

# Etiology and prevalence of fatigue in chronic liver disease: clinical view

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## Introduction and aim

Fatigue is one of the most common and prominent symptoms in liver cirrhosis and was reported in 60–80% of these patients. The study outcome was to prospectively evaluate the etiology and the degree of fatigue and how to improve it in chronic liver disease patients.

## Patients and methods

A prospective cross-sectional study on fatigue in chronic liver diseases was conducted on 500 patients: 475 patients had hepatitis C virus (HCV) and 25 had combined HCV and hepatitis B virus. They were divided into five groups: group 1 included 100 patients with chronic hepatitis, group 2 included 100 patients with Child class A cirrhosis, group 3 included 100 patients with Child class B cirrhosis, group 4 included 100 patients with Child class C cirrhosis, and group 5 included 100 patients with hepatocellular carcinoma (HCC). They were administered the Fatigue Impact Scale and the Fatigue Severity Scale questionnaires (translated into Arabic) as well as subjected to laboratory investigations, abdominal ultrasonography, and upper endoscopy.

## Results

All (100%) patients complained of longstanding fatigue. HCC had the highest prevalence of high fatigue (65%) and Child class C cirrhosis had the longest fatigue duration. Female sex and anemia were significantly related to both the Fatigue Impact Scale and the Fatigue Severity Scale in each group separately and all patients collectively. Age had a significant relation with all patients collectively but not separately. Fatigue scores were related to Child score but not related to liver profile,  $\alpha$ -fetoprotein, varices, ascites, and HCV load.

## Conclusion

Correction of anemia, not liver profile, helps in alleviating fatigue in cirrhotic patients. Female patients suffered from fatigue more frequently compared with male patients. HCC patients had highest fatigue and patients with Child class C cirrhosis had longest fatigue indices.

## Keywords:

fatigue, Fatigue Impact Scale, Fatigue Severity Scale, hepatocellular carcinoma, hepatitis C virus liver disease, quality of life

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## Introduction

Fatigue is one of the most common and prominent symptoms in patients with liver cirrhosis and can result in reduced physical activity, constraints on daily life, and even a decrease in working hours and social activities. In early reports on the clinical profile of cirrhosis, fatigue was reported to be present in 60–80% of these patients [1–3].

However, because of difficulties in defining and treating fatigue, this symptom is often overlooked or minimized by physicians caring for patients with liver disease.

Fatigue experienced by patients with cirrhosis has many possible contributing factors, including the severity of liver disease, anemia, and psychological distress.

Several previous studies found no significant correlation between fatigue level and disease duration or severity in patients with primary biliary cirrhosis (PBC) [4].

The pathogenesis of fatigue in general is poorly understood and this holds true for fatigue in the setting of liver disease [5].

## Study outcome

The primary outcome of this study was to prospectively evaluate the etiology and degree of fatigue and how to improve it in patients with chronic liver disease.

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## Patients and methods

### Study population

This was a prospective cross-sectional study evaluating the causes and prevalence of fatigue in chronic liver diseases conducted on 500 patients, 475 patients with hepatitis C virus (HCV) and 25 patients with combined HCV and hepatitis B virus (HBV), who attended the Hepatogastroenterology and Tropical Medicine Department, Faculty of Medicine, Cairo University, and the Police Hospital during the period between 2011 and 2013. These patients were divided into five groups:

- (1) Group 1 included 100 patients with chronic hepatitis.
- (2) Group 2 included 100 patients with Child class A cirrhosis.
- (3) Group 3 included 100 patients with Child class B cirrhosis.
- (4) Group 4 included 100 patients with Child class C cirrhosis.
- (5) Group 5 included 100 patients with hepatocellular carcinoma (HCC).

### Patients' eligibility

We included (a) patients with chronic liver disease due to HCV or HBV (b) between 18 and 65 years of age and (c) not previously treated with any specific treatment for HCV or HBV.

Exclusion criteria were as follows: (a) presence of any other primary comorbidity (cardiac, renal, pulmonary, hematologic, etc.); (b) currently on or had a history of Peg/Riba therapy for HCV, and (c) severe psychiatric disease.

### Study course

This study was approved by the institutional review board and ethics committee based on the 1975 Declaration of Helsinki (revised in 2000). A signed informed consent was obtained from all patients. They were subjected to the following: (a) history taking and full clinical assessment; (b) laboratory investigations, including complete blood count, liver biochemical profile [bilirubin, aspartate aminotransferase, alanine aminotransferase (ALT), alkaline phosphatase (ALP), albumin, and international normalized ratio], fasting blood glucose, hepatitis markers (HBsAg, HBsAb, HBcAb, HCVAb), quantitative HCV RNA using PCR, serum urea and creatinine, antinuclear antibody, and serum  $\alpha$ -fetoprotein (AFP); (c) abdominal ultrasonography; (d) upper endoscopy (for the cirrhosis and HCC groups); and (e) Fatigue

Impact Scale (FIS) and Fatigue Severity Scale (FSS) questionnaires.

### Fatigue Impact Scale and Fatigue Severity Scale questionnaires

These two questionnaires score the effect of fatigue in chronic disease; both questionnaires were translated professionally and objectively into Arabic and each patient completed both questionnaires.

The FIS is based on the patient's perceived functional limitations and impact of fatigue on patients' quality of life (QoL), considering cognitive, physical, and psychosocial aspects. It consists of 10 cognitive, 10 physical, and 20 social questions. The total score has a maximum of 160 points and a minimum of 0 point. Higher scores are considerable merit as a measure of patient's attribution of functional limitations to symptoms of fatigue [6].

The FSS can be used to assess the level of fatigue in patients and to monitor its change over time or in response to therapeutic interventions. It consists of nine statements that need a graded response from strongly agree to strongly disagree (seven grades). The total score of the FSS has a maximum of 63 points and a minimum of 9 points [7].

The short form 36 (SF-36) scale was not used as it focuses mainly on vitality and physical functioning and includes questions on bodily pain, which is not a common symptom in chronic liver disease. However, the FSS and the FIS are better used for any disorder for which fatigue is a major clinical component.

### Statistical analysis

Data were coded and entered using the statistical package for the social sciences (SPSS; SPSS Inc., Chicago, Illinois, USA). Data were summarized using mean, SD, and range (minimum and maximum) for quantitative variables and number and percent for qualitative variables.

Comparisons between groups were made using the  $\chi^2$ -test and Fisher's exact test for qualitative variables. The independent sample *t*-test was used for normally distributed quantitative variables and for nonparametric the Mann-Whitney test was used for quantitative variables, which are not normally distributed; the same applied on all patients collectively. *P* values less than 0.05 were considered statistically significant.

## Results

### Basic characteristics

This study included 500 patients with chronic liver disease. There were 270 (54%) male and 230 (46%) female patients. In cirrhotic patients (groups 2–5), 100 (20%) patients were of Child class A, 120 (24%) were of Child class B, and 180 (36%) were of Child class C. Demographic data and baseline laboratory parameters are shown in Table 1. The HBV coinfecting patients were not removed from the study to make it applicable for different etiologies of chronic liver disease. Twelve (2.4%) patients in the study had mild controlled diabetes mellitus (DM) (as severe uncontrolled DM patients were excluded); the relation to fatigue was not determined due to the small number and mildness of DM.

All (100%) patients complained of longstanding fatigue. Patients were classified as high fatigue (FIS>40) or low fatigue (FIS<40). The HCC group had the highest prevalence of high fatigue, 65 (65%) patients. Moreover, the mean of the FIS and the FSS of all studied groups showed that the HCC group had the highest score. These results were statistically significant (Table 2).

However, the Child class C cirrhosis group had the longest fatigue duration (46±99 months), followed by the HCC group (41±34 months). This finding did not record statistical significance ( $P>0.05$ ).

### Relation of fatigue with different parameters

There was a significant relation between age and FIS and FSS scores as predictors of fatigue level when applied on all patients collectively ( $P=0.03$  for FIS and 0.04 for FSS) (Table 3), but the relation did not reach significance when applied on each group separately. We believe the significant relation appeared when patients were analyzed collectively due to the much larger number of patients included.

Female patients had higher fatigue scores compared with male patients in both the FIS and the FSS with statistical significance ( $P=0.002$  for FIS and 0.04 for FSS). These results were also reflected in each group separately. Female patients suffered fatigue more frequently either subjectively or objectively compared with male patients (Tables 3 and 4).

Patients with anemia had a significant relation, with higher scores in both fatigue scales among each group separately and all patients collectively (Tables 5 and 6). However, no significant relation was found between fatigue scales and white blood cell or platelet count in all groups.

The relation between smoking and fatigue level was significant in the HCC group, as there was a significant difference between those who had and those who did not have a previous history of smoking as regards the

**Table 1 Demographic data and baseline laboratory parameters of the studied groups**

Items	Group 1	Group 2	Group 3	Group 4	Group 5
Age (years)	37±8.5	49±16	53.8±8.5	55.8±8	61±6
Fatigue duration (ms)	15±9.9	26.5±10.8	26±10	46±99	41±34
Hb (g/dl)	13.7±1.4	12.6±1.7	11±1.5	10±1.4	10±1.2
Total leukocytic count (TLC) ( $\times 10^3/\mu\text{l}$ )	6.02±2	6.7±2	5±16	5.8±21	5.6±19
Platelet ( $\times 10^3/\mu\text{l}$ )	202.7±53	305±58	144±57.9	6.8±2	60±28
Total bilirubin (mg/dl)	0.96±0.2	1.5±0.4	2.5±0.4	6.7±2.5	6.3±3.3
AST (IU/l)	60±32	71.5±25.4	79±21.7	91.6±3.3	97±41
ALT (IU/l)	77±39	92±31.8	92.9±32.9	107±4.4	75±39
Albumin (g/dl)	4.9±1.4	3.8±0.3	2.9±0.36	2.3±0.2	2.9±0.4
INR	1.04±0.08	1.2±0.4	1.5±0.3	1.9±0.5	1.8±0.6
AFP (ng/ml)	7.4±8	16.7±20.9	21.5±28	38.4±43.6	150±14
HCV load ( $\times 10^3$ IU/ml)	306±656	315±666	330±674	1433±239	160±392

AFP,  $\alpha$ -fetoprotein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; Hb, hemoglobin; HCV, hepatitis C virus; INR, international normalized ratio.

**Table 2 Mean and grade of the Fatigue Impact Scale and the Fatigue Severity Scale in each group**

	Group 1	Group 2	Group 3	Group 4	Group 5	All patients
FIS						
Mean	32	39.5	42	47.9	78*	47.8
High (%)	40	60	45	50	65*	52
Low (%)	60	40	55	50	35	48
FSS	44	33	41	48	53	43.8

FIS, Fatigue Impact Scale; FSS, Fatigue Severity Scale. \* $P$ -value significant.

**Table 3** The relation between age, sex, smoking, and fatigue scales in all patients collectively

Items	N	FIS (mean±SD)	P-value	FSS (mean±SD)	P-value
Age (years)					
>55	210	<b>47.5±24.4</b>	0.03	<b>47.7±11.8</b>	0.04
<55	290	42.3±12.5		40.2±6.2	
Sex					
Female	230	<b>55±23</b>	0.002	<b>52±10.8</b>	0.04
Male	270	34.7±18.3		41.2±12.4	
Smoking					
Yes	295	40.2±22	NS	46±13.4	NS
No	205	41.4±12		43.8±11.8	
Smoking in the HCC group					
Yes	70	<b>44.2±20.4</b>	0.01	51.9±8.5	NS
No	30	71.8±19.9		56.6±4.9	

FIS, Fatigue Impact Scale; FSS, Fatigue Severity Scale; HCC, hepatocellular carcinoma. Significant values are in bold.

**Table 4** The relation between fatigue scales and sex in the five groups

Groups	Sex	N	FIS (mean±SD)	P-value	FSS (mean±SD)	P-value
Group 1	Female	35	<b>41±17</b>	0.04	<b>51±13.5</b>	NS
	Male	65	27±12.4		40±11.6	
Group 2	Female	40	<b>52±7.4</b>	0.03	<b>53±39</b>	0.02
	Male	60	31±15.7		31±12	
Group 3	Female	50	<b>55±30</b>	0.02	<b>46.4±15.5</b>	0.01
	Male	50	28.7±13.8		35.6±12.8	
Group 4	Female	40	<b>62.3±22.6</b>	0.03	<b>54.7±6.7</b>	0.002
	Male	60	38.3±23.4		43.6±6.6	
Group 5	Female	25	<b>74.6±23</b>	0.02	<b>58±3.9</b>	0.01
	Male	75	45.2±19		51±8.2	

FIS, Fatigue Impact Scale; FSS, Fatigue Severity Scale. Significant values are in bold.

FIS; strangely, the patients who had a history of smoking reported lower scores of fatigue ( $P=0.01$ ), but significant difference was not found in FSS.

The current study could not demonstrate a significant relation between the fatigue scales and any item of liver profile (bilirubin, aspartate aminotransferase, ALT, ALP, albumin, and international normalized ratio) ( $P>0.05$ ), but strangely higher FIS and FSS scores were reported with lower ALT and ALP (Table 7). This applied when the groups were studied separately or collectively.

In 220 (44%) patients with AFP more than 10, the FIS and FSS mean scores were  $46\pm24.6$  and  $45.8\pm12.3$ , respectively, whereas in 280 (56%) patients with AFP less than 10 the FIS and FSS mean scores were  $48.9\pm26$  and  $41.7\pm22$ , respectively. The relation was nonsignificant ( $P>0.05$ ). Moreover, HCV viral load had a nonsignificant relation with the FIS and the FSS ( $P>0.05$ ). These relations applied when the groups were studied separately or collectively.

The presence of esophageal varices in relation to FIS and severity scales showed a nonsignificant relation, as

345 (69%) patients with esophageal varices (OV) (45, 100, 100, and 100 patients in groups 2, 3, 4, and 5, respectively) had FIS and FSS mean scores of  $42.2\pm24.7$  and  $46\pm12.8$ , respectively. Moreover, 155 (31%) patients without OV had FIS and FSS scores of  $40.3\pm34.5$  and  $39.7\pm12.7$ , respectively ( $P>0.05$ ). This applied regardless of whether the groups were studied separately or collectively.

The presence of ascites in relation to the FIS and the FSS showed a nonsignificant relation, as 300 (60%) patients with ascites (all patients in 3, 4, and 5 groups) had FIS and FSS mean scores of  $46\pm24$  and  $46.6\pm11.7$ , respectively. Moreover, 200 (40%) patients without ascites had FIS and FSS mean scores of  $41\pm31.5$  and  $42.7\pm15.5$ , respectively ( $P>0.05$ ). This applied regardless of whether the groups were studied separately or collectively.

However, despite the absence of correlation of fatigue with parameters of liver function or ascites, fatigue scores increased with the increase in degree of liver dysfunction indicated by Child–Pugh scoring and this was statistically significant (Table 2).

**Table 5 The relation between fatigue scales and hemoglobin in the five groups**

Groups	Hb	N	FIS (mean±SD)	P-value	FSS (mean±SD)	P-value	
Group 1	Female	<12	0	–	–	–	
		>12	35	35.9±4.8		44.4±4.5	
	Male	<13	10	<b>44.5±3.5</b>	0.01	<b>57±2.8</b>	0.004
		>13	55	23.9±5		48.4±6.9	
Group 2	Female	<12	20	<b>32.3±13.4</b>	0.03	<b>39.5±16.6</b>	0.02
		>12	20	29.8±11		32.7±5.9	
	Male	<13	30	<b>37.2±11.5</b>	0.04	<b>40.1±14.2</b>	0.02
		>13	30	29±5.4		34.9±7.8	
Group 3	Female	<12	35	<b>38±16.6</b>	0.04	<b>42.5±18</b>	0.01
		>12	15	33±7.9		36±11.2	
	Male	<13	50	<b>41.8±12.5</b>	0.03	<b>46.1±10.2</b>	0.02
		>13	0	–		–	
Group 4	Female	<12	30	<b>33.8±18.6</b>	0.03	<b>37.5±11</b>	0.02
		>12	10	28.5±6.8		30.6±16	
	Male	<13	45	<b>39.4±13.9</b>	0.04	<b>40.1±9.4</b>	0.04
		>13	15	31±11.2		36±7.7	
Group 5	Female	<12	20	<b>49.9±14</b>	0.04	<b>51±13.9</b>	0.01
		>12	5	42		44.8	
	Male	<13	55	<b>52±19.3</b>	0.04	<b>53±12</b>	0.03
		>13	20	46±12.2		46±4.5	

FIS, Fatigue Impact Scale; FSS, Fatigue Severity Scale; Hb, hemoglobin. Significant values are in bold.

**Table 6 The relation between complete blood count and fatigue scales in all patients**

CBCs	No	FIS (mean±SD)	P-value	FSS (mean±SD)	P-value
Hb					
Female					
<12	125	<b>44.7±17.9</b>	0.02	<b>41±23.6</b>	0.01
>12	105	39.6±12.6		37.4±24.7	
Male					
<13	195	<b>47±11.8</b>	0.04	<b>43.7±13</b>	0.03
>13	75	41.8±13.9		39.1±11	
TLC					
<4×10 <sup>3</sup>	15	60±15.9	NS	56.2±6	NS
>4×10 <sup>3</sup>	485	54.1±11.8		44.9±24	
Platelet					
<150×10 <sup>3</sup>	325	59±22	NS	48.2±23.8	NS
>150×10 <sup>3</sup>	175	51±13.9		42.8±33	

CBC, complete blood count; FIS, Fatigue Impact Scale; FSS, Fatigue Severity Scale; Hb, hemoglobin. Significant values are in bold.

## Discussion

Fatigue in chronic liver disease significantly impacts the QoL, interfering with physical activity, family life, and job performance. The exact prevalence of fatigue in patients with chronic liver disease is somewhat variable in different studies and with different specific liver

diseases [8]. However, this high prevalence of fatigue does not appear to hold for patients infected with hepatitis C who are unaware of their diagnosis.

The importance of determining the health-related QoL has gained quite a momentum in the past few decades [9]. Since 1947, the WHO has redefined

**Table 7** The relation between liver profile and fatigue scales in all patients

Liver profile	N	FIS (mean±SD)	FSS (mean±SD)
Total bilirubin			
>1	261	47.2±24.6	47.1±11.3
<1	239	44±25.4	51.3±7.8
AST			
>50	336	47.5±23	48.3±11.7
<50	164	40.9±26.3	45±12.8
ALT			
>50	331	45±21.5	47.9±11.5
<50	169	48.5±24	51.1±9
Albumin			
<2.8	277	37.5±19.7	42.5±14.4
>2.8	223	44.2±12	39.4±24.6
INR			
>1	289	50.2±10.5	48.2±15
<1	211	48.4±12	47.6±12
ALP			
>104	266	44.7±23.9	45.2±24.9
<104	234	45.9±27	47.4±22.9

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; FIS, Fatigue Impact Scale; FSS, Fatigue Severity Scale; INR, international normalized ratio.

health as not only the absence of disease but also a complete state of physical, mental, and social well-being [10].

Among the various generic instruments developed to measure health-related quality of life (HRQoL) are the FIS and the FSS. The FIS measures both qualitative and quantitative aspects of fatigue to assess fatigue and its effect on the QoL. This tool consists of a questionnaire that scores the effect of fatigue on 40 aspects of day-to-day life. These aspects broadly pertain to psychosocial, cognitive, and physical activity [11].

The FSS is one of the best known and most frequently used fatigue scales. The name is, however, slightly misleading. The FSS principally measures the impact of fatigue on specific types of functioning rather than the intensity of fatigue-related symptoms [12].

One of the main strengths of this study is the inclusion of all stages of chronic liver disease (even HCC). Moreover, our use of the FSS and the FIS with their easy-to-respond questionnaires and reliable assessment of fatigue adds to the study.

The relation between age and fatigue level was significant, in our study, when all patients were studied collectively but not separately. In the study by Sumskiene *et al.* [13] on 131 patients with liver cirrhosis, they reported that there was only small and nonsignificant impairment with age ( $P>0.05$ ).

Moreover, Mahmood *et al.* [14] studied 120 chronic hepatitis C patients and reported that chronic liver disease score was unaffected by age. Similar results were found by Cauch-Dudek *et al.* [15], Huet *et al.* [1], and Prince *et al.* [11].

However, the results of Gao *et al.* [16] and Afendy *et al.* [17] on 392 patients and 1103 patients of chronic liver diseases, respectively, concluded that age correlated weakly but significantly ( $P<0.05$ ) with every scale of the SF-36 (HRQoL questionnaire). We believe the relation between fatigue and age was reported when all patients together were analyzed due to the much larger number included.

In our study, female patients had higher scores in the FIS and the FSS compared with male patients, with a significant correlation between female sex and the two scales. These results were also reflected in each group separately. The studies conducted by Miaskowski [18], Baldwin *et al.* [19], Gao *et al.* [16], and Afendy *et al.* [17] also showed significantly greater initial levels of fatigue in female patients compared with male patients.

In contrast, in a study by Sumskiene *et al.* [13] on 131 liver cirrhosis patients, they reported that sex did not show any effect on the QoL of liver cirrhosis patients.

Mechanisms behind the sex difference in the fatigue experience are not clear. A component of the explanation for higher rates of symptom reporting in women is that there are differences in the way symptoms are perceived, evaluated, and acted upon [20]. Women may have a lower threshold for symptom reporting [21] or a greater readiness to perceive physical sensations as symptoms of illness [22]. Other theories pertain to the way symptoms are measured. Differences in symptom reporting may be the result of an artifact of measurement.

Similarly, a research by Stommel *et al.* [23] found that certain items on the Centre for Epidemiologic Studies Depression Scale produced biased responses when comparisons were made on men's and women's responses to these items. It is possible that other instruments may have sex bias in items that may artificially raise women's levels of these symptoms. Research has suggested that women have a more expansive vocabulary for fatigue, including terms such as 'tiredness', 'reduced energy', and 'lack of vigor', which may affect the likelihood of fatigue being detected and could argue for use of a sex-specific fatigue taxonomy [19,24].

The cirrhosis Child C group, in our study, had the longest fatigue duration, followed by the HCC group. This finding could not be explained, as the highest scores of fatigue of both scales were found in the HCC group, and, by logic, usually the clinicians find more fatigue in HCC patients. However, probably these patients were not asked about the duration of their fatigue, and probably patients with Child class C cirrhosis had more fluid overload (edema and ascites) that was gained over a period of time owing to the longer duration of perception of fatigue.

In our study, there was no significant relation between any item of liver profile and the two fatigue scales. Atiq *et al.* [25] in their study that included 56 patients, with hepatitis C in 52 of them, found that there was no association between prothrombin time or albumin and the scores in the Chronic Liver Disease Questionnaire. Similarly, Younossi *et al.* [10] found that there was no correlation between ALT levels and poor Chronic Liver Disease Questionnaire scores. Rosa *et al.* [26] also found no correlation between fatigue and liver function tests.

Another study involving 116 patients reported that the severity of fatigue does not correlate with markers of liver disease severity, such as age, serum albumin, bilirubin, and prothrombin time [1]. They also found a lack of correlation between stage of liver histology in PBC and fatigue, as fatigue severity did not correlate with stage of liver disease when patients with grade I–II PBC were compared with patients with grade III–IV. However, Gao *et al.* [16] reported that hyperbilirubinemia and prolonging prothrombin time were important factors reducing HRQoL.

This lack of correlation between fatigue and liver biochemical profile may have a clinical implication. Physicians may focus on reducing liver enzymes to alleviate the fatigue of patients using drugs such as silymarin, methionine, etc. It is now obvious that the main focus to alleviate fatigue should be on modifying factors such as anemia or depression. The focus on the liver profile should be complimentary.

However, despite the absence of correlation of fatigue with different laboratory parameters of liver profile, fatigue scores increased progressively with the degree of liver dysfunction as indicated by Child–Pugh scoring and reported statistical significance. Thus, if liver profile with ascites were studied collectively (in a parameter model) in relation to fatigue scales, this could give a significant result.

Relation between viral load and fatigue level, in our study, was not found. Sinakos *et al.* [27] also found that correlations between HRQoL and viral load lost showed statistical significance. This finding coincides with other facts that negate the role of viremia level *per se* in the progress or severity of liver disease, such as the fact that viremia level does not correlate with transaminases or fibrosis levels in patients with HCV.

There was a nonsignificant correlation, in our study, between the presence of OV or ascites and fatigue level. However, Gao *et al.* [16] reported that the presence of varices and ascites had an effect on physical and mental health area of the SF-36 questionnaire, and hence it had an effect on HRQoL.

There was a significant relation between the two fatigue scales and anemia in our study. Dan *et al.* [28] also reported that anemia was associated with poorer HRQoL in HCV patients. However, Rosa *et al.* [26] reported different results as they found that hemoglobin abnormalities were only weakly related to FSS score.

The correlation of fatigue with anemia is logical, and fortunately some causes of anemia are modifiable. In chronic liver disease, a body cannot use its stored iron as erythropoietin is suppressed and the bone marrow does not respond normally. The shortage of iron and erythropoietin can result in a shortage of red blood cells [29]. Gastrointestinal bleeding may also contribute to blood loss. Thus, patients with chronic HCV, fatigue, and anemia may get benefit from workup of hematological indices, including folate, vitamin B<sub>12</sub>, and iron studies. Correction of anemia will then be feasible and will positively reflect on the QoL.

A significant inverse relation was found, in our study, between smoking and fatigue level in the HCC group but not other groups; strangely, the patients who had a history of smoking reported less scores of fatigue. This finding was also reported in the FSS but did not reach statistical significance. The explanation of this finding is not clear and other studies arguing or covering it were not found, and more studies are needed to discuss this point.

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## Conclusion

Fatigue is a prominent symptom in patients with liver cirrhosis. Thus, determining health-related QoL becomes necessary in managing cirrhotic patients. Correction of anemia but not liver profile may

improve fatigue in cirrhotic patients. Female patients and HCC patients had significant fatigue indices. Studies should be carried out on the role of cognitive behavior therapy and graded exercise therapy in the management of fatigue.

In the era of new direct acting antiviral (DAAs) for treatment of HCV, assessment of fatigue should be carried out after eradication of HCV in different stages of chronic liver disease to confirm whether or not fatigue is related to the presence of HCV.

Summary of strengths of the study:

- (1) This study shows the magnitude of the forgotten symptom 'fatigue' in chronic liver disease.
- (2) Fatigue was recorded in all patients with chronic liver disease.
- (3) Fatigue was related significantly to female sex and anemia.
- (4) Thus, correction of anemia but not liver profile helps in alleviating fatigue in cirrhotic patients.
- (5) Fatigue was not related to liver profile, AFP, varices, ascites, and HCV load.
- (6) Fatigue questionnaires should be presented to all liver disease patients and should be managed and not ignored.

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#### Conflicts of interest

There are no conflicts of interest.

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