PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Is fatigue related to the severity of liver inflammation in patients with chronic liver disease? A cross-sectional study.
AUTHORS	Liu, Jing; Gong, Xiying; Lv, Haifeng; Liu, Shiyi; Jiang, Yanming; Zhu, Geli; Ma, Xiaojie; Wang, Jie; Ye, Xiaoping; Gao, Yidan; Wang, Dian; Chen, Gongying; Shi, Junping

VERSION 1 – REVIEW

REVIEWER	Lauridsen, Mette Munk Sydvestjysk Sygehus, Gastroenterology and Hepatology
REVIEW RETURNED	21-Jan-2023

GENERAL COMMENTS	General comments: Impressive patient cohort. Well-written and reads well. I think the results section is a bit difficult due to the many abbreviations. Consider using less of those. In example here: matched, and there were no statistically significant differences between the two groups in terms of sex, age, SBP, BMI, FPG, LDL-c, TG, TC, STB, AKP, and ALB levels. Introduction: No comments. Methods: The authors need to state how fatigue was defined. Which items in CLDQ were used? Results: I think you should drop most of lines 19 to 30 on page 9 and simply state the differences between groups without all the numbers and just refer to table 1. Discussion: In the discussion, the authors state that 'However, fatigue was not correlated with the severity of liver inflammation in patients with AILDs'. This is confusing as in the results it is said that 'Further multivariate analysis indicated that old age (OR= 2.026, 95% CI: 1.274-3.221, P=0.003), AILDs (OR=2.749, 95% CI: 1.446-5.226, P=0.002), and active inflammation (OR= 1.587, 95% CI: 1.164-2.164, P=0.003) were independent risk factors for fatigue. Does this mean that in AILD fatigue is associated with ADIL diagnosis but not to the degree of inflammation in AILD? This should be clarified. Since GGT is a risk factor for fatigue the authors could touch upon

	how bile acids play into neurotransmission. It seems hepatic inflammation causing elevated GGT and not ALAT or ASAT is implicated in fatigue. Why is that? I miss a section on perspectives. How can we use this knowledge in our meetings with the patients? Are there treatment options for fatigue? Psychosocial support? Figures: Figure 2 is not included/missing.

REVIEWER	Hartleb, Marek Medical University of Silesia
REVIEW RETURNED	25-Jan-2023

GENERAL COMMENTS	This is cross-sectional study investigating the relationships between fatigue reported by patients with etiologically different chronic liver diseases (CLD) and many clinical and histopathological variables. The study showed that fatigue was present in about 19% of population with CLD that rose progressively with rising severity of liver inflammation in young and middle-aged and not in elderly patients. The study was done on large group of patients with CLD (n=1374) who filled in “Chronic Liver Disease questionnaire” at close time proximity to liver biopsy. However, it was not noticed if blood collection was done at the same time. There are several limitations of this study, not all highlighted by the Authors. First, among retrived data some that could contribute to development of fatigue are missing, namely plasma iron level, markers of thyroid gland function, blood oxygen tension or past COVID-19 infection. Second, important limitation is dichotomic division of CLD population between suffering and not-suffering from weakness with no sel-assesment of fatigue severity. Third, there was not control group composed of sex- and aged-matched people with healthy liver that could be especially important in elderly population. Fourth, the autoimmune liver diseases were grouped together irrespective if they were parenchymatic or cholestatic, while it is known that pathophysiology of fatigue is different in primary biliary cholangitis and autoimmune hepatitis.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Comments 1: I think the results section is a bit difficult due to the many abbreviations. Consider using less of those. In example here: matched, and there were no statistically significant differences between the two groups in terms of sex, age, SBP, BMI, FPG, LDL-c, TG, TC, STB, AKP, and ALB levels.
Response:
Thank you for your comment. We have changed the sentence to “there were no statistically significant differences between the two groups in terms of sex, age, BMI, blood pressure, fasting blood glucose, lipid profile, and liver function (P>0.05).” We also deleted the last sentence “There were no significant differences in SBP, BMI, FPG, LDL-c, TG, TC, STB, ALT, AST, AKP, and ALB levels between the fatigue and non-fatigue groups (P>0.05) (Table 1)” in the first paragraph of the Results section.

Comments 2: Methods:The authors need to state how fatigue was defined. Which items in CLDQ were used?

Response: Thank you for your helpful suggestion, we have now added a section on fatigue assessment in the Methods section. “Fatigue was assessed by a professional physician within 1 week prior to liver biopsy using the Chronic Liver Disease Questionnaire (CLDQ), which defined fatigue as a score of less than 20 according to the items 2, 4, 8, 11, and 13.”

Comments 3:Results: I think you should drop most of lines 19 to 30 on page 9 and simply state the differences between groups without all the numbers and just refer to table 1.
Response: Thank you for your suggestion. We have deleted most of the suggested lines, have simply stated the differences between the groups without all the numbers, and have cited Table 1 there.

Comments 4:Discussion: In the discussion, the authors state that ‘However, fatigue was not correlated with the severity of liver inflammation in patients with AILDs’. This is confusing as in the results it is said that ‘Further multivariate analysis indicated that old age (OR= 2.026, 95% CI: 1.274-3.221, P=0.003), AILDs (OR=2.749, 95% CI: 1.446-5.226, P=0.002), and active inflammation (OR= 1.587, 95% CI: 1.164-2.164, P=0.003) were independent risk factors for fatigue.
Does this mean that in AILD fatigue is associated with ADIL diagnosis but not to the degree of inflammation in AILD? This should be clarified.
Response: We apologize for the confusion caused. Yes, we mean that fatigue is associated with the diagnosis of ADIL but not with the degree of inflammation in AILD. We have rewritten the corresponding sentence in the third paragraph of the Discussion section as follows: ”Though fatigue was associated with an AILD diagnosis, it was not correlated with the severity of liver inflammation in patients with AILDs.”

Comments 5: Since GGT is a risk factor for fatigue the authors could touch upon how bile acids play into neurotransmission. It seems hepatic inflammation causing elevated GGT and not ALAT or ASAT is implicated in fatigue. Why is that?
Response: In the second paragraph of the Discussion section, the following text and references have been added in response to this question. “Notably, our research suggested that liver inflammation caused by elevated GGT, and not elevated ALT or AST, was implicated in fatigue. Elevated GGT is usually a sign of cholestasis, and animal studies in bile duct-ligated rats have demonstrated cholestasis-disordered neurotransmission and the development of fatigue. This is suggested to be due to central nervous system damage caused by manganese accumulation. However, further studies are needed to understand the exact mechanism.”

Comments 6:I miss a section on perspectives. How can we use this knowledge in our meetings with the patients? Are there treatment options for fatigue? Psychosocial support?
Response: Thank you for your suggestion. We have added the following treatment options for fatigue in the last paragraph of the Discussion section: “Since the pathophysiology of fatigue is complex and poorly understood, developing therapeutic trials of symptom-directed therapies is challenging. For fatigue in CLD, the ‘TrACE’ method of Treating the treatable (co-morbid causes), Ameliorate the ameliorable causes (sleep, autonomic, and mood disorders), Coping strategies (lifestyle changes such as pacing the day, avoiding shift work) and Empathizing is generally suggested.”

Comments 7: Figure 2 is not included/missing.
Response: Figure 2 had been uploaded in our original file, but we have uploaded it again to ensure that you can see it.

Reviewer: 2
Comments 1::This is cross-sectional study investigating the relationships between fatigue reported by patients with etiologically different chronic liver diseases (CLD) and many clinical and histopathological variables. The study showed that fatigue was present in about 19% of population with CLD that rose progressively with rising severity of liver inflammation in young and middle-aged and not in elderly patients.
The study was done on large group of patients with CLD (n=1374) who filled in “Chronic Liver Disease questionnaire” at close time proximity to liver biopsy. However, it was not noticed if blood collection was done at the same time.
Response: Thank you for your comment. Blood samples were collected after 8 h of fasting within 1 week before liver biopsy. We have added this sentence in the second paragraph of the Methods section.

Comments 2:There are several limitations of this study, not all highlighted by the Authors. First, among retrived data some that could contribute to development of fatigue are missing, namely plasma iron level, markers of thyroid gland function, blood oxygen tension or past COVID-19 infection. Second, important limitation is dichotomic division of CLD population between suffering and not-suffering from weakness with no sel-assesment of fatigue severity. Third, there was not control group composed of sex- and aged-matched people with healthy liver that could be especially important in elderly population. Fourth, the autoimmune liver diseases were grouped together irrespective if they were parenchymatic or cholestatic, while it is known that pathophysiology of fatigue is different in primary biliary cholangitis and autoimmune hepatitis.
Response: Thank you for your valuable suggestion regarding the limitations of our study. We have added “past COVID-19 infection” as an exclusion criterion in the first paragraph of the Methods section. The other limitations that you suggested have been added to the fifth paragraph of the Discussion section and explained accordingly.
“ First, since this was a retrospective study, PSM was used to minimize the influence of available factors. However, some of the retrieved data that could contribute to the development of fatigue, namely plasma iron level, markers of thyroid gland function, and blood oxygen tension, were unavailable. Second, although we diagnosed fatigue based on responses to the CLDQ, an important limitation is the dichotomic division of the CLD population into suffering and not-suffering from fatigue with no self-assessment of fatigue severity. Therefore, we could only assess the relationship between the severity of inflammation and the presence or absence of fatigue, but could not clarify the relationship between the severity of liver inflammation and the severity of fatigue. Third, since the study was based on the liver biopsy, there was no control group composed of sex and aged-matched people with healthy livers, which is especially important in the older population. Fourth, since only 43 patients in this study had AILDs, it is difficult to perform statistical analysis after subdividing. Therefore, the AILDs were grouped together irrespective of whether they were parenchymatic or cholestatic, even though it is known that the pathophysiology of fatigue is different in primary biliary cholangitis, and autoimmune hepatitis may affect the results of AILDs to some extent.”

VERSION 2 – REVIEW

REVIEWER	Hartleb, Marek Medical University of Silesia
REVIEW RETURNED	07-Mar-2023

GENERAL COMMENTS	Thank you for addressing the comments from the first review. I have nor further comments.