International Journal of General Medicine

Dovepress

open access to scientific and medical research

Open Access Full Text Article

ORIGINAL RESEARCH

Rate and Associated Factors of Fatigue in Chinese Patients with Non-Alcoholic Fatty Liver Disease: A Cross-Sectional Survey

Xian Du[1,*], Jun Hu[1,*], Jianhua Xue[1], Yuan Zhuang[2], Xuefeng Tang[1], Zhiyue Xu[1]

[1]Health Examination Center, Shanghai Health and Medical Center (Huadong Sanatorium), Wuxi, People's Republic of China; [2]The Affiliated Hospital of Nantong University, Nantong, People's Republic of China

*These authors contributed equally to this work

Correspondence: Zhiyue Xu; Xuefeng Tang, Health Examination Center, Shanghai Health and Medical Center (Huadong Sanatorium), 67 Dajishan, Wuxi, 214065, People's Republic of China, Email hepenxiaozi@163.com; 978665164@qq.com

Purpose: Fatigue was a common symptom of non-alcoholic fatty liver disease (NAFLD), which seriously affected patients' quality of life. The aim of this study was to detect fatigue rate and to evaluate factors associated with fatigue in NAFLD patients.

Patients and Methods: A cross-sectional study was carried out from the Huadong Sanatorium between April 2022 and May 2023, and 133 NAFLD patients were included in this study. They completed Fatigue Severity Scale to assess fatigue, the Hospital Anxiety and Depression Scale to estimate psychological status, and the Pittsburgh Sleep Quality Index for sleep quality. Data were analyzed by independent samples *t*-tests, $\chi 2$ tests and logistic regression models.

Results: We found that 51.1% of NAFLD patients had fatigue. Exercise, anxiety, depression, subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disorders, daytime dysfunction and overall sleep quality were related to fatigue among NAFLD patients. Moreover, logistic regression models indicated anxiety, habitual sleep efficiency and sleep disorders as important predictors of fatigue.

Conclusion: This was the first time to explore demographic, clinical, psychological and sleeping correlated factors for fatigue in Chinese NAFLD patients. Our study showed that more than half of NAFLD patients had fatigue, and anxiety, habitual sleep efficiency and sleep disorders were significantly associated with fatigue in NAFLD. The findings indicated that it was very necessary to pay more attention to fatigue of NAFLD patients, especially those with negative emotions and poor sleep quality by favorable intervention to relieve fatigue symptoms, so as to improve quality of life.

Keywords: non-alcoholic fatty liver disease, fatigue, exercise, anxiety, sleep

Introduction

Non-alcoholic fatty liver disease (NAFLD), characterized by the abnormal fat accumulation in liver without excessive alcohol intake, is a common chronic liver disease.[1] It is the fastest growing liver disease in the world and the main cause of hepatocellular carcinoma.[2] Research showed that the global prevalence of NAFLD based on imaging was about 30%, which may continue to increase in the coming years.[3,4] Fatigue was reported to be the most frequent clinical symptom in NAFLD.[5] The study assessing NAFLD patients from different countries indicated that fatigue was the independent predictor of lower patient-reported outcome scores.[6] Huber et al[7] also found that fatigue score was the lowest in terms of quality of life among NAFLD patients. Fatigue seriously affected NAFLD patients' quality of life.[8]

In patients with chronic liver disease, fatigue was associated with neuroinflammation and altered neurophysiological mechanisms.[9] Previous research found that hepatic inflammation through vagal afferent and uptake of pro-inflammatory cytokines enhanced brain's sense of fatigue.[10] NAFLD was considered to be an inflammatory response-related disease, and inflammatory burden and metabolic abnormalities may be involved in the development of fatigue in NAFLD

Received: 2 March 2024
Accepted: 25 June 2024
Published: 4 July 2024

patients.[11] Inflammatory markers and metabolic abnormalities could have a negative impact on patients' emotions, which may be the cause or result of fatigue.[12,13] The study pointed out that the level of cytokeratin 18 was found to correlate positively with patient fatigue.[14] Interestingly, cytokeratin 18 serum levels were higher in NAFLD participants than in other chronic liver patients.[15] Moreover, the most common types of fatigue in patients with chronic liver disease were central and peripheral fatigue. Central fatigue was characterized by a lack of self-motivation, while peripheral fatigue typically manifested itself in neuromuscular dysfunction and muscle weakness. Fatigue could manifest itself as a lack of intention and inability to exercise.[8] Data from a cohort study showed that fatigue in NAFLD was associated with inactivity and excessive daytime sleepiness but not with liver disease severity or insulin resistance.[16] Newton et al[17] reported that fatigue had a strong relationship with the symptom of autonomic dysfunction and daytime sleepiness in patients with NAFLD. However, due to the complexity of fatigue, potential biological mechanisms and related factors of fatigue are still unclear.

Although NAFLD patients suffer from severe fatigue, only few studies related to fatigue have been conducted in China. The purpose of our cross-sectional study is 1) to investigate fatigue rate among NAFLD patients and 2) to evaluate demographic, clinical, psychological and sleeping related factors for patients' fatigue.

Materials and Methods

Participants

Patients were recruited from the Health Examination Center of Huadong Sanatorium between April 2022 and May 2023. A total of 138 NAFLD patients from the health examination center were invited to participate in a cross-sectional study, and 5 NAFLD patients did not complete the questionnaires, so 133 patients (96.4%) were eventually included in this study. The Chinese Guidelines for Diagnosis and Treatment of Non-Alcoholic Fatty Liver Disease (2018 Updated Edition) was used as the reference standard for the diagnosis of NAFLD patients, and all patients fulfilled NAFLD diagnostic criteria based on the evidence of ultrasound, computed tomography or magnetic resonance imaging in 6 months. Patients were excluded if they had any of the following points: 1) they had liver injury or hepatic steatosis due to other reasons (such as excess alcohol consumption or hepatitis virus, etc.); 2) they had comorbidities (for instance, malignancy, cardiopathy, respiratory or autoimmune diseases) that could affect fatigue; and 3) they had psychological diseases or the cognitive impairment. This study was approved by the Ethics Committee of the Huadong Sanatorium, and written informed consents were acquired from all Participants based on the Declaration of Helsinki.

Demographic and Clinical Characteristics

Demographic and relevant characteristic data included sex, age, body mass index (BMI), marital status, education level, occupation, yearly income, tobacco and alcohol usage, and exercise. Clinical data by viewing medical records combining with patients' self-report contained the levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), fasting plasma glucose (FPG), triglyceride (TG) and total cholesterol (TC).

Assessment of Patient-Reported Outcomes

Fatigue Severity Scale (FSS): We used the FSS to assess the severity of fatigue. It consisted of nine items: the cause of fatigue (item 2), fatigue experience itself (item 3), and how fatigue affected daily life (seven items). The subjects were asked to rate each item on a scale of 1 (completely disagree) to 7 (completely agree). The average score for the nine items was the final score, and higher scores indicated more fatigue. A cutoff score ≥ 4 was reliably used to differentiate subjects with fatigue from the controls, and the FSS had been proved to have reliability, high sensitivity and internal consistency in fatigue assessment.[13,18,19]

The Hospital Anxiety and Depression Scale (HADS): The HADS was used to estimate psychological status. This questionnaire contained fourteen items, and anxiety and depression were scored separately by the seven-item subscales. The higher the score (ranging from 0 to 21), the more severe the mood disorder.[20]

The Pittsburgh Sleep Quality Index (PSQI): We used PSQI to evaluate sleep quality. The scale had nineteen questions including seven aspects (subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disorders,

use of sleep medications and daytime dysfunction). The score of each section ranging from 0 (best) to 3 (worst sleep properties) was added to get an overall score, with the higher score demonstrating the worse sleep quality.[21]

Data Collection

Questionnaires and assessments were administered to all participants. Participants filled in questionnaires by themselves with the physician or nurse present. After finishing data collected, the results were calculated by nurses and then added to a computer database by two research assistants who had carefully examined original data.

Statistical Analysis

Descriptive analyses were performed using number (percentage) or mean (±standard deviation) depending on according to type and distribution of measured variables. The differences based on continuous variables and categorical variables were, respectively, measured with the *t* tests and $\chi 2$ tests in NAFLD patients who were grouped into non-fatigued patients and fatigued patients. Through univariate tests, all variables significantly associated with fatigue were included into the logistic regression models with dichotomous fatigue evaluated by FSS as the dependent variable. $P < 0.05$ (two-sided) was considered statistically significant, and we used SPSS (version 23.0) to analyze data.

Results

Patient Characteristics

Table 1 shows the demographic and clinical characteristics of participants. The majority of included patients were male (69.2%). Patients in this study had a mean (SD) age of 46.65 (9.43) years and a mean (SD) BMI of 27.48 (3.35) kg/m^2. About 32.3% of the patients smoked and more than half of the patients (51.9%) drank alcohol; 30.1% NAFLD patients

Table 1 Demographic and Clinical Characteristics of NAFLD Patients (n = 133)

Variables	Descriptives
Sex, male, n (%)	92 (69.2)
Age, mean ± SD, y	46.65 ± 9.43
BMI, mean ± SD, kg/m^2	27.48 ± 3.35
Marital status, n (%)	
Married	121 (91.0)
Unmarried	12 (9.0)
Education, n (%)	
≤12 years	21 (15.8)
>12 years	112 (84.2)
Occupation, n (%)	
White collar	62 (46.6)
Blue collar	10 (7.5)
Others	54 (40.6)
Unemployed	7 (5.3)

(*Continued*)

Table 1 (Continued).

Variables	Descriptives
Yearly income, n (%)	
<Local average	8 (6.0)
Local average	69 (51.9)
>Local average	56 (42.1)
Smoking use, n (%)	
Yes	43 (32.3)
No	90 (67.7)
Alcohol use, n (%)	
Yes	69 (51.9)
No	64 (48.1)
Exercise, n (%)	
Often	25 (18.8)
Occasionally	68 (51.1)
Hardly	40 (30.1)
ALT, mean ± SD, u/L	34.86 ± 21.30
AST, mean ± SD, u/L	22.92 ± 10.30
FPG, mean ± SD, mmol/L	6.02 ± 1.49
TG, mean ± SD, mmol/L	2.14 ± 1.32
TC, mean ± SD, mmol/L	5.02 ± 0.90

Abbreviations: NAFLD, non-alcoholic fatty liver disease; BMI, body mass index; ALT, alanine aminotransferase; AST, aspartate aminotransferase; FPG, fasting plasma glucose; TG, triglyceride; TC, total cholesterol.

hardly exercise. The mean (SD) of ALT, AST, TG and TC were 34.86 (21.30) u/L, 22.92 (10.30) u/L, 2.14 (1.32) mmol/L and 5.02 (0.90) mmol/L, respectively.

Self-Reported Fatigue

In previous studies, Fatigue Severity Scale was used to evaluate patients' fatigue level with 4 points as its cutoff.[13,19,22] According to this, 65 (48.9%) NAFLD patients had no fatigue and 68 (51.1%) patients had fatigue.

Differences Between Non-Fatigued and Fatigued Patients with NAFLD

Table 2 presents the differences in demographic, clinical, psychological and sleeping characteristics between NAFLD non-fatigued patients and NAFLD fatigued patients. Exercise ($p = 0.036$), subjective sleep quality ($p = 0.010$), sleep latency ($p = 0.001$), sleep duration ($p = 0.044$), habitual sleep efficiency ($p = 0.010$), sleep disorders ($p = 0.036$) and daytime dysfunction ($p = 0.003$) were associated with fatigue. Compared with NAFLD non-fatigued patients, fatigued patients tended to have higher levels of anxiety and depression and poorer overall sleep quality ($p < 0.001$). However, there were no significant differences in terms of laboratory-related indicators.

Table 2 Differences Between Non-Fatigued Patients and Fatigued Patients in NAFLD

Variables	FSS<4 (n = 65)	FSS≥4 (n = 68)	p value
Male	45 (69.2)	47 (69.1)	0.989
Age, y	47.77 ± 9.36	45.57 ± 9.45	0.181
BMI, kg/m^2	27.37 ± 3.03	27.59 ± 3.64	0.710
Marital status			0.083
Married	62 (95.4)	59 (86.8)	
Unmarried	3 (4.6)	9 (13.2)	
Education			0.726
≤12 years	11 (16.9)	10 (14.7)	
>12 years	54 (83.1)	58 (85.3)	
Occupation			0.774
White collar	31 (47.7)	31 (45.6)	
Blue collar	6 (9.2)	4 (5.9)	
Others	24 (36.9)	30 (44.1)	
Unemployed	4 (6.2)	3 (4.4)	
Yearly income			0.698
<Local average	4 (6.2)	4 (5.9)	
Local average	36 (55.4)	33 (48.5)	
>Local average	25 (38.5)	31 (45.6)	
Smoking use			0.263
Yes	18 (27.7)	25 (36.8)	
No	47 (72.3)	43 (63.2)	
Alcohol use			0.196
Yes	30 (46.2)	39 (57.4)	
No	35 (53.8)	29 (42.6)	
Exercise			0.036*
Often	18 (27.7)	7 (10.3)	
Occasionally	29 (44.6)	39 (57.4)	
Hardly	18 (27.7)	22 (32.4)	
ALT, u/L	34.03 ± 20.95	35.65 ± 21.76	0.664
AST, u/L	22.92 ± 10.35	22.92 ± 10.34	0.997
FPG, mmol/L	6.09 ± 1.40	5.94 ± 1.57	0.557
TG, mmol/L	2.32 ± 1.64	1.96 ± 0.90	0.115

(*Continued*)

Table 2 (Continued).

Variables	FSS<4 (n = 65)	FSS≥4 (n = 68)	p value
TC, mmol/L	4.97 ± 0.92	5.07 ± 0.89	0.516
HADS-A	1.57 ± 1.78	4.34 ± 3.26	0.000*
HADS-D	2.54 ± 2.24	4.35 ± 2.64	0.000*
Subjective sleep quality	1.03 ± 0.53	1.29 ± 0.62	0.010*
Sleep latency	0.58 ± 0.79	1.10 ± 0.98	0.001*
Sleep duration	1.09 ± 0.70	1.38 ± 0.93	0.044*
Habitual sleep efficiency	0.22 ± 0.52	0.50 ± 0.72	0.010*
Sleep disorders	1.11 ± 0.40	1.29 ± 0.60	0.036*
Use of sleep medications	0.08 ± 0.44	0.04 ± 0.36	0.641
Daytime dysfunction	0.23 ± 0.42	0.49 ± 0.53	0.003*
PSQI total	4.34 ± 2.25	6.10 ± 3.13	0.000*

Note: *$P < 0.05$.
Abbreviations: NAFLD, non-alcoholic fatty liver disease; FSS, Fatigue Severity Scale; BMI, body mass index; ALT, alanine aminotransferase; AST, aspartate aminotransferase; FPG, fasting plasma glucose; TG, triglyceride; TC, total cholesterol; HADS, the Hospital Anxiety and Depression Scale; PSQI, the Pittsburgh Sleep Quality Index.

Table 3 Logistic Regression Analysis of Demographic, Clinical, Psychological and Sleeping Variables Associated with FSS in NAFLD Patients

Predictors	Beta	SE	p value	Exp (B)	(95% CI)
HADS-A	0.579	0.112	0.000	1.784	1.433,2.222
Habitual sleep efficiency	0.956	0.367	0.009	2.602	1.267,5.342
Sleep disorders	1.390	0.500	0.005	4.014	1.508,10.687

Abbreviations: NAFLD, non-alcoholic fatty liver disease; FSS, Fatigue Severity Scale; HADS, the Hospital Anxiety and Depression Scale.

Determinants of Fatigue in NAFLD

As indicated in Table 3, we used logistic regression analysis to explore predictors of NAFLD patients' fatigue. HADS-A (odds ratio = 1.784, $p < 0.001$), habitual sleep efficiency (odds ratio = 2.602, $p = 0.009$) and sleep disorders (odds ratio = 4.014, $p = 0.005$) were found to be predictors of fatigue.

Discussion

Research reported that the prevalence of fatigue in patients with chronic liver disease was as high as 50%–85%, and fatigue was also common in NAFLD patients, which seriously affected patients' daily living activities and continuously increased the disease burden.[13,23,24] However, few studies have been conducted to explore fatigue in Chinese NAFLD patients. In this study, we used FSS to assess patients' fatigue and also found that over half of Chinese NAFLD patients (51.1%) had fatigue. A study encompassing 18 countries in 6 global burden of disease super-regions also showed that fatigue scores were lower in NAFLD than general population norms.[6] Therefore, fatigue in NAFLD patients was a serious problem requiring global attention.

Previous studies have indicated that exercise was a foundational treatment for NAFLD and it could improve mitochondrial function and lead to reduced hepatic steatosis, inflammation, fibrosis, and tumor genesis.[25,26] Exercise-induced changes of serotonin concentrations in signal transduction between neurons may affect patients' fatigue level.[27] Glass et al[28] found through investigation that 72% of patients with NAFLD reported limitations to exercise and fatigue was a very important factor affecting their exercise. Similarly, our study showed that exercise was associated with fatigue, and fatigued patients in NAFLD were more reluctant to exercise than non-fatigued patients. The study found that Sarcopenia, characterized by decreased muscle strength and mass, was common in NAFLD, and Sarcopenia may be an additional factor preventing increased physical activity and lifestyle changes. The adverse effect of this condition could worsen fatigue symptoms, resulting in a lack of willingness to exercise.[29] Research reported that self-efficacy and illness understanding were major determinants of lifestyle-modification among NAFLD patients.[30] This suggested that active intervention (regular follow-up communication, etc.) was necessary for NAFLD patients, especially those with fatigue, to help them improve their cognition of disease and understand benefits of reasonable exercise, so as to alleviate fatigue.

A recent systematic review and meta-analysis concluded that compared with the control group, patients with NAFLD had a significantly increased risk of depression.[31] These negative emotions, such as anxiety and depression, could damage patients' quality of life.[32] The study indicated that fatigue was associated with psychological conditions.[33] However, the results of a study from the United States showed that fatigue was closely correlated with depression in Hepatitis C but was not related to depression in NAFLD.[34] In our study, we found that HADS-A and HADS-D scores were markedly higher in NAFLD fatigued patients than in NAFLD non-fatigued patients. Furthermore, the logistic regression analysis suggested that HADS-A played a significant role in fatigue. The possible explanation for this was that NAFLD patients' psychological pressure and bad emotions may lead to the uncomfortable experience of fatigue. This demonstrated that systematic psychiatric screening and management should be implemented to early detect high-risk patients and help them enhance their ability to deal with negative emotions, ultimately relieving fatigue symptoms.

Sleep quality played a role in NAFLD risk and severity.[35,36] Studies showed that sleep efficiency, sleep disturbance score and sleep quality score differed significantly in NAFLD compared to controls.[37] Fatigue was reported to be associated with increased daytime somnolence, impaired working ability, and increased risk of mortality.[38] Previous research indicated that daytime sleepiness was related to fatigue in NAFLD patients.[16,17] Daytime sleepiness could result in poor sleep at night and frequent night awakenings, and this sleep disorder made patients feel tired. In the present study, we also found a significant relationship between sleep and fatigue in NAFLD, and logistic regression analysis showed that the sleep disorders had negative effects on fatigue, which was consistent with previous studies. Tana et al[39] through a prospective study in patients with chronic liver disease reported that fatigue severity was positively associated with higher peak melatonin levels and a delay in night-time melatonin peak and inversely associated with sleep efficiency. Interestingly, few studies have mentioned the relationship between sleep efficiency and fatigue in NAFLD, and our study found that habitual sleep efficiency was an important predictor of fatigue. It may be due to the reason that sleep efficiency could affect overall sleep quality, leading to patient fatigue. Therefore, we should encourage patients to develop good sleep habits, correct sleep disorders, and help them address confounding factors affecting sleep efficiency such as night pain and itching, which can improve overall sleep quality and reduce fatigue level.

To our knowledge, this study was the first to assess demographic, clinical, psychological and sleeping related factors for fatigue in Chinese patients with NAFLD. However, our study still had several limitations. First, since all NAFLD patients enrolled in our study were from a single center, generalizations of the results to other populations should be cautious. Second, relatively subjective measurement of fatigue may result in some deviations due to the lack of an objective standard for fatigue. Third, causal relationships between variables could not be examined on account of cross-sectional design. Future research will further understand the development of fatigue over time through longitudinal studies and take effective interventions according to the characteristics of fatigue development and fatigue-related factors to relieve fatigue symptoms in NAFLD patients.

Conclusion

This was the first known assessment of fatigue based on demographic, clinical, psychological and sleeping correlated factors in Chinese patients with NAFLD using FSS, HADS and PSQI. Our study found that 51.1% of Chinese NAFLD patients had fatigue, and anxiety, habitual sleep efficiency and sleep disorders had significant impacts on fatigue in NAFLD. These results suggested that more attention should be paid to fatigue of NAFLD patients and more effective measures such as the popularization of disease-related knowledge, psychological interventions and sleep guidance should be taken to relieve fatigue symptoms and finally improve patients' quality of life.

Acknowledgments

We declare that Zhiyue Xu and Xuefeng Tang contributed equally as co-corresponding authors. We acknowledge other members of the team for their assistance with this study.

Funding

This work was supported by "Qi Ming Xing" Young Medical Talents Training Program (grant number 2023QMX07) and the Youth Talents Project of Shanghai Health and Medical Center (grant number 202017).

Disclosure

The authors report no conflicts of interest in this work.

References

1. Hwang SJ, Choi YJ, Wang JH, Son CG. Lactobacillus casei-fermented amomum xanthioides mitigates non-alcoholic fatty liver disease in a high-fat diet mice model. *Biomed Pharmacother*. 2024;172:116250. doi:10.1016/j.biopha.2024.116250
2. Huang DQ, El-Serag HB, Loomba R. Global epidemiology of NAFLD-related HCC: trends, predictions, risk factors and prevention. *Nat Rev Gastroenterol Hepatol*. 2021;18(4):223–238. doi:10.1038/s41575-020-00381-6
3. Le MH, Yeo YH, Li X, et al. 2019 Global NAFLD Prevalence: a Systematic Review and Meta-analysis. *Clin Gastroenterol Hepatol*. 2022;20 (12):2809–2817. doi:10.1016/j.cgh.2021.12.002
4. Zhang R, Zhang Q, Cui Z, Huang B, Ma H. Dimethyl fumarate restores Ca2+ dyshomeostasis through activation of the SIRT1 signal to treat nonalcoholic fatty liver disease. *Life Sci*. 2024;341:122505. doi:10.1016/j.lfs.2024.122505
5. Castellanos-Fernández MI, Crespo-Ramírez E, Del Valle-Díaz S, et al. Non-alcoholic fatty liver disease in Cuba. *MEDICC Rev*. 2021;23(1):64–71. doi:10.37757/MR2021.V23.N1.11
6. Younossi ZM, Yilmaz Y, Yu ML, et al. Clinical and patient reported outcomes from patients with non-alcoholic fatty liver disease across the world: data from the global NASH/NAFLD registry. *Clin Gastroenterol Hepatol*. 2021;20(10):2296–2306.e6.
7. Huber Y, Boyle M, Hallsworth K, et al. Health-related quality of life in nonalcoholic fatty liver disease associates with hepatic inflammation. *Clin Gastroenterol Hepatol*. 2019;17(10):2085–2092. doi:10.1016/j.cgh.2018.12.016
8. Golubeva JA, Sheptulina AF, Yafarova AA, Mamutova EM, Kiselev AR, Drapkina OM. Reduced quality of life in patients with non-alcoholic fatty liver disease may be associated with depression and fatigue. *Healthcare*. 2022;10(9):1699. doi:10.3390/healthcare10091699
9. Funuyet-Salas J, Martín-Rodríguez A, Pérez-San-Gregorio MÁ, et al. Health-related quality of life in non-alcoholic fatty liver disease: a cross-cultural study between Spain and the United Kingdom. *PLoS One*. 2024;19(5):e0300362. doi:10.1371/journal.pone.0300362
10. Swain MG, Jones DEJ. Fatigue in chronic liver disease: new insights and therapeutic approaches. *Liver Int*. 2019;39(1):6–19. doi:10.1111/liv.13919
11. Yamamura S, Nakano D, Hashida R, et al. Patient-reported outcomes in patients with non-alcoholic fatty liver disease: a narrative review of chronic liver disease questionnaire-non-alcoholic fatty liver disease/non-alcoholic steatohepatitis. *J Gastroenterol Hepatol*. 2021;36(3):629–636. doi:10.1111/jgh.15172
12. Fava M, Ball S, Nelson JC, et al. Clinical relevance of fatigue as a residual symptom in major depressive disorder. *Depress Anxiety*. 2014;31 (3):250–257. doi:10.1002/da.22199
13. Gerber LH, Weinstein AA, Mehta R, Younossi ZM. Importance of fatigue and its measurement in chronic liver disease. *World J Gastroenterol*. 2019;25(28):3669–3683. doi:10.3748/wjg.v25.i28.3669
14. Alt Y, Grimm A, Schlegel L, et al. The impact of liver cell injury on health-related quality of life in patients with chronic liver disease. *PLoS One*. 2016;11(3):e0151200. doi:10.1371/journal.pone.0151200
15. Darweesh SK, AbdElAziz RA, Abd-ElFatah DS, et al. Serum cytokeratin-18 and its relation to liver fibrosis and steatosis diagnosed by FibroScan and controlled attenuation parameter in nonalcoholic fatty liver disease and hepatitis C virus patients. *Eur J Gastroenterol Hepatol*. 2019;31 (5):633–641. doi:10.1097/MEG.0000000000001385
16. Newton JL, Jones DE, Henderson E, et al. Fatigue in non-alcoholic fatty liver disease (NAFLD) is significant and associates with inactivity and excessive daytime sleepiness but not with liver disease severity or insulin resistance. *Gut*. 2008;57(6):807–813. doi:10.1136/gut.2007.139303
17. Newton JL. Systemic symptoms in non-alcoholic fatty liver disease. *Dig Dis*. 2010;28(1):214–219. doi:10.1159/000282089
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(10):1121–1123. doi:10.1001/archneur.1989.00520460115022
19. Van Den Berg-Emons R, Van Ginneken B, Wijffels M, et al. Fatigue is a major problem after liver transplantation. *Liver Transpl*. 2006;12 (6):928–933. doi:10.1002/lt.20684

20. Bjelland I, Dahl AA, Haug TT, Neckelmann D. The validity of the hospital anxiety and depression scale. An updated literature review. *J Psychosom Res*. 2002;52(2):69–77. doi:10.1016/S0022-3999(01)00296-3
21. Buysse DJ, Reynolds CF, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry Res*. 1989;28(2):193–213. doi:10.1016/0165-1781(89)90047-4
22. Du X, Zhao Q, Zhuang Y, Chen H, Shen B. Fatigue of systemic lupus erythematosus in China: contributors and effects on the quality of life. *Patient Prefer Adherence*. 2018;12:1729–1735. doi:10.2147/PPA.S170984
23. Golabi P, Sayiner M, Bush H, Gerber LH, Younossi ZM. Patient-reported outcomes and fatigue in patients with chronic hepatitis c infection. *Clin Liver Dis*. 2017;21(3):565–578. doi:10.1016/j.cld.2017.03.011
24. Younossi ZM, Paik JM, Golabi P, Younossi Y, Henry L, Nader F. The impact of fatigue on mortality of patients with non-alcoholic fatty liver disease: data from national health and nutrition examination survey 2005–2010 and 2017–2018. *Liver Int*. 2022;42(12):2646–2661. doi:10.1111/liv.15437
25. Takahashi H, Kotani K, Tanaka K, Egucih Y, Anzai K. Therapeutic approaches to nonalcoholic fatty liver disease: exercise intervention and related mechanisms. *Front Endocrinol*. 2018;9:588. doi:10.3389/fendo.2018.00588
26. Mohammad Rahimi GR, Attarzadeh Hosseini SR. Effect of aerobic exercise alone or in conjunction with diet on liver function, insulin resistance and lipids in non-alcoholic fatty liver disease. *Biol Res Nurs*. 2022;24(2):259–276. doi:10.1177/10998004211068026
27. Strasser B, Geiger D, Schauer M, Gatterer H, Burtscher M, Fuchs D. Effects of exhaustive aerobic exercise on tryptophan-kynurenine metabolism in trained athletes. *PLoS One*. 2016;11(4):e0153617. doi:10.1371/journal.pone.0153617
28. Glass O, Liu D, Bechard E, et al. Perceptions of exercise and its challenges in patients with nonalcoholic fatty liver disease: a survey-based study. *Hepatol Commun*. 2022;6(2):334–344. doi:10.1002/hep4.1808
29. Sheptulina AF, Yafarova AA, Golubeva JA, Mamutova EM, Kiselev AR, Drapkina OM. Clinically meaningful fatigue and depression are associated with sarcopenia in patients with non-alcoholic fatty liver disease. *J Pers Med*. 2023;13(6):932. doi:10.3390/jpm13060932
30. Zelber-Sagi S, Bord S, Dror-Lavi G, et al. Role of illness perception and self-efficacy in lifestyle modification among non-alcoholic fatty liver disease patients. *World J Gastroenterol*. 2017;23(10):1881–1890. doi:10.3748/wjg.v23.i10.1881
31. Gu Y, Zhang W, Hu Y, Chen Y, Shi J. Association between nonalcoholic fatty liver disease and depression: a systematic review and meta-analysis of observational studies. *J Affect Disord*. 2022;301:8–13. doi:10.1016/j.jad.2021.12.128
32. Alrasheed M, Guo JJ, Lin AC, Wigle PR, Hardee A, Hincapie AL. The effect of polypharmacy on quality of life in adult patients with nonalcoholic fatty liver disease in the United States. *Qual Life Res*. 2022;31(8):2481–2491. doi:10.1007/s11136-022-03090-6
33. Finsterer J, Mahjoub SZ. Fatigue in healthy and diseased individuals. *Am J Hosp Palliat Care*. 2014;31(5):562–575. doi:10.1177/1049909113494748
34. Weinstein AA, Price JK, Stepanova M, et al. Depression in patients with nonalcoholic fatty liver disease and chronic viral hepatitis B and C. *Psychosomatics*. 2011;52(2):127–132. doi:10.1016/j.psym.2010.12.019
35. Um YJ, Chang Y, Jung HS, et al. Sleep duration, sleep quality, and the development of nonalcoholic fatty liver disease: a cohort study. *Clin Transl Gastroenterol*. 2021;12(10):e00417. doi:10.14309/ctg.0000000000000417
36. Um YJ, Chang Y, Jung HS, et al. Decrease in sleep duration and poor sleep quality over time is associated with an increased risk of incident non-alcoholic fatty liver disease. *J Pers Med*. 2022;12(1):92. doi:10.3390/jpm12010092
37. Marin-Alejandre BA, Abete I, Cantero I, et al. Association between sleep disturbances and liver status in obese subjects with nonalcoholic fatty liver disease: a comparison with healthy controls. *Nutrients*. 2019;11(2):322. doi:10.3390/nu11020322
38. Kośnik A, Wójcicki M. Fatigue in chronic liver disease patients: prevalence, pathophysiology, and management. *Prz Gastroenterol*. 2022;17(1):21–27. doi:10.5114/pg.2022.114594
39. Tana MM, Alao H, Morris N, et al. Fatigued patients with chronic liver disease have subtle aberrations of sleep, melatonin and cortisol circadian rhythms. *Fatigue*. 2018;6(1):5–19. doi:10.1080/21641846.2018.1408539