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Liver, Pancreas and Biliary Tract

Psychological status and depression in patients with liver cirrhosis

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See related commentary, on pages 564–565

Abstract

Background. Previous studies reported an impairment of both the physical and mental dimensions of quality of life in patients with cirrhosis. Very few data are available on the psychological impact of the disease and its relation to liver function.

Aim. To measure the psychological status of patients with cirrhosis in relation to the severity of the liver impairment.

Patients and methods. One hundred and fifty-six patients with cirrhosis were studied. Two questionnaires (the Beck Depression Inventory and the Psychological General Well-Being Index) were self-administered in random order. Clinical and laboratory data were collected using standardised forms.

Results. The global score of Psychological General Well-Being Index was severely reduced compared to Italian population norm. Among individual domains, the more severely affected was General Health, the less compromised was Positive Well-Being. A negative relation was found between Child–Pugh score (a comprehensive measure of disease severity) and global Psychological General Well-Being Index and several individual subscales. The Beck Depression Inventory scores were indicative of a depressed mood in over 50% of patients, in relation to the presence of clinical symptoms.

Conclusions. Patients with cirrhosis have signs of psychological distress and depression, as assessed by Beck Depression Inventory and Psychological General Well-Being Index, in relation to the severity of liver disease. Accordingly, a non-negligible number of patients warrant treatment.

Keywords: Anxiety; Depression; Liver cirrhosis; Psychological well-being

1. Introduction

Cirrhosis carries a high burden on the psychological status of patients with advanced disease [1,2]. The physical dimension of health may be impaired in the presence of advanced disease and complications, whereas the mental dimension, social performance and behaviour may be altered by the sole awareness of viral infection, independently of liver function [3]. Both dimensions contribute to the poor health-related quality of life (HRQL), repeatedly demonstrated in liver disease patients [4–12].

A few reports, limited to patients with chronic hepatitis C [13] and primary biliary cirrhosis [14], also showed an increased prevalence of clinical depression or depressive disorders. Depression is only one of the possible determinants of the psychological well-being of the patients. The Psychological General Well-Being Index (PGWBI), originally proposed by Dupuy [15], provides a comprehensive measure of the psychological profile, and normative data

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are available for comparison with the Italian population [16].

The relation of psychological profile to liver function might also be more complex than expected. Psychological status and depression itself could influence disease history and response to treatment. Among patients with end-stage cirrhosis awaiting liver transplantation, mortality was higher in depressed patients, independently of the severity of liver disease and complications [17].

Our study was aimed at measuring psychological well-being in patients with liver cirrhosis, not limited to the sole presence of depression. The relation of psychological status to liver function and to clinical signs and symptoms was also tested.

2. Materials and methods

2.1. Patients

One hundred and fifty-six consecutive patients with liver cirrhosis (85 males, 71 females), aged 37–87 years (median 65 years) were enrolled from January to December 2002. Inclusion criteria were a diagnosis of liver cirrhosis, documented by histology or by clinical, sonographic and endoscopic evidence of portal hypertension and confirmed by laboratory data. Exclusion criteria were suspected hepatocellular carcinoma (sonographic focal liver lesion or α-fetoprotein exceeding 10× upper limits of normal).

The aetiology was alcohol-related in 23 patients, viral (HBV and/or HCV) in 100 patients. Two patients had a disease of autoimmune origin, while in 18 patients the aetiology of the disease was cholestatic or metabolic; 13 patients had a mixed (alcohol and virus) aetiology. Twenty-five patients (16%) were active drinkers at the time of the study and 13 (8%) were drinking more than 80 g alcohol per day. Patients with HBV or HCV infection were not actively treated with interferon either at the time of investigation or in the previous year.

During a regular ambulatory follow-up visit, we prospectively recorded data, using a pre-defined Case Report Form. The database included information on education, marital status, employment, disease duration, current therapy, previous and current drinking habits, routine biochemistry (performed within 4 weeks), including the five items of the Child–Pugh score [18] (albumin and total bilirubin levels, prothrombin activity, presence and severity of ascites and encephalopathy) and associated diseases (Table 1). Associated diseases were diagnosed either on previous medical records or on the basis of specific drug treatment.

Patients were informed about the aims of the study and the absolute respect of their privacy. All subjects gave their written informed consent to take part in the study and to fill in the questionnaires.

The study was approved by the Senior staff committee of S. Orsola University Hospital, a board regulating non-interventional studies, comparable to an Institutional Review Board.

Table 1
Clinical data of patients with liver cirrhosis

Males/females	85/71	
Age (years)	65 (37–87)	
Duration of the disease (months)	60 (0–328)	
≥5 years	70 (45%)	
Aetiology of the liver disease (%)		
Viral/alcohol/mixed/others	64/15/8/13	
Associated diseases (one or more) (%)	112 (72)	
Endocrino-metabolic	25	
Cardiovascular	33	
Gastrointestinal	30	
Other	36	
Previously admitted to hospital (%)	69	
Causes of previous hospital admission (%)		
Ascites	31	
Encephalopathy	12	
Gastrointestinal bleeding	3	
Sepsis	8	
Mixed	23	
Previous variceal sclerosis (%)	13	
Clinically-detectable ascites (1/2/3) (%)[a]	58/29/13	
Grade I encephalopathy (%)	19	
Child–Pugh class (A/B/C) (%)	40/37/23	
Daily medications (%)[b]		
None/1–5/6 or more	10/33/57	
Pruritus in the last month (%)	47	
Muscle cramps in the last month (%)	58	
Laboratory data		
Albumin (g/L)	32.0 [6.6]	>5.0
Cholesterol (mg/dL)	129 (27–319)	150–200
Prothrombin activity (%)	68 [19]	>70
Creatinine (mg/dL)	0.95 [0.37]	0.50–1.20
Total bilirubin (mg/dL)	1.48 (0.20–12.70)	<1.00
Child–Pugh score	7.5 (5–14)	
Alkaline phosphatase (U/L)	283 (92–1008)	98–280
Blood glucose (mg/dL)	92 (60–551)	70–110

Data are reported as mean [S.D.], as number of cases (percentage on the total of the patients) or as median (range).

[a] According to Child–Pugh score.

[b] The number of daily medications is the sum of pills, oral liquid and powder medications, i.m. injections, i.v. infusions and enemas, prescribed to any individual patient. For laboratory data, normal values are given beside the data of the pathologic values of the group.

2.2. Methods

Two previously validated questionnaires were used to assess the psychological status: the PGWBI [15] and the Beck Depression Inventory (BDI) [19] administered during the same regular follow-up ambulatory visit in random sequence, half the patients completing PGWBI first and the other half BDI first. The questionnaires were rigidly self-administered, but investigators were trained to check the completeness of

data and to interview patients on missing data. The final data sets were almost complete, and the individual domains of PGWBI and/or BDI scales were computable in 148 patients or more.

Medical personnel also recorded clinical data using standardised forms. Patients were asked about the presence of symptoms as pruritus, cramps and sleep disorders.

2.3. Questionnaires

2.3.1. Psychological General Well-Being Index

PGWBI is a self-assessed inventory, specifically developed to measure present well-being, perception of health status and distress by means of 22 questions, arranged into six domains (Anxiety, Depression (or Depressed mood), Positive Well-Being, Self-Control, General Health and Vitality). Each domain is based on three to five items, scoring from 0 to 5, in relation to the intensity and/or the frequency of the affective experience explored. The general index score ranges from 0 to 110. Higher scores reflect more positive well-being. Reference database values for PGWBI, obtained in a large Italian population study, included 1129 subjects, randomly-selected via registry offices, independent of their present health status [16].

2.3.2. Beck Depression Inventory

The BDI is a highly reliable, multilingual, specific instrument that has been found to be both sensitive and valid when compared to psychiatric ratings of depression-severity in subjects older than 13 years. It is largely used not only to measure the severity of an already-diagnosed depression, but also to pick up a so-far undetected depressive status.

It contains 21 multiple-choice questions, each related to an aspect of depression. The four possible options represent increasing levels of depression, with scores from 0 to 3. The total BDI score is derived as the sum of individual scores.

The total possible score ranges from 0 to 63 (from 0 to 9, no depression; 10 to 18, mild depression; 19 to 29, moderate depression; >29, severe depression (scores >21 indicate clinical depression)) [19–22]. Levels above 18 indicate a complete psychiatric evaluation and a possible pharmacological therapy.

2.4. Data analysis

Data obtained in patients with cirrhosis were analysed by means of Cronbach's coefficient α [23]. Estimates for PGWBI domains gave α values ranging from 0.90 to 0.93, always exceeding the conventional threshold of 0.70 [24].

Following this, PGWBI values measured in individual patients were compared with normative values. The age and gender distribution of the control population had been balanced to make this population representative of the whole Italian population.

Data were averaged according to sex and age in the following age ranges: <25 years, 25–34 years, 35–44 years, 45–54 years, 55–64 years, 65–74 years and >74 years.

For BDI, we calculated the global score and the score of subscales as sum of the score of individual items. Subscales were introduced in BDI analysis to describe better the different components of the complete set of BDI items, and were calculated according to different methodologies (Table 2) [25–28]. A special attention was given to the 'somatic aspects' of the depression [25–27,29].

2.4.1. Statistical analysis

The values of individual PGWBI domains of each patient were compared to the age- and sex-matched control group using the *Z*-score (difference between patient value and control mean, divided by control standard deviation). The average *Z*-score indicates the 'effect size' [30]. In this type of analysis,

Table 2
Scores of the BDI and its subscales in 150 patients with cirrhosis

	Score (95% CI)	Score range	Number with altered score
Global score	11 (0–37)	0–63	85 (56.7%)
Steer classification [25]			
Psychological scale	4 (0–26)	0–39	
Somatic scale	6.5 (0–19)	0–24	
Schotte classification [26]			
Psychological scale	2 (2–16)	0–24	
Somatic scale	6 (0–18)	0–21	
Bouman and Kok classification [27]			
Mood and inhibition	1 (0–5)	0–5	125 (83.3%)
Guilt and failure scale	0 (0–4)	0–4	71 (47.3%)
Somatic scale	4 (0–8)	0–8	141 (94.0%)
Clinical classification [28]			
Affective scale	1 (0–3)	0–3	105 (70.0%)
Cognitive scale	1 (0–6)	0–6	103 (68.7%)
Vegetative scale	3 (0–5)	0–5	138 (92.0%)

Data are reported as median (range) or as number of patients with a pathological score (prevalence in percentage), according to classifications where normal values are reported.

any confidence interval (CI) not crossing the zero line may be considered statistically significant. ANOVA and *t*-test were used for comparison between groups.

Regression analysis was performed using either the *Z*-scores or individual domains as dependent variables. Independent variables were marital status, education, employment status, age, aetiology, previous or active alcohol abuse, associated diseases, daily medications, duration of cirrhosis, number of hospital admissions, Child–Pugh class and score, ascites, encephalopathy, sleep disturbances, pruritus and muscle cramps.

Only variables significantly associated with the scores of various domains were used in stepwise multiple regression analysis (SPSS-PC+ v.8.0 SPSS Inc., Chicago, IL, USA). The relations between the domains of the questionnaires and symptoms were searched using non-parametric analysis (Spearman correlation coefficient).

Logistic regression analysis was performed using the dichotomised *Z*-scores of comprehensive indices and/or individual domains as dependent variables. The cut-off value vas set at −1.0.

The significance limit was set at $P < 0.05$.

3. Results

3.1. Psychological distress

The psychological status of cirrhotic patients was significantly impaired in comparison with age- and gender-matched subjects. The effect size of PGWBI global index and all PGWBI domains were significant. The most severely affected was General Health (*Z*-score, −0.76; 95% CI, −0.60 to −0.92; $P < 0.0001$), the least impaired was Positive Well-Being (*Z*-score, −0.32; 95% CI, −0.17 to −0.48; $P < 0.0001$) (Fig. 1).

A relevant proportion of patients had values of domains more than 1S.D. lower than matched population norm (*Z*-score ≤−1.0). The prevalence of these severely altered domains varied from 25.2% for Depression to 39.5% for General Health.

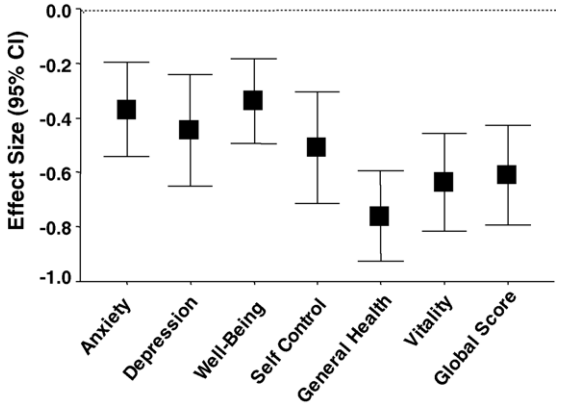

Fig. 1. Effect size of Psychological General Well-Being in patients with cirrhosis. Data of individual domains and global score are reported as mean and 95% CI.

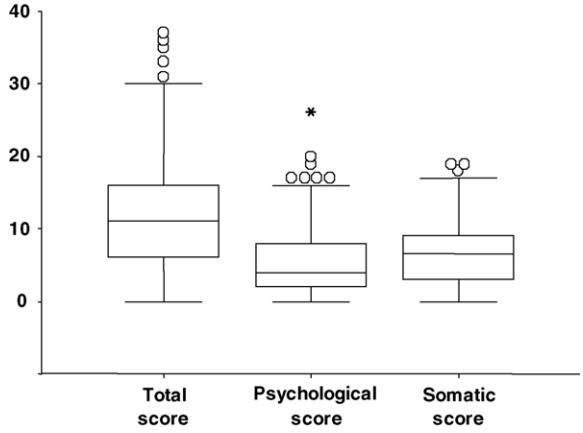

Fig. 2. Box plots representation of scores of BDI in patients with liver cirrhosis. In these 'box and whiskers' plots, the bar within each column represents the median value, the upper and lower borders of the box are the quartiles (75th and 25th percentile, respectively) and the 'whiskers' (error bars) at the extremities indicate the 10th and the 90th percentiles. Open circles indicate individual outliers.

The global score and a few domains of PGWBI were significantly correlated with severity of the liver failure as assessed by the Child–Pugh score, the presence of encephalopathy and ascites (Table 3). The impairment in the General Health domain was significantly related with nearly all the tested variables, with the notable exclusion of sleep disorders.

The effect sizes were larger in patients with active alcohol abuse compared with abstaining patients with a previous history of alcohol consumption (Table 4).

3.2. Depression

The median global score of BDI was 11 (range, 0–37) (Table 2, Fig. 2). Eighty-five patients (56.7%) had scores suggestive of depression, 61 (40.7%) had mild to moderate depression, 15 (10%) moderate to severe depression and 9 (6%) severe to extremely severe depression.

Only 14/150 patients who completed the BDI questionnaire reported a previous episode of depression as history. Their median BDI global score was 15 (range, 6–35) ($P = 0.013$; Mann–Whitney *U*-test versus patients with negative history of depression). Among these patients, only four patients were on antidepressant drugs (median BDI, 19; range, 15–30). The somatic subscale was more severely compromised compared with the psychological subscale, independently of the system used to calculate both subscales (Fig. 2).

A significant correlation was present between BDI (both total score and psychological subscale) and the global score ($r = -0.737$ and $r = -0.663$, respectively; $P < 0.001$), the Anxiety ($r = -0.712$ and $r = -0.634$; $P < 0.001$) and the Depression ($r = -0.674$ and $r = -0.636$; $P < 0.001$) domains of PGWBI.

Table 3
Association of clinical variables and symptoms to psychological status (Psychological General Well-Being) and depression (BDI) in patients with liver cirrhosis

	Ascites	Encephalopathy	Child–Pugh score	Sleep disorders	Daily therapy	Muscle cramps
PGWBI						
Anxiety	0.369	0.084	0.330	0.027	0.348	0.542
Depression	0.245	0.083	0.090	0.005	0.526	0.765
Positive Well-Being	0.022	0.009	0.084	0.119	0.834	0.573
Self-Control	0.037	0.003	0.044	<0.001	0.145	0.525
General Health	0.011	<0.001	0.020	0.072	0.004	0.017
Vitality	0.074	0.028	0.006	0.004	0.036	0.046
Global score	0.031	0.002	0.008	0.003	0.117	0.164
BDI						
Total	0.101	0.026	0.011	0.003	0.024	0.208
Psychological	0.647	0.097	0.918	0.627	0.266	0.659
Somatic	0.046	0.050	<0.001	<0.001	0.013	0.158

The reported *P* values refer to Mann–Whitney test for dichotomous variables (muscle cramps and sleep disorders) and to Spearman rank correlation for multiple-level variables (ascites, encephalopathy, Child–Pugh score and daily medications). Number of daily medications is the sum of pills, oral liquid and powder medications, i.m. injections, i.v. infusions and enemas.

Total BDI score was also related to impaired liver function but not to demographic parameters. It significantly correlated with Child–Pugh score ($r_s = 0.217$; $P = 0.011$) and was different in relation to present drinking habits (Table 4).

The relationship between clinical and functional parameters was largely attributable to the somatic/vegetative subscale. It correlated better than the total BDI with the Child–Pugh score ($r_s = 0.313$; $P < 0.001$), and with the severity of ascites, the presence of sleep disorders and the number of daily medications. It showed higher scores in presence of active alcohol abuse (drinkers versus abstaining: Mann–Whitney *U*-test: $P = 0.024$).

The psychological subscale did not correlate with any functional parameter but produced higher scores in presence of alcohol abuse (Table 4).

3.3. Relation of psychological status to clinical variables

A proportion of patients varying from 25 to 40% had effect sizes of the PGWBI domains <−1.0 or a global score of BDI higher than 18 [22] (Table 5).

Logistic regression analysis identified the presence of sleep disorders as the independent variable more frequently associated with low domains of PGWBI (Table 5). Child–Pugh score was the independent parameter more strictly related to global BDI score and PGWBI-General Health, and was entered as a determinant of the effect size of PGWBI-Vitality.

No correlation was observed between PGWBI and BDI scores and the severity of hepatic necroinflammation expressed by aminotransferase levels. Patients with HCV infection did not differ from the general population in the scores of PGWBI and BDI (not reported in detail).

4. Discussion

The psychological status of patients with liver cirrhosis is severely compromised; this occurs both in patients with compensated disease and, more markedly, in the presence of liver failure. These results expand previous data [1,2,13,14,31,32] and show that depression is a relatively common finding. The results of BDI are also supported by the validated PGWBI questionnaire, strictly related to BDI, indicating that the impaired psychological function extends to different aspects of mental status, and depression is

Table 4
Psychological scales and subscales in relation to drinking habits in cirrhosis (Mann–Whitney *U*-test)

	Actively drinking ($n = 25$)	Abstaining ($n = 65$)	*P*-value
Psychological General Well-Being			
Global score	−1.06 (−1.64 to −0.48)	−0.55 (−0.81 to −0.29)	0.074
Anxiety	−0.88 (−1.48 to −0.28)	−0.29 (−0.54 to −0.04)	0.065
Depression	−1.16 (−1.87 to −0.44)	−0.28 (−0.57 to +0.00)	0.006
Positive Well-Being	−0.51 (−0.96 to −0.05)	−0.23 (−0.47 to +0.01)	0.217
Self-Control	−0.93 (−1.59 to −0.26)	−0.49 (−0.81 to −0.17)	0.285
General Health	−1.06 (−1.53 to −0.59)	−0.84 (−1.09 to −0.60)	0.427
Vitality	−0.85 (−1.43 to −0.27)	−0.67 (−0.94 to −0.39)	0.605
BDI			
Global	15.4 (11.4 to 19.3)	10.2 (8.4 to 11.9)	0.006
Somatic	7.4 (5.8 to 9.1)	5.6 (4.6 to 6.7)	0.024
Psychological	7.9 (5.2 to 10.6)	4.5 (3.5 to 5.6)	0.020

The values of Psychological General Well-Being are reported as effect sizes. Data are reported as mean (95% CI).

Table 5
Prevalence of an impaired response in BDI global score (score >18) and in scores of global scale and different domains of PGWBI (*Z*-score less than −1.0)

	Prevalence (%) (95% CI)	Associated factors	OR (95% CI)	*P*-value
PGWBI				
Global	30 (23–37)	Sleep disorders	4.43 (0.31–0.87)	0.004
Anxiety	26 (20–33)	Active drinking	2.16 (1.26–3.69)	0.005
Depression	25 (19–32)	Sleep disorders	4.66 (1.53–14.19)	0.007
Positive Well-Being	25 (19–32)	Sleep disorders	6.21 (1.78–21.67)	0.004
Self-Control	30 (23–37)	Sleep disorders	4.55 (1.64–12.62)	0.004
General Health	40 (32–47)	Child–Pugh score	1.21 (1.04–1.40)	0.011
Vitality	35 (28–43)	Sleep disorders	2.71 (1.11–6.59)	0.028
		Child–Pugh Score	1.19 (1.02–1.39)	0.029
BDI				
Global	16 (11–22)	Child–Pugh Score	1.18 (0.99–1.41)	0.067

Factors associated with poor HRQL are reported in the order they enter logistic regression (odds ratio [95% CI]). Sleep disorders were considered a dichotomous variable. The Child–Pugh score was considered a continuous variable.

nothing but the tip of the iceberg of poor psychological health status.

PGWBI has advantages over other generic instruments. It is able to detect the balance between emotional and affective states, both negative and positive. It lacks a connection with physical symptoms produced by emotive stress, and is suitable for use in stress situations in different diseases, independent of psychiatric disorders. Finally, the scores of individual domains are well-correlated with other instruments measuring the mental dimension of health [33,34].

The depression syndrome measured by BDI reflects a constellation of signs and symptoms, which can be present in non-affective psychiatric disorders [20].

The subscales cover the different aspects of the depression. The 'psychological' subscale consists mainly of the self-denigratory items, together with the items of suicidal ideation, irritability and indecisiveness. The 'somatic' subscale consists of items representing the symptoms of sleep disorders, fatigue, loss of appetite and weight, body image concern, loss of libido, and inability at work and during daylife activities [26]. Irrespective of the criteria used to define subscales (sum of scores, prevalence of altered items, etc.), the somatic subscale was more severely compromised in comparison with the psychological subscale (Table 2).

Only few studies are available on depression in patients with liver disease. In primary biliary cirrhosis, depression correlated with poor perceived quality of life, mental health and fatigue [14]. Similarly, in patients with chronic hepatitis C, the severity of depressive reports was a highly significant predictor of fatigue [13], a subjective symptom also associated with somatic illnesses, psychological disturbances and stress reaction. These two studies were performed in well-selected groups, independent of the absence/presence of cirrhosis, and no relation was found with parameters of liver impairment. On the contrary, in subjects with overt liver failure in the waiting list for orthotopic liver transplantation, a correlation with liver failure was reported [32], and the prevalence of a BDI indicative of depression (any grade) was perfectly similar to the one we observed in our population [31]. This prevalence is similar to figures reported in different chronic diseases, as heart failure (48% [35]), renal failure (67% [36]), diabetes (22–60% [37]) and multiple sclerosis (40% [38]). The close association between global BDI and its somatic/vegetative scale and liver function supports the existence of a large reactive component of psychological status and depression, due to the patients' perception of a 'failing health status', possibly independent of any specific function. This conclusion is supported by a previous study where the severity of liver disease was related to HRQL [11], measured by two generic questionnaires largely covering mental dimensions.

The presence of sleep disorders is an important determinant of the psychological profile. Sleep disorders were reported by 69% of patients, and were significantly associated with psychological distress and depression. Only 38% of cases referred daily somnolence, potentially related to hepatic encephalopathy. Sleep disorders were also reported in advanced liver diseases independently of hepatic encephalopathy [39,40]. Also in the present series, disturbed sleep was not associated with clinically detectable hepatic encephalopathy ($\chi^2 = 1.616$). A third of patients (32%) had problems in falling asleep, as previously reported in different series [11,40]; 36% had an early morning wake-up, and a larger proportion of patients (55%) reported to wake up several times during the night for intervening problems (muscle cramps, use of diuretics, etc.). Logistic regression highlighted this symptom, referred to by patients during ambulatory control visits, but frequently under-rated and untreated by physicians.

The disturbed sleep pattern might be a sign of an unrecognised affective disorder [12]. This interpretation fits with data reported in subjects submitted to liver transplantation, who greatly improved in a scale of sleeplessness or insomnia, 1 year after surgery [41]. On the other side, sleep disorders, whatever their origin, could worsen psychological profile. Disruption of the circadian rhythm of melatonin may also contribute to altered sleep profile [42].

Both BDI and the Depression scale of PGWB were significantly impaired in actively drinking patients in comparison with abstaining cirrhotic subjects. BDI has been extensively used in alcoholics to score depression [43,44]. Because

alcohol dependence and major depressive events are very prevalent psychiatric disorders, they may coexist independently of a cause–effect relationship, but alcohol abuse is also reported to induce depression per se [45].

A remarkable proportion of patients with cirrhosis (16%) had a global BDI score higher than 18, i.e. a score indicative of a moderate to severe depression [20–22]. Altered psychological status and depression, although not involved in the pathogenesis of liver disease, might influence its history and response to treatment. In patients with end-stage cirrhosis awaiting a liver transplantation, a depressive state was associated with higher mortality [1], independent of the severity of liver disease and complications. Longitudinal studies have further strengthened the association between depression and functional disability by showing that changes in disability rating over time are synchronous with changes in the severity of depressive symptoms [46]. Accordingly, the altered psychological status of cirrhotic subjects theoretically might warrant a therapeutic/pharmacological treatment, but no data are available on the pharmacological management of depression in patients with liver failure. This is an area where carefully controlled clinical trials are eagerly awaited.

Conflict of interest statement

None declared.

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