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ORIGINAL PAPER

Correlation between degree and quality of sleep disturbance and the level of neuropsychiatric impairment in patients with liver cirrhosis

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Abstract Sleep disturbances are common in patients of cirrhosis and has a significant effect on their health related quality of life (HRQOL). Thus far, no study has demonstrated a systematically studied significant correlation between the sleep disturbance observed and the neuropsychiatric impairment status of patients of cirrhosis. On the basis of PHES, we divided 100 cirrhotics into those having minimal hepatic encephalopathy (MHE) (PHES≤−5) and those not (NMHE). Now, in these MHE (n=46) and NMHE (n=54) patients, sleep disturbance was measured with Pittsburgh Sleep Quality Index (PSQI) and Epworth Sleepiness Scale (ESS) and HRQOL with SF-36(v2) questionnaire. Sixty (60 %) patients were found to be 'poor sleepers' (PSQI>5) while 38 (38 %) patients had excessive daytime sleepiness (ESS≥11). Univariate and multivariate analyses showed MHE has significant effect among 'poor sleepers' (P<0.0001) as well as on those with EDS (P<0.0001). Significant correlation existed between PHES and both the sleep parameters of PSQI (r = −0.518, P <0.0001) as well as ESS (r = −0.383, P <0.0001), implying independently strong correlation between poor cognition and the presence of night time sleep disturbance and excessive daytime sleepiness among cirrhotics. Significant correlation existed between PSQI and ESS and the various scales and component scores of SF-36(v2) signifying the negative impact of sleep disturbance on the HRQOL. In conclusion, both night time sleep disturbance and excessive daytime sleepiness have significant relation with the neuropsychiatric impairment in patients of cirrhosis and are significantly associated with the observed impairment in HRQOL.

Keywords Hepatic encephalopathy · Sleep disturbance · Quality of life · Cognition · Somnolence

Abbreviations

ALT	alanine aminotransferase
BP	bodily pain
CTP	Child-Turcotte-Pugh
ESS	Epworth Sleepiness Scale
EDS	excessive daytime sleepiness
GH	general health
HRQOL	health related quality of life
HE	hepatic encephalopathy
MCS	mental component summary
MH	mental health
MHE	minimal hepatic encephalopathy
MMSE	mini-mental state examination
MELD	model for end-stage liver disease
NMHE	no-MHE
PCS	physical component summary
PF	physical functioning
PSQI	Pittsburgh Sleep Quality Index
PHES	psychometric hepatic encephalopathy score
RE	role-limitation emotional
RP	role-limitation physical
SF	social functioning
VT	vitality

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Introduction

Hepatic encephalopathy (HE) reflects a spectrum of neuropsychiatric abnormalities seen in patients with liver dysfunction in the absence of other known brain disease (Ferenci et al. 2002). Spectrum of HE varies from minor cognitive dysfunction to lethargy, depressed consciousness and coma. The minor cognitive dysfunction in patients with cirrhosis is termed minimal HE (MHE), which is estimated to affect up to 60 % to 80 % of patients with cirrhosis and may seriously impair a patient's daily functioning and health-related quality of life (HRQOL) (Groeneweg et al. 1998; Prasad et al. 2007; Dhiman and Chawla 2009; Dhiman et al. 2010a).

Night-time sleep disturbances and excessive daytime sleepiness (EDS) have been reported in patients with cirrhosis of liver. Studies using HRQOL questionnaire have confirmed higher frequency of sleep disturbance in cirrhotic patients (Groeneweg et al. 1998; Marchesini et al. 2001). Cordoba et al. (1998) demonstrated abnormalities in quality of sleep in nearly half (47.7 %) the cirrhotic patients without overt HE compared with 38.6 % of subjects with chronic renal disease and 4.5 % of healthy controls; unsatisfactory sleep in patients with liver cirrhosis was associated with delayed bedtime, delayed wake-up time, and evening chronotypology. The sleep disturbances in cirrhosis were not associated with clinical parameters or with cognitive impairment. Montagnese et al. (2009) showed 70 % of the patients with cirrhosis had decreased sleep efficiency but no relationship between night-time sleep disturbance/day-time sleepiness and the presence of HE per se, but interestingly pronounced day-time sleepiness was associated with slowing of the EEG. Mostacci et al. (2008) reported that patients with MHE complained of more daytime sleepiness and had more pronounced night-time sleep disturbance than controls. Sleep disturbances have been reported to be associated with poor survival (HR, 0.96; 95 % CI, 0.94−0.98) among 156 patients with cirrhosis awaiting liver transplantation (Kanwal et al. 2009).

Thus far only a few data are available on the correlation between degree of sleep disturbances and the level of cognitive impairment. Futher, sufficient systematically studied data is lacking in relation to the significance of sleep disturbances contributing to the impairment of HRQOL in patients with liver cirrhosis. Hence, the present study was performed, (i) to study the degree and quality of sleep disturbances in patients with cirrhosis of liver, (ii) to study the correlation between degree and quality of sleep disturbance and the level of neuropsychiatric impairment and (iii) to study the correlation between sleep disturbance and HRQOL in these patients.

Materials and methods

The Ethics Committee of Postgraduate Institute of Medical Education and Research (PGIMER), a tertiary-level health care centre in Chandigarh, India, approved the study. Each subject gave written informed consent before being included in the study.

It was a cross sectional study where one hundred consecutive patients with cirrhosis of liver without evidence of overt HE were included in the study. The patients were divided in two groups based upon the presence or absence of MHE, i.e., MHE group and no-MHE (NMHE) group.

Eligibility criteria

Patients diagnosed as having cirrhosis of liver at the Inpatient or Outpatient Liver Clinic of Department of Hepatology, PGIMER, Chandigarh were candidates for enrolment. The diagnosis of cirrhosis of liver was based on clinical, biochemical, and ultrasonography or liver histological data.

Exclusion criteria

Exclusion criteria were history of or the presence of overt HE; history of recent (<3 months) alcohol intake; infection, recent (<6 weeks) antibiotic use or gastrointestinal bleeding; history of recent (<6 weeks) use of drugs affecting psychometric performances like benzodiazepines, antiepileptic, psychotropic drugs, any substance having dependence producing potential such as opium etc.; history of shunt surgery or transjugular intrahepatic portos—systemic shunt for portal hypertension; renal impairment; presence of hepatocellular carcinoma; severe medical problems such as congestive heart failure, pulmonary disease, neuropsychiatric disorder, etc., or those working in night shifts that could influence performance of neuropsychiatric tests.

Clinical and laboratory assessment

Clinical examination included a thorough general physical examination, vitals, and systemic examination including complete neurological. Mini-mental state examination (MMSE) was performed to exclude overt cognitive impairment in all patients before formal tests for the diagnosis of MHE were administered. West Haven Criteria and MMSE score were used for grading mental state in patients with cirrhosis to differentiate between grade 0 and grade 1 HE (Ferenci et al. 2002; Dhiman et al. 2010a). Laboratory investigations included a complete hemogram, renal and liver function tests, and complete coagulogram. Upper gastrointestinal endoscopy was performed in all patients for the presence of esophageal varices. Severity of the liver disease

was determined by Child-Turcotte-Pugh (CTP) and model for end-stage liver disease (MELD scores). Detailed psychiatric evaluation by a psychiatrist ruled out presence of any major psychiatric disorders like affective disorders, psychosis and anxiety disorders.

Neuropsychological assessment

The diagnosis of MHE was made with the administration of psychometric hepatic encephalopathy score (PHES), which has been validated in Indian population and can be performed in 15–20 min (Dhiman et al. 2010b). In Indian patients PHES ≤−5 was considered diagnostic of MHE (Dhiman et al. 2010b).

Sleep-wake profile

Subjects were asked to complete two validated, self-rated assessment tools.

Pittsburgh Sleep Quality Index (PSQI)

It was used to differentiate "poor" from "good" sleep by measuring seven areas - subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction over the last 1 month (Buysse et al. 1989). The client self-rated each of these seven areas of sleep. Scoring of answers was based on a 0 to 3 scale, whereby 3 reflect the negative extreme on the Rensis Likert Scale: 0 = very good; 1 = fairly good; 2 = fairly bad; 3 = very bad. A global sum of >5 indicates a "poor" sleeper (Buysse et al. 1989).

Epworth Sleepiness Scale (ESS)

This was used to assess day-time sleepiness (Johns 1991). Subjects rated their likelihood of 'dozing off' in eight different day-time situations on a scale of zero (unlikely), to three (very likely) on the Rensis Likert Scale: 0 = would never fall asleep in that situation; 1 = there is a slight chance of falling asleep in that situation; 2 = there is a medium chance of falling asleep in that situation; 3 = there is a high chance of falling asleep in that situation.

Eight different day-time situations include sitting and reading, watching TV, sitting inactive in a public place like a theatre or meeting, as a passenger in a car for an hour without a break, lying down to rest in the afternoon when circumstances permit, sitting and talking to someone, sitting quietly after lunch without alcohol, in a car, while stopped for a few minutes in traffic. The component scores were summated to provide a total score (range: 0–24); a score of ≥11 was considered abnormal and labelled as having EDS (Johns 1991).

Health-Related Quality of Life (HRQOL)

The study population was also asked to complete Short Form (SF)-36 (v2) questionnaires for the assessment of HRQOL (Ware and Sherbourne 1992). SF-36(v2) is designed to measure the full range of health status and wellbeing by means of 36 multiple-choice questions. It measures 4 scales in the area of physical health [physical functioning (PF), role-limitation physical (RP), bodily pain (BP), general health (GH)] and 4 in the area of mental-health [vitality (VT), social functioning (SF), role-limitation emotional (RE) and mental health (MH)]. Two comprehensive indexes of HRQOL were also computed, physical component summary (PCS) and mental component summary (MCS). Finally, it includes a question on perception of change in health status in the previous 12 months. The questionnaire used in this study were both in English and a Hindi translated version, the patients were asked to read in the language they preferred and mark those related to their health at that time. Those subjects who wished to be administered the questionnaire verbally, rather than reading it on their own, had the questions read aloud to them in order listed in the printed questionnaire. Scoring was done using the SF-36(v2) software after procuring the license for the same from the "Quality Metric Incorporated", Lincoln, Rhode Island, USA.

Statistical analysis

Data are presented as means and 95 % confidence intervals (CIs) for quantitative variables and as proportions with 95 % CI for qualitative variables (Newcombe 1998). Unpaired *t*-test (parametric analysis) was used for comparing the quantitative data for continuous variables of normally distributed population and for skewed data Mann–Whitney *U* test. For a comparison of categorical variables, Chi square or Fisher exact tests were used. A multivariate logistic regression analysis using the block method was performed on variables reaching a significance of $P < 0.10$ on univariate analysis to identify variables independently associated with the poor sleep status or the EDS. Correlation between the PHES and different measures of PSQI and ESS, and the SF-36(v2) scores including PCS and MCS were assessed using the Spearman's rank correlation coefficient. *P* value of <0.05 was considered significant. Statistical analysis was performed with SPSS software for Windows, version 17.0 (SPSS Inc., Chicago, IL).

Results

Between July 1, 2010, and July 30, 2011, 239 patients with cirrhosis were screened; 100 patients (41.8 %) who met the eligibility criteria were included in the study. Figure 1 shows

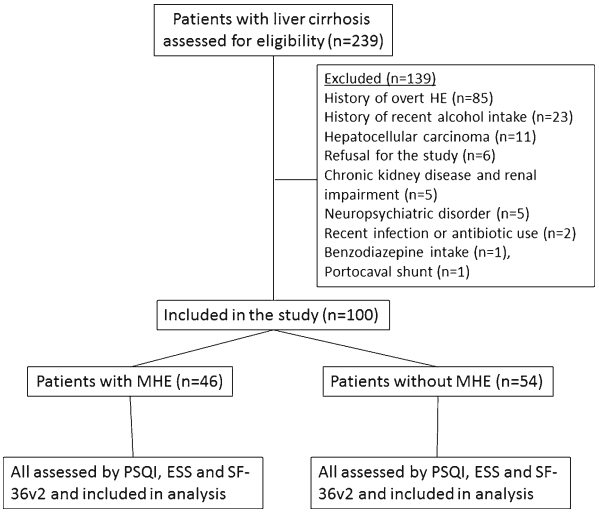

Fig. 1 Flow chart of patients in the study. PSQI, Pittsburgh Sleep Quality Index; ESS, Epworth Sleepiness Scal; SF-36v2, Short Form-36v2

the flow of patients into the study and reasons for the exclusion of 139 patients (58.2 %). Reasons that the 139 patients were excluded from the study were: history of overt HE (85 patients), history of recent alcohol intake (23 patients), hepatocellular carcinoma (11 patients), refusal for the study (6 patients), chronic kidney disease and renal impairment (5 patients), neuropsychiatric disorder (5 patients), recent infection or antibiotic use (2 patients), benzodiazepine intake (1 patient), portocaval shunt (1 patient). The clinical and demographic characteristics of the patients enrolled were shown in Table 1. Of the 100 patients included in the study, 87 were men and 13 were women. The etiologies of cirrhosis were: alcohol abuse, 55 patients (including alcohol and hepatitis B, 4; alcohol and hepatitis C, 2); chronic viral hepatitis, 21 (hepatitis B virus, 7; hepatitis C virus, 14); and other causes, 24 (non-alcoholic steatohepatitis, 8; autoimmune hepatitis, 4; cryptogenic cirrhosis, 11; Budd-Chiari syndrome, 1).

Minimal hepatic encephalopathy

Prevalence

All components of PHES score were performed in 100 patients. MHE, as diagnosed by PHES score of ≤−5, was detected in 46 (46 %) out of 100 patients with cirrhosis of liver; 18 (34 %) of 53 patients were in CTP class A, 19 (55.9 %) of 34 patients were in CTP class B and 9 (69.2 %) of 13 patients were in CTP class C (χ^2=7.25, P=0.027). MHE was found in 28 (50.9 %) of 55 patients with alcohol related cirrhosis and in 18 (40.0 %) of 45 patients with non-alcohol related cirrhosis (P= 0.317). There were significant correlations between PHES score and PCS (r = −0.360, P <0.0001) and between PHES score and MCS (r = −0.194, P <0.05), implying a link between poor cognition (MHE) and poor HRQOL.

Sleep-wake profile

Good sleepers versus poor sleepers

Patients with cirrhosis of liver were classified as good sleepers (PSQI ≤ 5) and poor sleepers (PSQI >5). Sixty

Table 1 Clinical and demographic characteristics of patients

Parameter	Patients screened (n=239)	Patients enrolled (n=100)	MHE* (n=46)	NMHE[a] (n=54)
Male : Female	210 : 29	87 : 13	39 : 7	48 : 6
Age (in years)	49.1 (47.7−50.5)	48.8 (46.9−50.8)	49.4 (46.6−52.3)	48.3 (45.6−51.0)
Education (years)	10.2 (9.7−10.7)	10.5 (9.7−11.3)	9.9 (8.4−10.9)	11.2 (10.2−12.3)
CTP class				
A	59 (24.6 %)	53 (53.0 %)	18 (39.1 %)	35 (64.8 %)
B	71 (29.7 %)	34 (34.0 %)	19 (41.3 %)	15 (27.8 %)
C	109 (45.6 %)	13 (13.0 %)	9 (19.6 %)	4 (7.4 %)
Varices Yes	194 (81.2 %)	87 (87.0 %)	42 (91.3 %)	45 (83.3 %)
No	45 (18.8 %)	13 (13.0 %)	4 (8.7 %)	9 (16.7 %)
Etiology Alcohol	158 (66.1 %)	55 (55.0 %)	28 (60.9 %)	27 (50.0 %)
HBV	13 (5.4 %)	7 (7.0 %)	4 (8.7 %)	3(5.6 %)
HCV	27 (11.3 %)	14 (14.0 %)	6 (13.0 %)	8 (14.8 %)
Others[b]	41 (17.2 %)	24 (24.0 %)	8 (17.4 %)	16 (29.6 %)

Data are presented as mean (95 % confidence interval) or as number (percentage); *CTP* Child-Turcotte-Pugh; *HBV* hepatitis B virus; *HCV* hepatitis C virus; *MHE* minimal hepatic encephalopathy; *NMHE* no minimal hepatic encephalopathy; [a] MHE and NMHE columns describe patients who have been enrolled; distinction between the two groups was based on the results of psychometric hepatic encephalopathy score; [b] others include NASH 13, autoimmune hepatitis 8, cryptogenic cirrhosis 18 and Budd-Chiari syndrome 2

(60 %) patients with cirrhosis of liver were 'poor sleepers (PSQI >5)', 40 (66.7 %) of whom belonged to MHE group. PSQI total score was significantly higher among patients with MHE compared to NMHE [mean 8.72 (95 % CI 7.83 −9.60) *vs* mean 5.02 (95 % CI 4.18−5.86); $P<0.0001$] (Fig. 2a). There was a significant correlation between PHES score and total PSQI score ($r = -0.518$, $P < 0.0001$), indicating association between poor cognition (MHE) and poor sleep parameters.

Univariate analysis We studied the different factors such as; age, sex, etiology, presence of varices, ascites, serum bilirubin, serum alanine aminotransferase (ALT), serum alkaline phosphatase, serum albumin, serum urea, serum creatinine, presence of hyponatremia (serum sodium <135 mEq/L), presence of hypokalemia (serum potassium <3.5 mEq/L), INR, hemoglobin, total leukocyte counts, CTP score, MELD score and PHES score among the two groups, good and poor sleepers (Table 2). Poor sleepers were found to

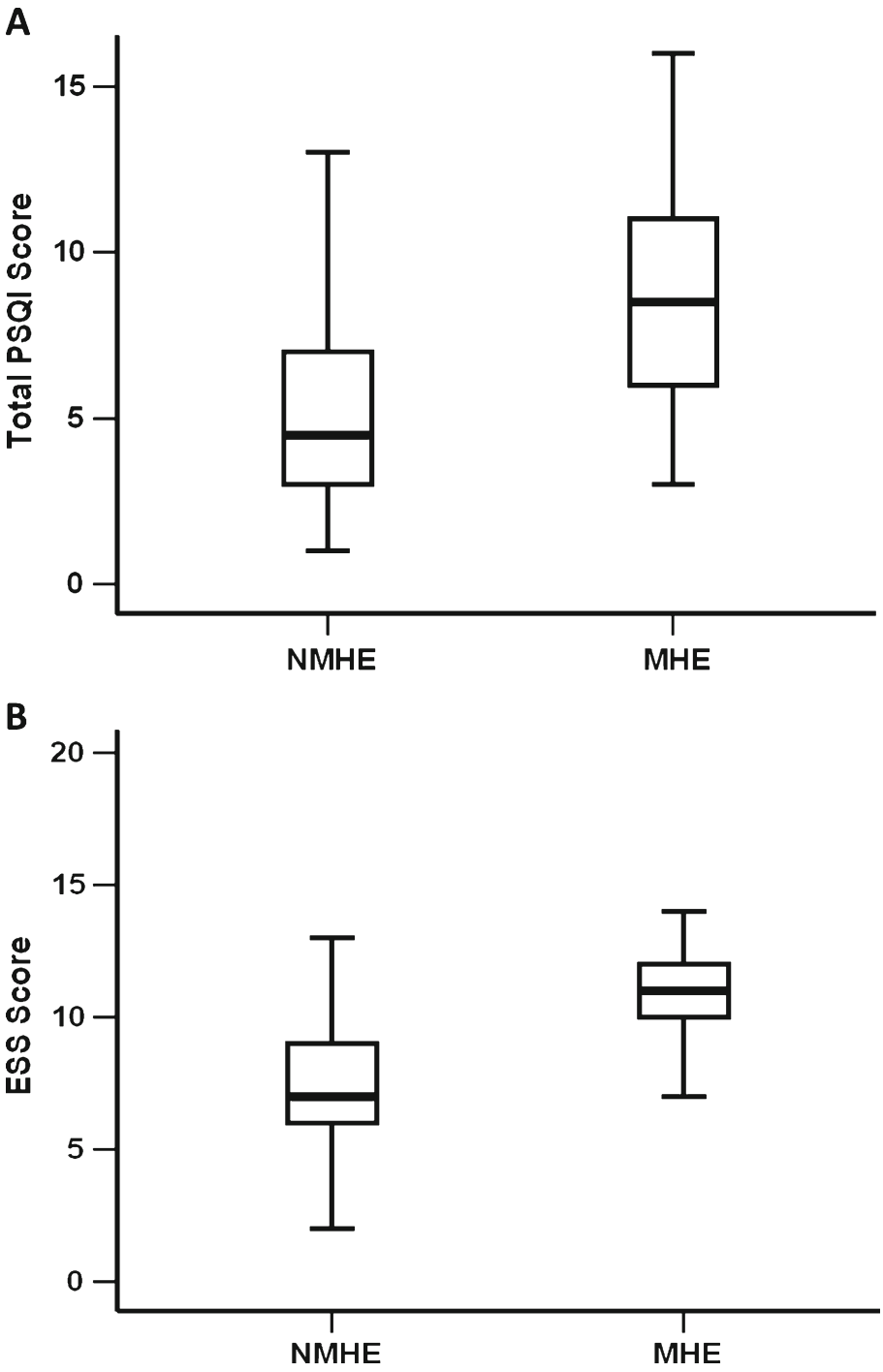

Fig. 2 **a** Pittsburgh Sleep Quality Index (PSQI) total score in patients with and without minimal hepatic encephalopathy. *Box plots* show mean, range and interquartile range of PSQI total score in patients of minimal hepatic encephalopathy (MHE) and no-MHE (NMHE). **b** Epworth Sleepiness Scale (ESS) scores in patients with and without minimal hepatic encephalopathy. *Box plots* show mean, range and interquartile range of ESS score

Table 2 Univariate and multivariate analysis of different parameters

Parameter	Univariate			Multivariate	
	Good Sleepers* (*n*=40) PSQI ≤5	Poor Sleepers* (*n*=60) PSQI >5	*P*	aOR	*P*
Age (years)	47.2 (44.0−50.3)	50.0 (47.5−52.5)	0.16		
Sex Male	35 (40.2 %)	52 (59.8 %)	1.0		
Female	5 (38.5 %)	8 (61.5 %)			
Etiology Alcohol	20 (36.4 %)	35 (63.6 %)	0.42		
Non-alcohol	20 (44.4 %)	25 (55.6 %)			
Education (years)	10.4 (9.2−11.6)	10.6 (9.5−11.6)	0.59		
Varices Yes	33 (37.9 %)	54 (62.1 %)	0.37		
No	7 (53.9 %)	6 (46.2 %)			
Ascites Yes	7 (36.8 %)	12 (63.2 %)	0.80		
No	33 (40.7 %)	48 (59.3 %)			
Bilirubin (mg/dL)	2.5 (1.5−3.6)	1.9 (1.5−2.4)	0.65		
ALT (IU/L)	54.1 (44.8−63.5)	45.4 (36.5−54.4)	0.02		
Alkaline phospahtase (IU/L)	225.5 (151.0−300.0)	215.9 (165.9−266.0)	0.64		
Albumin (g/dL)	3.7 (3.5−3.9)	3.5 (3.3−3.7)	0.11		
Urea (mg/dL)	30.8 (26.8−34.8)	29.8 (26.3−33.3)	0.595		
Creatinine (mg/dL)	0.9 (0.8−1.0)	1.0 (0.9−1.1)	0.38		
Hyponatremia (Na^+< 135 mEq/L)	0 (0 %)	10 (16.7 %)	0.005		
Hypokalemia (K^+< 3.5 mEq/L)	2 (4.2 %)	3 (5.3 %)	1.0		
INR	1.4 (1.3−1.5)	1.4 (1.4−1.5)	0.77		
Hemoglobin (g/dL)	11.6 (11.1−12.1)	11.0 (10.4−11.6)	0.13		
Total leukocyte count (K/mm^3)	6.4 (5.1−7.6)	6.5 (5.8−7.2)	0.83		
Platelets (K/mm^3)	110 (89−131)	124 (110−139)	0.23		
CTP class A	25 (47.2 %)	28 (52.8 %)	0.26		
B & C	15 (31.9 %)	32 (68.1 %)			
CTP score	6.9 (6.2−7.5)	7.1 (6.5−7.6)	0.71		
MELD score	10.8 (9.1−12.5)	11.2 (10.0−12.4)	0.72		
PHES	−2.4 (−3.3 − −1.6)	−5.9 (−6.8 − −5.1)	<0.0001		
MHE	6 (13.0 %)	40 (87.0 %)	<0.0001	9.925 (3.313 −29.735)	<0.0001

*Data are presented as mean (95 % confidence interval) or as number (percentage); *aOR* adjusted Odd's Ratio; *PSQI* Pittsburgh Sleep Quality Index; *Na^+* serum sodium levels; *K^+* serum potassium levels; *K*=1000; *CTP* Child-Turcotte-Pugh; *MELD* model for end stage liver disease; *ALT* alanine aminotransferase; *INR* International Normalized ratio; *PHES* Psychometric Hepatic Encephalopathy Score; *MHE* minimal hepatic encephalopathy; *NMHE* no minimal hepatic encephalopathy

have higher prevalence of hyponatremia (*P*=0.005), lower serum ALT levels (*P* = 0.023), and lower PHES scores (*P* <0.0001) with higher frequency of MHE (*P* <0.0001). There was no significant difference in the remaining parameters.

Multivariate analysis The above-mentioned significant variables on univariate analysis were selected for multivariate analysis. To find out the effect of age, CTP class and etiology of cirrhosis (alcoholic versus non-alcoholic) on poor sleep status we also included these parameters in the multivariate analysis. On multivariate analysis, only the presence of MHE (*P* <0.0001) was found to be associated with poor sleep status (Table 2).

PSQI component scores among MHE and NMHE patients Various domains of PSQI namely sleep duration, sleep disturbance, sleep latency, daytime dysfunction, habitual sleep efficiency, subjective sleep quality as well as the PSQI total score were compared among MHE and NMHE patients. Although no cut-off values for individual subscales of PSQI are available, significantly higher scores for all the component scales were found in MHE patients as compared to NMHE patients (Fig. 3).

Health-Related Quality of Life (HRQOL) among good and poor sleepers Comparison between the two groups showed that poor sleepers had significant impairment in the scales of PF, SF and RE (Table 3).

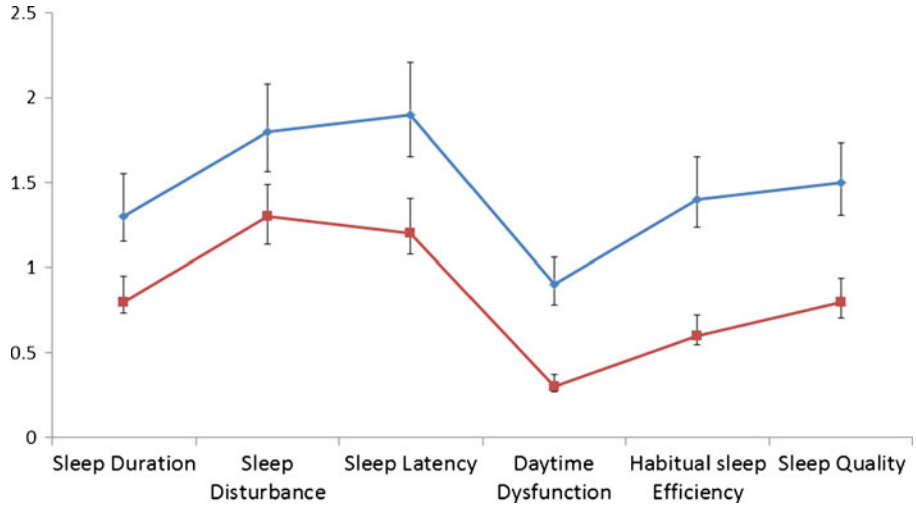

Fig. 3 Mean (95 % confidence interval [CI]) Pittsburgh Sleep Quality Index (PSQI) component scores in patients with cirrhosis with minimal hepatic encephalopathy (MHE, *blue line*) and no-MHE (NMHE, *red line*) [P <0.0001 for all scales except sleep duration (P=0.009)]

The correlation between the various scores of the SF-36(v2) and the PSQI scores showed significant negative correlation with scales of PF (r = −0.30, P = 0.003), BP (r = −0.29, P = 0.004), SF (r = −0.34, P <0.0001), RE (r = −0.38, P <0.0001) and component scores of PCS (r = −0.24, P = 0.02) and MCS (r = −0.26, P = 0.0009).

Excessive Daytime Somnolence (EDS)

EDS (ESS ≥11) were found in 38 (38 %) patients, 34 (89.5 %) of whom were MHE patients. ESS score was significantly higher among patients with MHE compared to NMHE [mean 10.72 (9.71−11.73) *vs* mean 7.35 (6.57−8.13); P<0.0001] (Fig. 2b). There was a significant correlation between PHES score and total ESS score (r = −0.383, P <0.0001), indicating association between poor cognition (MHE) and EDS.

Univariate analysis We studied the different factors such as; age, sex, etiology, presence of varices, ascites, serum bilirubin, serum ALT, serum alkaline phosphatase, serum albumin, serum urea, serum creatinine, presence or absence of hyponatremia (serum sodium < 135 mEq/L), hypokalemia (serum potassium < 3.5 mEq/L), INR, hemoglobin, total leukocyte counts, platelets, CTP score, MELD score and PHES among the two groups, with EDS and without EDS. Patients having EDS had lower serum ALT (P=0.031) and serum albumin (P=0.044) levels while they had higher INR (P=0.01), CTP score (P=0.024) with significant difference between the CTP classes (P= 0.039), higher MELD score (P=0.08), worse PHES scores (P<0.0001) and high prevalence of MHE (P<0.0001) (Table 4).

Multivariate analysis Multivariate analysis was applied for the above-mentioned significant variables to evaluate their impact on the presence of EDS in these patients. To find out the effect of age and etiology of cirrhosis (alcoholic versus non-alcoholic) on EDS we

Table 3 SF-36(v2) scores in good and poor sleepers

SF-36(v2) scores	Good sleepers* (n=40)	Poor sleepers* (n=60)	P value
Scales			
Physical health			
Physical functioning (PF)	71.75 (65.59−77.91)	61.33 (55.99−66.68)	0.013
Role-limitation physical (RP)	47.81 (41.51−54.11)	46.67 (39.78−53.55)	0.816
Bodily pain (BP)	74.78 (67.21−82.340	65.65 (58.47−72.83)	0.091
General health (GH)	43.63 (35.24−52.01)	41.22 (35.08−47.35)	0.635
Mental health			
Vitality (VT)	44.06 (39.04−49.08)	45.63 (40.19−51.06)	0.689
Social functioning (SF)	74.69 (66.57−82.81)	62.29 (56.42−68.16)	0.012
Role-limitation emotional (RE)	65.42 (58.42−72.42)	51.53 (44.91−58.14)	0.006
Mental health (MH)	60.75 (55.12−66.38)	57.33 (51.25−63.41)	0.435
Component summary			
Physical component summary (PCS)	43.96 (42.12−45.8)	42.16 (40.04−44.28)	0.233
Mental Component Summary (MCS)	41.71 (38.52−44.90)	38.15 (35.25−41.04)	0.107

*Data presented as mean (95 % confidence interval); SF-36(v2), Short Form 36, version 2

Table 4 Univariate and multivariate analysis of different parameters

Parameter	Univariate			Multivariate	
	No EDS* (*n*=62)	EDS* (*n*=38)	*P*	aOR	*P*
Age (years)	47.7 (45.3−50.1)	50.7 (47.4−54.0)	0.13		
Sex Male	54 (62.1 %)	33 (37.9 %)	1.0		
Female	8 (61.5 %)	5 (38.5 %)			
Etiology Alcohol	33 (60 %)	22 (40.0 %)	0.68		
Non Alcohol	29 (64.4 %)	16 (35.6 %)			
Education (years)	10.8 (9.8−11.7)	10.0 (8.6−11.5)	0.56		
Varices Yes	51 (58.6 %)	36 (41.4 %)	0.12		
No	11 (84.6 %)	2 (15.4 %)			
Ascites Yes	9 (47.4 %)	10 (52.6 %)	0.19		
No	53 (65.4 %)	28 (34.6 %)			
Bilirubin (mg/dL)	2.3 (1.6−3.1)	1.9 (1.5−2.4)	0.69		
ALT (IU/L)	54.4 (45.1−63.8)	39.9 (32.6−47.2)	0.031		
Alkaline Phosphatase (IU/L)	230.0 (166.6−293.4)	202.9 (164.2−241.7)	0.541		
Albumin (g/dL)	3.7 (3.5−3.8)	3.4 (3.2−3.6)	0.04		
Urea (mg/dL)	30.1 (27.1−33.1)	30.4 (25.5−35.3)	0.90		
Creatinine (mg/dL)	0.9 (0.9−1.0)	1.0 (0.9−1.1)	0.524		
Hyponatremia (Na^+ < 135 mEq/L)	6 (9.7 %)	4 (1.1 %)	1.0		
Hypokalemia (K^+ < 3.5 mEq/L)	2 (3.2 %)	3 (7.9 %)	0.365		
INR	1.4 (1.3−1.4)	1.5 (1.4−1.6)	0.01		
Hemoglobin (g/dL)	11.3 (10.8−11.8)	11.1 (10.5−11.8)	0.66		
Total leukocyte count (K/mm^3)	6.7 (5.8−7.6)	6.0 (5.2−6.8)	0.28		
Platelets (K/mm^3)	120 (107−138)	112 (95−130)	0.42		
CTP class A	39 (73.6 %)	14 (26.4 %)	0.039		
B & C	23 (48.9 %)	24 (51.1 %)			
CTP score	6.6 (6.1−7.1)	7.6 (6.9−8.3)	0.024		
MELD score	10.4 (9.2−11.5)	12.2 (10.4−14.0)	0.08		
PHES	−3.0 (−3.7 − −2.3)	−7.1 (−8.1 − −6.0)	<0.0001		
MHE	12 (26.1 %)	34 (73.9 %)	<0.0001	26.715 (7.717−92.478)	<0.0001

ESS Epworth sleepiness scale; *EDS* excessive daytime sleepiness; *aOR* adjusted Odd's ratio; Na^+ serum sodium levels; K^+ serum potassium levels; *K*=1000; *CTP* Child-Turcotte-Pugh; *MELD* model for end stage liver disease; *ALT* alanine aminotransferase; *INR* International Normalized Ratio; *PHES* psychometric hepatic encephalopathy score; *MHE* minimal hepatic encephalopathy; *NMHE* no minimal hepatic encephalopathy; *data presented as mean (95 % confidence interval) or as number (percentage)

also included these parameters in the multivariate analysis. On multivariate analysis, only the presence of MHE (P<0.0001) was found to be associated with EDS (Table 4).

Health-related quality of life BP, SF and RE were found to be significantly worse among those with EDS as compared to those without EDS (Table 5).

Correlation between ESS and SF-36(v2) scores There were significant correlations between ESS score and the SF-36(v2) scales of PF (r = −0.22, P = 0.02), BP (r = −0.25, P = 0.01), SF (r = −0.40, P <0.0001) and RE (r = −0.23, P = 0.02).

Discussion

The results of this study for the first time demonstrated the high prevalence of MHE among patients with cirrhosis who were poor sleepers and had EDS. Amongst 100 patients with cirrhosis of liver studied in this study, 60 (60 %) were 'poor sleepers', 40 (66.7 %) of whom had MHE and EDS were found in 38 (38 %), 34 (89.5 %) of whom had MHE. Multivariate analyses demonstrated that MHE status of the patients was independently associated with poor sleep status and EDS (both P<0.0001). This study also demonstrated a significant correlation between PHES score and total PSQI score and total ESS score, indicating association

Table 5 SF-36(v2) scores in patients with or without EDS

SF-36(v2) Scales	EDS (-)* (*n*=62)	EDS (+)* (*n*=38)	*P* value
Physical health			
Physical functioning (PF)	67.42 (61.89−72.95)	62.37 (56.25−68.49)	0.238
Role-limitation physical (RP)	46.88 (41.21−52.54)	47.53 (38.71−56.36)	0.895
Bodily pain (BP)	75.32 (69.03−81.61)	59.47 (50.76−68.18)	0.003
General health (GH)	41.53 (35.31−47.75)	43.24 (34.95−51.52)	0.739
Mental health			
Vitality (VT)	44.05 (39.65−48.45)	46.55 (39.44−53.66)	0.527
Social functioning (SF)	74.4 (68.93−79.86)	55.59 (47.45−63.74)	<0.0001
Role-limitation emotional (RE)	61.56 (55.71−67.41)	49.78 (41.01−58.55)	0.022
Mental health (MH)	60.0 (55.42−64.58)	56.58 (48.05−65.11)	0.439
Component summary			
Physical component summary (PCS)	43.32 (41.42−45.22)	42.16 (39.82−44.50)	0.447
Mental Component Summary (MCS)	41.14 (38.77−43.51)	37.01 (32.87−41.14)	0.063

*Data are presented as mean (95 % Confidence interval); SF-36(v2), Short Form 36, version 2; *EDS* excessive daytime sleepiness

between poor cognition (MHE) and poor sleep parameters, PSQI and EDS respectively.

The relationship between HE and sleep disturbances exhibited by patients with cirrhosis is debatable. Studies using HRQOL questionnaire have confirmed higher frequency of sleep disturbance in cirrhotic patients with MHE (Groeneweg et al. 1998; Prasad et al. 2007). The prevalence of sleep disturbance in patients with cirrhosis of liver varies between 26 % and 70 % depending upon the patient population studied and the heterogeneity of the assessment tools utilized (Cordoba et al. 1998; Bianchi et al. 2005; Mostacci et al. 2008; Montagnese et al. 2009). In the present study, among 100 consecutive cirrhotic patients, 60 % of the patients had night-time sleep disturbance and were labelled as 'poor sleepers', two-third of whom had MHE. Significant correlation between PHES score and the PSQI score further strengthens the relationship between poor cognition and poor sleep status. These findings are contrary to those reported by Montagnese et al. (2009) in a recent study, which showed no significant association between the presence of night time sleep disturbance and either the presence or degree of HE. A possible explanation for this contrast could be the very small number of MHE patients (*n*=9) studied in the latter study as compared to ours (*n*=46); also, differences in the population studied cannot be ruled out. Cordoba et al. (1998) and Bianchi et al. (2005) reported no difference in the prevalence of sleep disturbance in relation to psychometric performance, and Mostacci et al. (2008) had shown more pronounced night-time sleep disturbance and day time sleepiness among cirrhotic patients.

More recent data indicate that day-time sleepiness is part of the HE spectrum (Cordoba et al. 1998; Montagnese et al. 2009). In this study, EDS were found in 38 % of the patients, 34 (89.47 %) of whom were MHE patients. Multivariate analysis demonstrated that presence of MHE is independently associated with EDS. Significant correlation existed between PHES score and ESS score ($r = -0.383$, $P < 0.0001$). Although the study by Montagnese et al. (2009) did not show relationship between EDS and the presence of HE per se, it did reveal association between EDS and slowing of the EEG. The latter finding of their study gave a strong hint at the relationship between EDS and neuropsychiatric impairment as had been demonstrated in the current study. Same group from Padova reported that patients who complained of EDS had significantly slower EEG than their counterparts with no difficulties staying awake. EDS was also associated with both a history of HE, the presence of portal-systemic shunt and an increased risk of HE-related hospitalisation (De Rui et al. 2012). A recent study also lends support to the association between EDS and HE (Bersagliere et al. 2012).

We did not find any association between sleep disturbance and age, degree of liver dysfunction, etiology of cirrhosis or portal hypertension as has been reported earlier (Cordoba et al. 1998; Mostacci et al. 2008; Montagnese et al. 2009; Ichikawa et al. 2010).

Analysing the pathogenesis of the MHE and sleep disturbances would further help justify the findings of the current study. Rats with mild hyperammonemia show a significant reduction in rapid eye movement (REM) while higher levels of hyperammonemia was required to produce non-rapid eye movement (NREM) sleep time and increased sleep fragmentation (Llansola et al. 2012). Moreover, a recent study has shown that induced hyperammonemia had opposite effects on sleep and nap EEG changes among healthy volunteers and cirrhosis patients. The amount of NREM sleep displayed an increasing trend in healthy volunteers but not in patients. In addition, healthy volunteers showed a decrease in fast sleep EEG activity, while patients showed a reduction in delta activity, thus more superficial

and disturbed sleep.(Bersagliere et al. 2012) This highlights ammonia to be an important contributor for sleep disturbance among cirrhotics. Another factor that could contribute to these sleep alterations is neuroinflammation. Activation of microglia and increased levels of inflammatory cytokines and PGE2 have been demonstrated to contribute to sleep alterations in rats infected with *Trypanosoma brucei* (Kristensson et al. 2010). Neuroinflammation has also been shown to contribute to the cognitive and motor alterations in both PCS and hyperammonemic rats; treatment with ibuprofen restores learning ability and motor function in both rat models (Cauli et al. 2007; Rodrigo et al. 2010). Therefore, ammonia and proinflammatory cytokines may act synergistically to produce both to sleep disturbances and cognitive alterations in patients with MHE (Tranah et al. 2012). However this presumption needs further studies on the role of inflammation on sleep disturbance in these patients

HE is associated with the development of circadian abnormalities (De Cruz et al. 2012). Rats after porta-caval anastomosis, a model of MHE, showed disruption of circadian rhythms (Zee et al. 1991). This has been hypothesized that sleep disturbance in cirrhosis may be a manifestation of minor forms of encephalopathy (Cordoba et al. 1998). Earlier studies have attributed sleep disturbances in cirrhosis to circadian rhythm abnormalities or homeostatic sleep regulation or both. The existence of a "biologic clock" in the suprachiasmatic nucleus allows the body to anticipate external environment modifications during the day-night cycle (Zee et al. 1991; Steindl et al. 1995). However, recent study by Montagnese et al. (2010) had shown that neither any obvious association exists between circadian and impaired sleep quality, nor the plasma melatonin profile abnormalities exhibited by patients with mild to moderately decompensated cirrhosis have any relation to the sleep disturbances observed in this patient population.

Individuals with clinical sleep disorders have great impairment in quality of life (Zammit et al. 1999). Significant relationships were identified, in the present study, as in the Montagnese et al. study (2009) between HRQOL and the sleep–wake profile. In this study, impaired HRQOL was associated with night-time sleep disturbance as evident by significant correlation between the PSQI score and the various SF-36(v2) scales of PF, SF, BD and RE. Patients with sleep disturbances are reported to have compromised occupational adjustment, physical and social role functioning, and mental health. This could possibly explain the cause of impaired PF and SF among 'poor sleepers' in this study. Moreover, Bajaj et al. (2011a) have shown that cirrhotics and MHE patients have loss of slow wave sleep (SWS), referred to as deep sleep determining sleep restorative ability and sleep continuity, associated with reduced ghrelin levels. Gulbay et al. (2008) have shown a significant correlation between SWS and the SF-36 scales of PF, BP, GH and SF in a population of sleep related breathing disorders. Bodily pain is known to cause poor sleep, but it is also possible that sleep deprivation and poor sleep may increase the sensitivity of patients to pain (Affleck et al. 1996), supported by Leger et al. (2001) in his study where a strong link existed between insomnia and bodily pain, similar to the current study. Leger et al. (2001) have also categorically demonstrated significant correlation between sleep disturbance and RE, similar to the current study.

Daytime difficulties are not simply the result of sleep deprivation and improvement of night time sleep does not guarantee improvement in daytime symptoms (Means et al. 2000). In fact, previous studies suggest that both physical and mental components of the SF-36 are affected independently in patients with EDS and higher ESS scores (Gulbay et al. 2008), explaining the decline in SF and RE scales in our study was significantly related to diurnal sleepiness.

One of the limitations of this study was a cross sectional design with onetime assessment and may not reflect the true relationship between sleep disturbance and neuropsychiatric impairment. A model of assessment of sleep disturbance before and after reversal of the MHE status with treatment would better help in understanding the nature of the relationship. Future studies should focus on the impact of treatment of MHE (Prasad et al. 2007; Sidhu et al. 2011; Bajaj et al. 2011b) on the reversal of sleep disturbances in these patients.

In conclusion, both night time sleep disturbance and excessive daytime somnolence linked to the neuropsychiatric impairment in patients of cirrhosis and are significantly associated with the observed impairment in HRQOL. Further longitudinal studies are required to demonstrate the effect of reversal of MHE on the reversal of sleep disturbances in these patients.

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Conflicts of interest None

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