How to Cite:
Hussain, H. M., Farooq, M., Fazal, N., & Mohummad, A. (2023). Etiology and prevalence of fatigue in chronic liver disease. *International Journal of Health Sciences*, *7*(S1), 17–24. https://doi.org/10.53730/ijhs.v7nS1.14145

Etiology and prevalence of fatigue in chronic liver disease

Dr Hadi Meeran Hussain
Consultant Physician PAF Hospital Lahore
Corresponding author email: drhadihussain234@gmail.com

Dr Mohummad Farooq
Head of Department of Medicine PAF Hospital, Lahore

Dr Nadeem Fazal
Head of Department of Medicine, Combined Military Hospital, Lahore

Dr Ali Mohummad
Classified Medical Specialist, PAF Hospital, Rafiqui

***Abstract*---**Background and Aim: One of the most common and obvious signs of liver cirrhosis is fatigue, which can limit daily activities, minimizes physical activity. Fatigue was reported to be prevalent in 60-80% of cirrhotic individuals in early publications on the clinical profile. The purpose of the current study was to evaluate the prevalence and etiology of fatigue in chronic liver disease. Patients and Methods: This cross-sectional study was carried out on 320 chronic liver disease patients in Department of Medicine PAF Hospital Lahore and Department of Gastroenterology CMH Lahore from June 2022 to December 2022. Study protocol was approved by institute ethical committee. We recruited (a) those who had ongoing liver disease caused by HCV or HBV, (b) patients between the ages of 16 and 70, and (c) patients who had not previously received any particular HCV or HBV therapy. Patients were divided into five groups: Group-I comprised of chronic hepatitis patients, Group-II had Child class A Cirrhosis, Group-III had Child class B cirrhosis, Group-IV had Child class C cirrhosis, and Group-V had hepatocellular carcinoma (HCC) patients. Patients were subjected to abdominal ultrasonography, laboratory investigations, and upper endoscopy. Fatigue was assessed and administrated using Fatigue Severity Scale questionnaires and Fatigue Impact Scale. Results: Of the total 320 patients, there were 186 (58.1%) male and 134 (41.9%) females. Patients were distributed as follows: Group-I, Group-II, Group-III, Group-IV, and Group-V. Each group had 64 patients. All the patients reported complaint of longstanding fatigue. High fatigue (FIS>40) and

International Journal of Health Sciences ISSN 2550-6978 E-ISSN 2550-696X © 2023.
Manuscript submitted: 09 Dec 2022, Manuscript revised: 18 Feb 2023, Accepted for publication: 27 March 2023

low fatigue (FIS<40) were the classifications of patients. Out of five groups, the group-V (HCC) had higher incidence (68.8%) of high fatigue patients. Additionally, FSS and FIS mean score was significantly higher than other groups. The longest fatigue duration (45±96 months) was observed in group-III (Child class C cirrhosis group) followed by HCC group (40±32 months) with no statistically significant. Conclusion: The present study found that fatigue is a common symptom in liver cirrhosis patients. Assessment of health-related QoL is therefore crucial in the treatment of cirrhotic patients. In cirrhotic people, fatigue may be reduced if anemia is treated but not the liver profile. Female and HCC patients reported significantly higher fatigue indices.

***Keywords*---**fatigue, chronic liver cirrhosis, fatigue severity scale, fatigue impact scale.

Introduction

Fatigue is the most prevalent symptom of chronic liver disease (CLD). Patients with ESLD frequently have weakness, malnutrition, and muscular atrophy. Fatigue significantly reduce the quality of life as a complication. Additionally, fatigue is an associated with social disorders, decreased working performance, and increased mortality rate [1]. The incidence of fatigue in chronic liver cirrhosis is quickly growing, owing in part to an increase nonalcoholic fatty liver disease (NAFLD) patients. Various factors such as viral hepatitis and primary biliary cholangitis (PBC) might be the causes for CLD [2, 3]. CLD care is generally focused on preventing cirrhosis advancement by liver cirrhosis effective complications in terms of end-stage liver disease and even liver transplantation and treatment [4]. Quality of life (QoL) might be adversely affected by chronic liver cirrhosis disease. Prior until now, treating symptoms has been considered incidental [5]. However, it is now becoming better acknowledged that CLD might lower quality of life (QoL) [6]. Related changes includes increasing fatigue, cognitive impairment, and poor appetites.

Peripheral or central are two categories of fatigue as a symptom of chronic liver disease was reported in numerous studies [7, 8]. Peripheral Fatigue is characterized by weakness in muscle and is linked to peripheral nervous system and muscular neuromuscular dysfunction [9, 10]. Recent investigations have documented abnormalities in muscle metabolism in CLD patients [11]. According to a previous study conducted on comparison of fatigue incidence in patients with and without chronic condition, chronic disease patients are more susceptible to fatigue as a prominent symptom [12]. This implies that fatigue is associated with a specific chronic condition. Moreover, because the incidence of severe exhaustion appears to differ between prolonged diseases. The link between conventional illness indicators (severity and activity) and weariness, on the other hand, is often low or non-existent. About 40% of T1DM patients have persistent fatigue, while fatigue is very marginally related to aberrant glucose parameters [13]. The current study sought to determine the incidence of chronic fatigue in patients with and without chronic disease.

Methodology

This cross-sectional study was carried out on 320 chronic liver disease patients in Medicine Department of Tertiary Care Hospital Lahore from June 2021 to December 2022. Study protocol was approved by institute ethical committee. We recruited (i) those who had ongoing liver disease caused by HCV or HBV, (ii) patients between the ages of 16 and 70, and (iii) patients who had not previously received any particular HCV or HBV therapy. Patients were divided into five groups: Group-I comprised of chronic hepatitis patients, Group-II had Child class A Cirrhosis, Group-III had Child class B cirrhosis, Group-IV had Child class C cirrhosis, and Group-V had hepatocellular carcinoma (HCC) patients as shown in Table-I. Patients were subjected to abdominal ultrasonography, laboratory investigations, and upper endoscopy. Fatigue was assessed and administrated using Fatigue Severity Scale questionnaires and Fatigue Impact Scale. Patients with comorbidities such as hematology, cardiac, and pulmonary, previously treated for HCV, and had severe mental disorder were excluded. Clinical assessment, history taking, laboratory investigations such as alkaline phosphate (ALP), complete blood count, fasting blood glucose, liver biochemical profile, and hepatitis markers were recorded. Fatigue impacting quality of life (QoL) and patient's perceived functional limitations were calculated based on FIS. FIS score has 160 point as a maximum point and o as minimum point [14]. Patient's fatigue level was assessed by FSS score that varies with time. The maximum and minimum assigned value of FSS total score is 63 and 9 points respectively [15].

SPSS version 27 was used for data analysis. For quantitative variables were expressed as mean and SD, whereas qualitative variables were described as frequencies and percentages. For qualitative variables, Fisher's exact test were used to compare groups. Statistical significance was defined as P values less than 0.05.

Table-I Patients distribution into different groups

Groups	Number
Group-I (chronic hepatitis patients)	64
Group-II (Child class A Cirrhosis)	64
Group-III (Child class B Cirrhosis)	64
Group-IV (Child class C Cirrhosis)	64
Group-V (HCC)	64
Total	320

Results

Of the total 320 patients, there were 186 (58.1%) male and 134 (41.9%) females. Patients were distributed as follows: Group-I, Group-II, Group-III, Group-IV, and Group-V. Each group had 64 patients. All the patients reported complaint of longstanding fatigue. High fatigue (FIS>40) and low fatigue (FIS<40) were the classifications of patients. Out of five groups, the group-V (HCC) had higher incidence (68.8%) of high fatigue patients. Additionally, FSS and FIS mean score was significantly higher than other groups. The longest fatigue duration (45±96 months) was observed in group-III (Child class C cirrhosis group) followed by HCC

group (40±32 months) with no statistically significant. Demographic details and baseline characteristics are shown in Table-II. Fatigue severity scale and fatigue impact scale mean and grade of each group is represented in Table-III. Association of fatigue score with different parameters such as age, gender, and smoking history are described in Table-IV. Table-V represents the association of fatigue score with gender in each group. Table-VI depicts the association of fatigue score with CBC. An association of fatigue score with liver profile are shown in Table-VII.

Table-II Demographic details and baseline characteristics

Variables	Group-I	Group-II	Group-III	Group-IV	Group-V
Age (yrs.)	35±7.6	46±14	49.9±9.7	52.6±7.8	59.7±6.3
Duration of Fatigue (months)	16±8.8	27.4±9.7	45±96	38±46	40±32
TLC $\times 10^3$	6.01±1.9	6.8±1.9	5.1±13	5.9±19	5.5±18
Hb (g/dL)	12.9±1.6	12.7±1.8	10.5±1.6	9.9±1.3	10±1.3
Total bilirubin (mg/dl)	0.95±0.1	1.4±0.3	2.4±0.3	6.8±2.6	6.2±3.1
Platelet ($\times 10^3/\mu l$)	201.5±51	302±55	142±56.5	6.7±1.9	59±26
AST (IU/l)	59±30	70.9±24.6	78±20.8	90.7±3.1	96±40
Albumin (g/dl)	4.8±1.3	3.7±0.4	2.8±0.37	2.2±0.3	2.8±0.5
ALT (IU/l)	76±38	91±30.6	91.8±31.8	106±4.3	74±38
AFP (ng/ml)	7.2±7	16.6±19.8	20.6±27	37.8±42.7	149±13

Table-III Fatigue severity scale and fatigue impact scale mean and grade of each group

Scores	Group-I	Group-II	Group-III	Group-IV	Group-V
FIS Mean	31.6	38.8	41.6	48.3	77.8
FSS	43	32	40	47	52

Table-IV Association of fatigue score with different parameters such as age, gender, and smoking history

Variables	Mean FIS score	Mean FSS	P-value
Age (yrs.)			0.03
<50 (N= 142 (44.4%))	41.6±11.6	40.6±7.1	
>50 (N=78 (55.6%)	46.6±23.8	47.8±10.9	
Gender			0.03
Male [186 (58.1%)]	33.9±16.8	40.5±10.5	
Females [134 (41.9%)]	54.6±22.8	51.8±11.9	
Smoking			NS*
Yes [189 (59.1%)]	39.6±21.6	45.6±12.7	
No [131 (40.9%)]	40.6±11.8	42.9±10.6	

*NS= Non-significant

Table-V association of fatigue score with gender in each group

Groups	Mean FIS score	Mean FSS	P-value
Group-I Male (N=41) Female (N=23)	 26.8±11.8 40±16	 39.8±10.8 50±12.7	NS
Group-II Male (N=43) Female (21)	 30±16.8 51±8.5	 31.4±11.9 52±38	0.01
Group III Male (N=32) Female (N=32)	 27.8±12.9 54±29	 34.8±11.9 45.8±14.6	0.01
Group-IV Male (N=43) Female (N=21)	 37.6±22.6 61.2±21.9	 42.8±7.5 53.8±7.8	0.02
Group-V Male (N=47) Female (N=17)	 44.6±18 73.8±22	 50±9.4 57±4.8	0.01

Table-VI an association of fatigue score with liver profile

CBCs variables	Mean FIS	Mean FSS	P-value
Hb (g/dL) Male Females	 44.4±12.9 31.3±15.3	 41.4±12 39.2±24.2	0.01
TLC $\times 10^3$	57.1±13.9	50.6±15	NS
Platelet	55±17.9	45.5±28.4	NS

Discussion

The present study mainly focused on the assessment of chronic liver cirrhosis disease patients for etiology and prevalence of fatigue and found that CLD patients had significant levels of Fatigue. Fatigue was associated to anemia and dyspnea, according to the univariate analysis. Our findings corroborate previous research that found an association between fatigue and anemia in patients of cirrhotic disease [16]. Dyspnea, a typical symptom in individuals with chronic liver disease, is directly linked to fatigue and significantly limits daily tasks and quality of life [17]. Fatigue is a common issue among end-stage liver transplant candidates [18]. It is crucial to note that measuring fatigue can be challenging, and numerous forms have been designed in CLD patients [19]. The FSS, a validated fatigue scale known to yield accurate findings in this situation, was used in this investigation [20].

The previous study also demonstrated the effect of multimorbidity on severe and chronic tiredness. The chance of developing severe and chronic tiredness increased significantly with each new chronic condition. Anxiety condition was connected with fatigue intensity in all chronic illnesses besides stroke and blood clotting problem. A previous study on post-stroke patients reported that fatigue and anxiety are associated to each other in CLD patients [21, 22].

Fatigue in chronic liver disease has a negative influence on quality of life, intrusive with work performance and physical activity. The actual incidence of tiredness in individuals with chronic liver disease varies across studies and between specific liver disorders [23]. Yet, this high incidence of weariness does not appear to apply to hepatitis C patients who are ignorant of their infection. The FIS and FSS are two general tools intended to assess health-related quality of life (HR-QoL). The FIS assesses fatigue and its impact on QoL by measuring both qualitative and quantitative components of tiredness. This instrument is a questionnaire that assesses the impact of tiredness on 40 facets of daily living [24, 25].

Fatigue could be easily assessed by well-known FSS tool. The FSS primarily assesses the fatigue impact on certain functioning categories as opposed to the fatigue-related symptoms severity [26]. In our investigation, the relationship between fatigue level and age was substantial upon analyzing these patients together. Female patients in our study had higher FIS and FSS scores compared to male patients, with a strong association between FIS and FSS scales with females. Such findings were replicated in patients independently. Lee et al. [27], Nevens et al. [28], Overman et al. [29], and Khanna et al. [30] all found that female patients had much higher initial levels of weariness than male patients.

In contrast, Hogan et al. [31] found that gender had no influence on the QoL of liver cirrhosis patients in a study of 131 individuals with the disease. The mechanisms behind the gender variation in tiredness sensation are unknown. In our study, the HCC group had the highest exhaustion scores on both measures, and doctors normally observe higher fatigue in HCC patients. This absence of association between fatigue and biochemical profile of the liver may have therapeutic implications. Doctors may focus on lowering liver enzymes to improve patients' fatigue by employing medications.

Conclusion

The present study found that fatigue is a common symptom in liver cirrhosis patients. Assessment of health-related QoL is therefore crucial in the treatment of cirrhotic patients. In cirrhotic people, fatigue may be reduced if anemia is treated but not the liver profile. Female and HCC patients reported significantly higher fatigue indices.

References

1. An K, Jallo N, Menzies V, et al. Integrative review of co-occurring symptoms across etiologies of chronic liver disease and implications for symptom management research and practice. J Nurs Scholarsh 2015; 47: 310-7.
2. Andersson M, Stridsman C, Ronmark E, Lindberg A, Emtner M. Physical activity and fatigue in chronic obstructive pulmonary disease - A population based study. Respiratory Medicine 2015; 109: 1048-1057.
3. Arcuri JF, Borghi-Silva A, Labadessa IG, Sentanin AC, Candolo C, Pires Di Lorenzo VA. Validity and Reliability of the 6-Minute Step Test in Healthy Individuals: A Cross-sectional Study. Clin J Sport Med. 2016;26:69-7.

4. Bhandari K, Kapoor D. Fatigue in cirrhosis. Journal of Clinical and Experimental Hepatology. 2022 Mar 1;12(2):617-24.
5. Chen SS, Yu KK, Huang C, et al. The characteristics and clinical outcome of drug-induced liver injury in a Chinese hospital: a retrospective cohort study. Medicine 2016; 95: 4683.
6. D'Mello C, Almishri W, Liu H, et al. Interactions between platelets and inflammatory monocytes affect sickness behavior in mice with liver inflammation. Gastroenterology 2017; 153: 1416-28.
7. D'Silva A, Fox DE, Nasser Y, Vallance JK, Quinn RR, Ronksley PE, Raman M. Prevalence and risk factors for fatigue in adults with inflammatory bowel disease: a systematic review with meta-analysis. Clinical Gastroenterology and Hepatology. 2022 May 1;20(5):995-1009.
8. De Bandt JP, Jegatheesan P, Tennoune-El-Hafaia N. Muscle loss in chronic liver diseases: the example of nonalcoholic liver disease. Nutrients 2018; 10: 1195.
9. Elliott C, Frith J, Day CP, et al. Functional impairment in alcoholic liver disease and non-alcoholic fatty liver disease is signifcant and persists over 3 years of follow-up. Dig Dis Sci 2013;58: 2383-91.
10. Fisk JD, Ritvo PG, Ross L, Haase DA, Marrie TJ, Schlech WF. Measuring the functional impact of fatigue: initial validation of the fatigue impact scale. Clin Infect Dis 1994; 18(Suppl 1):S79–S83.
11. Golabi P, Sayiner M, Bush H, et al. Patient-reported outcomes and fatigue in patients with chronic hepatitis C infection. Clin Liver Dis 2017; 21: 565-78.
12. Hogan PS, Chen SX, Teh WW, Chib VS. Neural mechanisms underlying the effects of physical fatigue on effort-based choice. Nat Commun. 2020 ;11(1):4026.
13. Janik MK, Wunsch E, Raszeja-Wyszomirska J, et al. Autoimmune hepatitis exerts a profound, negative effect on health-related quality of life: a prospective, single-centre study. Liver Int 2019; 39: 215-21.
14. Jopson L, Dyson JK, Jones DE. Understanding and treating fatigue in primary biliary cirrhosis and primary sclerosing cholangitis. Clin Liver Dis 2016; 20: 131-42.
15. Kaltsakas G, Antoniou E, Palamidas AF, Gennimata S, Paraskeva P, Smyrnis A, Koutsoukou A, Milic-Emili J, Koulouris NG. Dyspnea and respiratory muscle strength in end-stage liver disease. World J Hepatol. 2013;5:56-63.
16. Khanna A, Jopson L, Howel D, et al. Rituximab is ineffective for treatment of fatigue in primary biliary cholangitis: a phase 2 randomized controlled trial. Hepatology. 2018;. https://doi.org/10.1002/hep.30099.
17. Kośnik A, Wójcicki M. Fatigue in chronic liver disease patients: prevalence, pathophysiology, and management. Gastroenterology Review/Przegląd Gastroenterologiczny. 2022 Mar 18;17(1):21-7.
18. Krupp LB, LaRocca NG, Muir-Nash J, Steinberg AD. The fatigue severity scale. Application to patients with multiple sclerosis and systemic lupus erythematosus. Arch Neurol 1989; 46:1121–1123.
19. Lee JY, Danford CJ, Trivedi HD, et al. Treatment of fatigue in primary biliary cholangitis: a systematic review and meta-analysis. Dig Dis Sci 2019; 64: 2338-50.
20. Magalhães CB, Nogueira IC, Marinho LS, Daher EF, Garcia JHP, Viana CFG, et al. Exercise capacity impairment can predict post-operative pulmonary complications after liver transplantation. Respiration. 2017;94:272-8.

21. Moon AM, Singal AG, Tapper EB. Contemporary epidemiology of chronic liver disease and cirrhosis. Clin Gastroenterol Hepatol 2020; 18: 2650-66.
22. Nagy A Szabados E, Simon A, Mezey B, Sándor B, Tiringer I, Tóth K, Bencsik K & Csathó A Association of Exercise Capacity with Physical Functionality and Various Aspects of Fatigue in Patients with Coronary Artery Disease. Behav Med. 2016;44:28-35.
23. Nevens F, Andreone P, Mazzella G, et al. A placebo-controlled trial of obeticholic acid in primary biliary cholangitis. N Engl J Med. 2016; 375:631–643. https://doi.org/10.1056/NEJMoa1509840.
24. Overman CL, Kool MB, Da Silva JAP, Geenen R. The prevalence of severe fatigue in rheumatic diseases: an international study. Clin Rheumatol. 2016;35:409–415. https://doi.org/10.1007/s10067-015-3035-6.
25. Raszeja-Wyszomirska J, Wunsch E, Krawczyk M, et al. Assessment of health related quality of life in Polish patients with primary biliary cirrhosis. Clin Res Hepatol Gastroenterol 2016;40: 471-9.
26. Rossi D, Galant LH, Marroni CA. Psychometric property of fatigue severity scale and correlation with depression and quality of life in cirrhotics. Arq Gastroenterol. 2017; 54:344-8.
27. Salama ZA, Darweesh SK, Shehab HM, Abd-Elhameed MA. Etiology and prevalence of fatigue in chronic liver disease: clinical view. The Egyptian Journal of Internal Medicine. 2016 Jun; 28:78-85.
28. Silveira MG, Gossard AA, Stahler AC, et al. A randomized, placebo-controlled clinical trial of efficacy and safety: modafinil in the treatment of fatigue in patients with primary biliary cirrhosis. Am J Ther. 2017; 24:e167–e176. https://doi.org/10.1097/MJT.0000000000000387.
29. Swain MG, Jones DEJ. Fatigue in chronic liver disease: new insights and therapeutic approaches. Liver Int 2019; 39: 6-19.
30. Tandon P, Raman M, Mourtzakis M, Merli M. A practical approach to nutritional screening and assessment in cirrhosis. Hepatology. 2017;65:1044-57.
31. Woodhouse CA, Patel VC, Singanayagam A, et al. Review article: the gut microbiome as a therapeutic target in the pathogenesis and treatment of chronic liver disease. Aliment Pharmacol Ther 2018; 47: 192-202.