Williams R. Transection of the oesophagus for bleeding oesophageal varices. Br J Surg 1973; 60:646–649.

11 Kamath PS, Kim WR. The model for end-stage liver disease (MELD). Hepatology 2007; 45:797–805.

12 Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. Arch Gen Psychiatry 1961; 4:561–571.

13 Martins PD, Sankarankutty AK, Silva Ode C, Gorayeb R. Psychological distress in patients listed for liver transplantation. Acta Cir Bras 2006; 21 (Suppl 1):39–41.

14 Singh N, Gayowski T, Wagener MM, Marino IR. Vulnerability to psychologic distress and depression in patients with end-stage liver disease due to hepatitis C virus. Clin Transplant 1997; 11:406–411.

15 Bianchi G, Marchesini G, Nicolino F, Graziani R, Sgarbi D, Loguercio C, *et al.* Psychological status and depression in patients with liver cirrhosis. Dig Liver Dis 2005; 37:593–600.

16 Memon SA, Zuberi BF, Ashfaq MN, Kiran Z, Qadeer R, Memon AR, Afsar S. Frequency of depression in chronic hepatitis C naïve patients. Pak J Med Sci 2011; 27:780–783.

17 Gill ML, Atiq M, Sattar S, Khokhar N. Psychological implications of hepatitis C virus diagnosis. J Gastroenterol Hepatol 2005; 20:1741–1744.

18 Guimaro MS, Lacerda SS, Karam CH, Ferraz-Neto BH, Andreoli PB. Psychosocial profile of patients on the liver transplant list. Transplant Proc 2008; 40:782–784.

19 Dieperink E, Willenbring M, Ho SB. Neuropsychiatric symptoms associated with hepatitis C and interferon alpha: a review. Am J Psychiatry 2000; 157:867–876.

20 Russell RT, Feurer ID, Wisawatapnimit P, Salomon RM, Pinson CW. The effects of physical quality of life, time, and gender on change in symptoms of anxiety and depression after liver transplantation. J Gastrointest Surg 2008; 12:138–144.

21 Bona MD, Rupolo G, Ponton P, Iemmolo RM, Boccagni P, Destro C, *et al.* The effect of recurrence of HCV infection of life after liver transplantation. Transpl Int 1998; 11:S475–S479.

22 Dudley T, Chaplin D, Clifford C, Mutimer DJ. Quality of life after liver transplantation for hepatitis C infection. Qual Life Res 2007; 16:1299–1308.

23 Gayowski T, Wagener MM, Marino IR, Singh N. Quality of life and functional status of liver transplant recipients with recurrent viral hepatitis C. Transplant Proc 1999; 31:1386–1387.

24 O'Carroll RE, Couston M, Cossar J, Masterton G, Hayes PC. Psychological outcome and quality of life following liver transplantation: a prospective, national, single-center study. Liver Transpl 2003; 9:712–720.

25 Pérez-San-Gregorio MA, Martín-Rodríguez A, Asián-Cháves E, Gallego-Corpa A, Correa-Chamorro E, Pérez Bernal J. Psychopathological features in transplant patients. Transplant Proc 2003; 35:744–745.

26 Nardelli S, Pentassuglio I, Pasquale C, Ridola L, Moscucci F, Merli M, *et al.* Depression, anxiety and alexithymia symptoms are major determinants of health related quality of life (HRQoL) in cirrhotic patients. Metab Brain Dis 2013; 28:239–243.

27 Chang CH, Chen SJ, Liu CY. Risk of developing depressive disorders following hepatocellular carcinoma: a nationwide population-based study. PLoS One 2015; 10:e0135417.

28 Fan SY, Eiser C, Ho MC. Health-related quality of life in patients with hepatocellular carcinoma: a systematic review. Clin Gastroenterol Hepatol 2010; 8:559.e1-10–564.e1-10.

29 Palmieri VO, Santovito D, Margari F, Lozupone M, Minerva F, Di Gennaro C, *et al.* Psychopathological profile and health-related quality of life (HRQOL) in patients with hepatocellular carcinoma (HCC) and cirrhosis. Clin Exp Med 2015; 15:65–72.

30 Connor TJ, Leonard BE. Depression, stress and immunological activation: the role of cytokines in depressive disorders. Life Sci 1998; 62:583–606.

31 Ko FY, Yang AC, Tsai SJ, Zhou Y, Xu LM. Physiologic and laboratory correlates of depression, anxiety, and poor sleep in liver cirrhosis. BMC Gastroenterol 2013; 13:18.

32 Rocca P, Cocuzza E, Rasetti R, Rocca G, Zanalda E, Bogetto F. Predictors of psychiatric disorders in liver transplantation candidates: logistic regression models. Liver Transpl 2003; 9:721–726.