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## Fatigue related to the severity of liver inflammation in young and middle-aged but not elderly patients with chronic liver disease : A cross-sectional study

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## **Fatigue related to the severity of liver inflammation in young and middle-aged but not elderly patients with chronic liver disease: A cross-sectional study**

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**Abbreviations:** AFLD, alcoholic liver disease; AIH, autoimmune hepatitis; AILDs, autoimmune liver diseases; AKP, alkaline phosphatase; ALB, albumin; ALD, alcoholic liver disease; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CHB, chronic hepatitis B; CI, confidence interval; CLD, chronic liver disease; CP,

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3 child Pugh; DBP, diastolic blood pressure; FPG, fasting plasma glucose; GGT,  
4 gamma-glutamyl- transferase; HbA1c, glycated haemoglobin; HDL-c/LDL-c,  
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6 high/low-density lipoprotein cholesterol; HRQL, health-related quality of life; NAFLD,  
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8 non-alcoholic fatty liver disease; OR, odds ratio; PBC, primary biliary cholangitis; PSC,  
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10 primary sclerosing cholangitis; PSM, propensity score matching; SBP, systolic blood  
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12 pressure; STB, serum total bilirubin; TC, total cholesterol; TG, triglycerides.  
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20  
21 interest to disclose.  
22

23  
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25  
26 Health project (grant number 2020KY715).  
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29 **Data Availability Statement:** The datasets used and/or analysed during this study are  
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31 available from the corresponding author upon reasonable request.  
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34 **Ethics Approval Statement:** This study was performed according to the ethical guidelines of  
35  
36 the Declaration of Helsinki and was approved by the Ethics Committee of the Affiliated  
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38 Hospital of Hangzhou Normal University (approval number: 2020(02)-KS-022).  
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41 **Patient Consent Statement:** As this was an observational retrospective study, the  
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43 requirement for informed consent was waived by the Ethics Committee.  
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## Abstract

**Objectives:** Fatigue is common in patients with chronic liver disease; however, its pathogenesis is unclear. This study aimed to provide insights into the pathogenesis of chronic liver disease-related fatigue by assessing the relationship between fatigue and the degree of inflammation in chronic liver disease.

**Design:** We performed a cross-sectional study of 1,374 patients with pathologically proven chronic liver disease diagnosed at the Affiliated Hospital of Hangzhou Normal University in Hangzhou, China.

**Setting:** Primary single-centre study

**Participants:** 1,374 patients with liver biopsy proven chronic liver disease.

**Interventions:** The patients were divided into fatigue and non-fatigue groups according to the Chronic Liver Disease Questionnaire. Propensity score matching was used to match the baseline features of the patients in the two groups.

**Primary and secondary outcome measures:** Liver steatosis, ballooning, inflammation and fibrosis were measured according to the pathological results of liver biopsy. Fatigue was measured using the Chronic Liver Disease Questionnaire. Propensity score

**Results:** Of the 1,374 patients, 262 (19.67%) experienced fatigue. There were 242 and 482 patients with and without fatigue, respectively, who were successfully matched for sex, age, and classification of chronic liver disease by propensity score matching. After matching, the fatigue group showed higher liver enzyme levels, inflammation grades, and fibrosis stages than the non-fatigue group ( $P<0.05$ ). Multivariate analysis showed that age (odds ratio: 2.026;  $P=0.003$ ), autoimmune liver disease (OR: 2.749;  $P=0.002$ ), and active inflammation (odds ratio: 1.587;  $P=0.003$ ) were independent risk factors for fatigue after adjusting for confounders. The odds ratio of the risk for fatigue increased in a stepwise manner with

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3 increasing inflammation grade in young and middle-aged patients ( $P<0.05$ ). This tendency  
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5 was not observed in elderly patients ( $P>0.05$ ).  
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8 **Conclusion:** Chronic liver disease patients were burdened by fatigue, which increased  
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10 progressively with rising liver inflammation severity in young and middle-aged rather than  
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12 elderly patients.  
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### 14 15 16 17 **Strengths and limitations of this study**

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19 • Strength: To the best of our knowledge, this is the first study to use liver  
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21 histopathology to explore the relationship between fatigue and the severity of liver  
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23 inflammation.  
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- 25  
26 • Limitation: This was a retrospective study design in which we diagnosed fatigue  
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28 based on responses to the Chronic Liver Disease Questionnaire.  
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- 30  
31 • Limitation: The cross-sectional study design meant that we could not determine a  
32  
33 causal relationship between the severity of inflammation and fatigue.  
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38 **Keywords:** hepatology, histopathology, health management  
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### 42 43 **Introduction**

44  
45 Chronic liver disease (CLD) affects approximately 1.5 billion people worldwide. The  
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47 prevalence of CLD is rising rapidly owing to the ongoing impact of viral hepatitis and the  
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49 rapidly increasing incidence of non-alcoholic fatty liver disease (NAFLD).[1-3] Fatigue is  
50  
51 commonly experienced by patients with CLD and significantly impairs their quality of life.[4]  
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53 The findings of previous studies suggest that the impact of fatigue on patients with CLD can  
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55 be substantial,[5] with patients reporting that it interferes with several aspects of their lives,  
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57 including physical activities, family life, and job performance.[6] These issues add to the  
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3 personal and societal burdens associated with CLD and indirectly contribute to financial costs.  
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5 In addition to affecting quality of life, CLD-related fatigue has a negative impact on survival.  
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7 In a 4-year follow-up study of patients with primary biliary cholangitis (PBC), fatigue was  
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9 associated with poor outcomes, as patients with higher fatigue scores at the start of the study  
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11 period had significantly lower survival rates.[7]  
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15 It is difficult to characterize, define, and treat fatigue because it encompasses a complex  
16  
17 interaction between biological, psychosocial, and behavioural processes.[8,9] Our  
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19 understanding of CLD-related fatigue is still incomplete and its pathogenesis remains unclear.  
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21 The most common view is that there are peripheral pathways between the liver and the brain  
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23 that, when activated, lead to changes in neurotransmission within the brain and the  
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25 development of disease-related behaviours, including fatigue.[10-12] Better understanding of  
26  
27 the relationship between fatigue and liver histology features in different CLD populations  
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29 may provide further evidence of the mechanism underlying liver disease-related fatigue and  
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31 facilitate the development of specific and appropriate treatment for it.  
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35 In this study, we explored the risk factors for fatigue in CLD by comparing the clinical  
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37 and histological features of patients with and without fatigue using a large cohort of patients  
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39 with biopsy-proven CLD. In addition, we analysed the correlation between the severity of  
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41 liver histology features and CLD-related fatigue in different CLD populations.  
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## 47 **Methods**

### 48 **Patients and Study Design**

49  
50 This was a cross-sectional study of patients with pathologically proven CLD, including  
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52 NAFLD, alcoholic liver disease (ALD), PBC, primary sclerosing cholangitis (PSC),  
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54 autoimmune hepatitis (AIH), chronic hepatitis B (CHB), and CHB with fatty liver, diagnosed  
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56 at the Affiliated Hospital of Hangzhou Normal University in Hangzhou, China between 2011  
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3 and 2021. Patients with the following conditions were excluded: psychiatric or mental  
4 disorders, or cognitive difficulties that could hinder reliable description of symptoms; CLD  
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6 disorders, or cognitive difficulties that could hinder reliable description of symptoms; CLD  
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8 combined with any other chronic disorders that may affect fatigue; and causes of CLD other  
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10 than NAFLD, ALD, autoimmune liver diseases (AILDs) (including PBC, PSC, AIH), and  
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12 CHB. The included patients were divided into fatigue and non-fatigue groups according to the  
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14 presence or absence of fatigue.  
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### 17 18 19 **Clinical Examination and Biochemical Analysis**

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21 The clinical examination consisted of a physical examination and a health habit assessment,  
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23 which were performed by professional physicians. Diastolic blood pressure (DBP), systolic  
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25 blood pressure (SBP), height, and body weight were measured according to standard  
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27 protocols. Body mass index (BMI) was calculated as weight (kg) divided by height (m)  
28  
29 squared ( $\text{kg}/\text{m}^2$ ). Blood samples were collected after 8 h of fasting, and the biochemical tests  
30  
31 performed included measurement of fasting plasma glucose (FPG), triglyceride (TG), total  
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33 cholesterol (TC), high/low-density lipoprotein cholesterol (HDL-c/LDL-c), alanine  
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35 aminotransferase (ALT), gamma-glutamyl-transferase (GGT), aspartate aminotransferase  
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37 (AST), alkaline phosphatase (AKP), serum total bilirubin (STB), albumin (ALB), and  
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39 glycated hemoglobin (HbA1c) levels. The biochemical tests were performed using an  
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41 automated biochemical analyser according to the manufacturer's instructions (OLYMPUS,  
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43 Japan AU5821+ISE; OLYMPUS).  
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### 51 **Histological Analysis**

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53 All liver biopsies were reassessed by three professional histopathologists who were blinded to  
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55 patient details. The steatosis score (positive if  $>5\%$ , according to the Brunt classification  
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57 [S0-S3]), fibrosis stage (based on a meta-analysis of histological data on viral hepatitis score  
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59 [S0-S3]), fibrosis stage (based on a meta-analysis of histological data on viral hepatitis score  
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3 [S0-S4]), ballooning score (S0-S2), and inflammation grades (G0-G4) of the patients were  
4 evaluated.[12-14]. Fibrosis stage  $\geq 2$ , inflammation grade  $\geq 2$ , and steatosis score  $\geq 2$  were  
5 defined as indicative of significant liver fibrosis, active inflammation, and severe steatosis,  
6 respectively.  
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### 15 **Fatigue Assessment**

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17 Fatigue was assessed by a professional physician within 1 week prior to liver biopsy using  
18 the Chronic Liver Disease questionnaire.[15]  
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### 24 **Statistical Analysis**

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26 Continuous variables were compared between the two groups using Student's *t*-test or the  
27 Mann–Whitney *U* test. Categorical variables were compared using the Chi-square test.  
28 Propensity score matching (PSM) was performed in a ratio of 1:2 and with a calliper value of  
29 0.2 to balance age, sex, and CLD classification between the two patient groups. Univariate  
30 and multivariate logistic regression analysis was conducted to analyse the factors that  
31 contribute to fatigue. We estimated adjusted odds ratios (ORs) and relevant 95% confidence  
32 intervals (CIs) using a parametric proportional hazard model. SPSS 26.0 (IBM, Armonk, NY,  
33 USA) was used for statistical analyses. Statistical significance was set at  $P < 0.05$ .  
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### 47 **Ethical Considerations**

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49 This study was performed according to the ethical guidelines of the Declaration of Helsinki  
50 and was approved by the Ethics Committee of the Affiliated Hospital of Hangzhou Normal  
51 University (approval number: 2020(02)-KS-022). As this was an observational retrospective  
52 study, the requirement for informed consent was waived by the Ethics Committee.  
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## Results

### Comparison of the Clinical and Histological Features of Chronic Liver Disease Patients with and without Fatigue

A total of 1,374 patients with biopsy-proven CLD were included in this study. Of these, 262 (19.07%) patients had symptoms of fatigue, while 1,112 (80.93%) had no fatigue. The patients with fatigue were older, had lower BMI and higher HDL-c and GGT levels than the patients without fatigue ( $P<0.05$ ). There were significant differences between the proportions of patients with NAFLD, CHB with fatty liver, CHB, AFLD, and AILDs in the two groups (respectively, fatigue group: 16.03%, 17.94%, 52.67%, 6.11%, and 7.25% vs non-fatigue 18.44%, 25.45%, 47.75%, 6.20%, and 2.16%;  $P<0.05$ ). 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).

After PSM, 242 patients with fatigue and 482 patients without fatigue were successfully 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. In addition, there were no differences between the proportions of patients with NAFLD, CHB with fatty liver, CHB, AFLD, and AILDs in the two groups ( $P>0.05$ ) (Table 1). The fatigue group had higher ALT, AST, and GGT levels than the non-fatigue group. Further comparison of the histological features of the two groups is shown in Figure 1. The inflammation grades and liver fibrosis stages of the patients with fatigue were significantly higher than those of the patients without fatigue ( $P<0.05$ ). There was no difference in hepatic steatosis and ballooning scores between the two groups ( $P>0.05$ ) (Figure 1, A-D).

### Distribution and Risk Factors of Fatigue in Patients with Chronic Liver Disease

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3 The prevalence of fatigue significantly increased with age ( $R=0.087$ ,  $P=0.001$ ) (Figure  
4 2a). There was no correlation between fatigue and BMI and sex ( $P>0.05$ ) (Figures 2b and c).  
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6 The prevalence of fatigue among patients with different types of CLD varied. For patients  
7  
8 with AILDs, the prevalence of fatigue was 44.19%, which is more than twice that of patients  
9  
10 with other CLDs ( $P<0.001$ ) (Figure 2d). The prevalence of fatigue significantly increased  
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12 with the degree of liver inflammation and fibrosis stage ( $P<0.001$ ) (Figures 2e and f).  
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17 Univariate and multivariate analyses were performed to define the association between  
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19 fatigue using clinical and histological features (Table 2). Univariate analysis showed that old  
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21 age (OR=2.122, 95% CI: 1.379-3.267,  $P=0.001$ ), AILDs (OR=3.545, 95% CI: 1.911-6.574,  
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23  $P<0.001$ ), elevated GGT level (OR=1.356, 95%CI: 1.012-1.816,  $P=0.042$ ), active  
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25 inflammation (OR=1.768, 95%CI: 1.329-2.353,  $P<0.001$ ), and advanced fibrosis stage  
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27 (OR=1.743, 95%CI: 1.282-2.370,  $P<0.001$ ) were risk factors for fatigue in CLD. Further  
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29 multivariate analysis indicated that old age (OR= 2.026, 95% CI: 1.274-3.221,  $P=0.003$ ),  
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31 AILDs (OR=2.749, 95% CI: 1.446-5.226,  $P=0.002$ ), and active inflammation (OR= 1.587, 95%  
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33 CI: 1.164-2.164,  $P=0.003$ ) were independent risk factors for fatigue.  
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#### 40 **Analysis of the Correlation between Histological Features and Fatigue in Chronic Liver** 41 **Disease** 42 43

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45 Multivariate analysis was performed to explore the correlation between fatigue and the  
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47 severity of histological features. Two different models were utilized to estimate the ORs for  
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49 different outcomes. After adjusting for age, sex, BMI, hypertension, type 2 diabetes mellitus,  
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51 disease classification, ALT level, AST level, and GGT level, the OR for the risk of fatigue  
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53 increased in a stepwise manner from inflammation grades G0-G1 (as a reference) and G2  
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55 (OR=1.609, 95% CI: 1.085-2.386,  $P=0.018$ ) to G3 (OR=1.745, 95% CI: 1.019-2.986,  
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3  $P=0.042$ ) (Table 3). The severity of steatosis, ballooning, and fibrosis were not associated  
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5 with fatigue ( $P>0.05$ ).  
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### 10 **Sensitivity Analysis**

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12 Subgroup analysis of the risk of fatigue in CLD showed a significant association  
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14 between fatigue and increasing severity of liver inflammation among patients aged < 60 years  
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16 old without AILDs ( $P<0.05$ ). However, the severity of inflammation was not associated with  
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18 fatigue among patients > 60 years old or with AILDs ( $P>0.05$ ) (Table 4).  
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### 24 **Discussion**

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26 Fatigue is a critical component of CLD.[11] The findings of the present study indicate  
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28 an association between fatigue and liver inflammation. In the present study, CLD patients  
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30 with fatigue had significantly higher inflammation grades and liver fibrosis stages than  
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32 patients without fatigue. In addition, multivariate analysis showed that age, AILDs, and  
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34 active inflammation were independent risk factors for fatigue, and that the severity of liver  
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36 inflammation was strongly associated with fatigue after adjustment for confounders. Further  
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38 sensitivity analysis showed that this association was present in the young and middle-aged  
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40 population of the present study but not in the elderly population.  
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45 The clinical and liver histological features of CLD-related fatigue have not been  
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47 uniformly demonstrated.[16,17] In the present study, the CLD patients with fatigue were  
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49 older, had lower BMI, and higher HDL-c and GGT levels than patients without fatigue. In  
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51 addition, the fatigue group showed significantly higher inflammation grades and liver fibrosis  
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53 stages than the non-fatigue group after PSM for age and sex (Table 1, Figure 1). The results  
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55 of the present study are in-line with those of most studies that showed that old age, AILDs,  
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57 and active inflammation are independent risk factors for fatigue (Table 2).[18-21] The  
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3 findings of the present study and previous studies indicate that early evaluation and  
4 intervention for fatigue are necessary for patients with CLD. The results of the present study  
5 also indicated that the risk of fatigue increased with the severity of inflammation, but not with  
6 the severity of hepatic steatosis, ballooning, and liver fibrosis (Table 3). Although the issue of  
7 fatigue in patients with CLD, including PBC, PSC, CHB, CHC, and NAFLD, has been  
8 extensively studied, the relationship between fatigue and the histological features of CLD  
9 remains controversial. Fatigue in NAFLD has been associated with inactivity and excessive  
10 daytime sleepiness but not with the severity of liver disease or insulin resistance.[16]  
11 However, a recent study indicated that the detection of lobular inflammation in biopsies is  
12 correlated with lower health-related quality of life (HRQL) in patients with NAFLD.[17]  
13 Data from clinical trials on chronic hepatitis B or C virus infection also support the dominant  
14 role of inflammation in fatigue. In these trials, viral elimination or suppression after antiviral  
15 therapy was associated with improved HRQL, which suggests an effect of inflammation on  
16 fatigue, whereas improvement of fibrosis did not affect HRQL.[22-24]

17  
18 Further subgroup analysis in the present study revealed a significant association between  
19 fatigue and the severity of liver inflammation in patients <60 years old, but not in patients  
20  $\geq 60$  years old (Table 4). Our findings suggest that the severity of liver inflammation may play  
21 a dominant role in fatigue in young and middle-aged patients with CLD, whereas age-related  
22 factors may play dominant roles in fatigue in elderly patients. Previous studies have shown  
23 that fatigue is a significant component of the clinical presentation of patients with AIH, often  
24 paralleling hepatic inflammation.[25] In line with previous research, the data of the present  
25 study showed that patients with AILDs had the highest prevalence of fatigue, and that AILDs  
26 was an independent risk factor for CLD-related fatigue. However, fatigue was not correlated  
27 with the severity of liver inflammation in patients with AILDs. This may be related to the  
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3 relatively small number of AILD cases in the present study. Thus, studies with larger samples  
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5 are needed to confirm this finding.  
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8 The strength of this study is that it is the first study, to the best of our knowledge, in  
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10 which the relationship between fatigue and the severity of liver inflammation in different  
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12 CLD populations was explored using liver histopathology features. However, the limitations  
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14 of this study should be noted as well. First, as this was a retrospective study, we diagnosed  
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16 fatigue based on responses to the Chronic Liver Disease Questionnaire, which included  
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18 questions on fatigue. The severity of fatigue cannot be defined; thus, we could only assess the  
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20 relationship between the severity of inflammation and the presence or absence of fatigue, but  
21  
22 could not clarify the relationship between the severity of liver inflammation and the severity  
23  
24 of fatigue. Second, as this was a cross-sectional study, we could not determine the causal  
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26 relationship between the severity of inflammation and fatigue. Further studies with  
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28 longitudinal cohorts are needed to confirm the effects of the severity of inflammation on  
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30 fatigue in patients with CLD.  
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35 In conclusion, the present study demonstrates that fatigue is correlated with the severity  
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37 of liver inflammation in young and middle-aged patients with CLD. However, this correlation  
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39 was not observed in elderly patients. These findings contradict the perception that fatigue is  
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41 not associated with the severity of liver disease. Since age is an important factor that  
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43 influences fatigue, our findings highlight the need for age stratification during the evaluation  
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45 and treatment of CLD patients with fatigue.  
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### 51 **Author contributions**

52  
53 Research idea and study design: Junping Shi; data acquisition: Jing Liu, Xiying Gong, Shiyi  
54  
55 Liu, Yanming Jiang, Geli Zhu, Xiaojie Ma, Jie Wang, Xiaoping Ye, Yidan Gao, Dian Wang,  
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57 Gongying Chen; data analysis/interpretation: Jing Liu, Haifeng Lv; statistical analysis: Jing  
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3 Liu, Haifeng Lv; supervision or mentorship: Junping Shi. Each author contributed important  
4 intellectual content during manuscript drafting and revision, agreed to be personally  
5 accountable for the individual's contributions, and ensured questions about the accuracy or  
6 integrity of any portion of the work, even one in which the author was not directly involved,  
7 are appropriately investigated and resolved.  
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For peer review only



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TABLE 1 Comparison of clinical and laboratory characteristics between patients with and without fatigue in CLD

Variables	Before propensity score matching			After propensity score matching(1:2)		
	Fatigue	No fatigue	P Value	Fatigue	No fatigue	P Value
n	262	1112		242	484	
Male(%)	175(66.79)	785(70.59)	0.228‡	167(69.01)	337(69.63)	0.527‡
Age (year)	45.30 ±11.12	41.36 ±11.33	<0.001	44.02 ± 10.48	42.46 ± 11.26	0.071
BMI(kg/m <sup>2</sup> )	24.05 ±3.86	24.82 ±4.62	0.032	24.26 ± 3.88	24.18 ±4.02	0.840
BP(S)(mmHg)	124.33 ±15.26	125.70 ±15.52	0.204	123.86 ± 15.43	125.96 ± 16.01	0.098
FPG (mmol/L)	5.56 ± 1.66	5.65 ±1.54	0.493	5.56 ± 1.65	5.61 ± 1.40	0.718
HbA1c(%)	6.18 ± 1.54	6.12 ± 1.52	0.823	6.24 ±1.61	6.09 ± 1.52	0.639
TG (mmol/L)	1.23(0.95-1.85)	1.08(1.55-2.18)	0.793†	1.19(0.93-1.84)	1.31(0.90-2.00)	0.543
TC (mmol/L)	4.74 ± 1.20	4.68 ± 1.11	0.504	4.67 ± 1.16	4.63 ± 0.95	0.733
LDL-c (mmol/L)	2.76 ± 0.88	2.75 ± 0.82	0.875	2.72 ± 0.88	2.70 ± 0.75	0.788
HDL-c(mmol/L)	1.30 ± 0.36	1.24 ± 0.33	0.035	1.28 ± 0.35	1.25 ± 0.35	0.298
STB(μmmol/l)	16.65(12.82-22.45)	16.20(12.90-21.10)	0.511†	16.60(12.85-22.00)	15.50(12.50-20.80)	0.153†
ALT (U/L)	51.00(32.00-83.00)	49.00(30.00-80.00)	0.432†	51.00 (32.00-82.00)	41.00(26.00-66.00)	<0.001†
AST (U/L)	35.00(26.00-52.00)	33.00(25.00-49.00)	0.093†	34.00 (26.00-51.00)	28.00(23.00-41.00)	<0.001†
GGT(U/L)	37.00(23.00-77.00)	33.00(20.00-60.00)	0.005†	35.00(21.00-66.00)	27.00(17.00-49.00)	<0.001†
AKP(U/L)	110.00(88.00-137.00)	108.00(87.00-136.00)	0.650†	107.00(87.0-129.00)	106.00(83.00-133.00)	0.797†
ALB (g/L)	44.08 ± 4.15	44.51 ± 5.85	0.297	44.37 ± 3.95	44.70 ± 5.77	0.460
<b>CLD Category</b>						
NAFLD n(%)	42(16.03)	205(18.44)	<0.001‡	42(17.36)	70(14.46)	0.190‡
CHB with fatty liver n(%)	47(17.94)	283(25.45)		47(19.42)	103(21.28)	
CHB n(%)	138(52.67)	531(47.75)		137(56.61)	254(52.78)	
AFLD n(%)	16(6.11)	69(6.20)		12(4.96)	46(9.51)	
AILDs n(%)	19(7.25)	24(2.16)		4(1.65)	11(2.27)	

\*P-value calculated using the  $\chi^2$  test.

†P-value calculated using the Mann–Whitney U-test.

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3 Abbreviations: Data are expressed as mean  $\pm$  standard deviation or median (interquartile range).  
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5 Abbreviations: AFLD, alcoholic fatty liver disease; AILD, autoimmune liver disease; ALB, albumin; AKP, alkaline phosphatase; ALT, alanine  
6 aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; BP, blood pressure; CHB, chronic hepatitis B; CLD, chronic liver  
7 disease; DBP, diastolic blood pressure; FPG, fasting plasma glucose; GGT, gamma-glutamyl-transferase; HDL-c, high-density lipoprotein  
8 cholesterol; LDL-c, low-density lipoprotein cholesterol; SBP, systolic blood pressure; STB, serum total bilirubin; SUA, serum uric acid; TC,  
9 total cholesterol; TG, triglycerides.  
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**Table 2.** Univariate and multivariable regression analysis of risk factors for fatigue in chronic liver disease

Variables	Univariate Analysis		Multivariate Analysis	
	OR (95% CI)	P Value	OR (95% CI)	P Value
Old Age				
No	Ref.		Ref.	
Yes	2.122(1.379-3.267)	0.001	2.026(1.274-3.221)	0.003
Male				
No	Ref.			
Yes	0.838(0.628-1.117)	0.228	--	--
AILDs				
No	Ref.			
Yes	3.545(1.911-6.574)	<0.001	2.749(1.446-5.226)	0.002
<b>Metabolic factors</b>				
Obesity				
No	Ref.			
Yes	0.813(0.591-1.121)	0.207	--	--
Hypertension				
No	Ref.			
Yes	0.735(0.536-1.008)	0.056	--	--
T2DM				
No	Ref.			
Yes	0.694(0.436-1.103)	0.122	--	--
Hypertriglyceridemia				
No	Ref.			
Yes	0.804(0.577-1.121)	0.198	--	--
Hypercholesterolemia				
No	Ref.			
Yes	1.448(0.974-2.153)	0.068	--	--
Hyperuricemia				
No	Ref.			
Yes	0.835(0.570-1.222)	0.353	--	--
High LDL-c				
No	Ref.			
Yes	0.943(0.675-1.316)	0.728	--	--
Low HDL-c				
No	Ref.			
Yes	1.104(0.764-1.569)	0.599	--	--
<b>Liver enzymes</b>				
Elevated ALT				
No	Ref.			
Yes	1.164(0.662-2.441)	0.306	--	--
Elevated AST				
No	Ref.			
Yes	1.205(0.906-1.602)	0.199	--	--
Elevated GGT				
No	Ref.			

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3	Yes	1.356(1.012-1.816)	0.042	--	--
4	<b>Histopathology</b>				
5	Severe ballooning				
6	No	Ref			
7	Yes	1.049(0.606-1.815)	0.865	--	--
8	Severe steatosis				
9	No	Ref			
10	Yes	0.850(0.488-1.482)	0.567	--	--
11	Active inflammation				
12	No	Ref.			
13	Yes	1.768(1.329-2.353)	<0.001	1.587(1.164-2.164)	0.003
14	Advanced fibrosis				
15	No	Ref			
16	Yes	1.743(1.282-2.370)	<0.001	--	--

Abbreviations: AILDs, autoimmune liver diseases; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol; T2DM, type 2 diabetes mellitus; OR, odds ratio; CI, confidence intervals.

Table 3 Odds ratio of liver histological severity for fatigue in chronic liver disease

	Crude		Model 1		Model 2	
	OR(95% CI)	P Value	OR(95% CI)	P Value	OR(95% CI)	P Value
<b>Steatosis score</b>						
S0	Ref.		Ref.		Ref.	
S1-2	1.205(0.793-1.833)	0.383	1.204(0.787-1.841)	0.392	1.360(0.761-2.428)	0.299
S3	0.870(0.498-1.519)	0.624	0.918(0.522-1.615)	0.767	1.328(0.648-2.724)	0.493
<b>Ballooning score</b>						
B0	Ref.		Ref.		Ref.	
B1	0.665(0.405-1.090)	0.979	0.620(0.376-1.023)		0.942(0.521-1.703)	0.468
B2	1.007(0.581-1.747)	0.106	0.871(0.498-1.525)		1.310(0.632-2.716)	0.843
<b>Inflammation grade</b>						
G0-1	Ref.		Ref.		Ref.	
G2	1.618(1.190-2.200)	0.002	1.570(1.152-2.140)	0.004	1.609(1.085-2.386)	0.018
G≥3	2.170(1.486-3.169)	<0.001	2.014(1.372-2.056)	<0.001	1.745(1.019-2.986)	0.042
<b>Liver fibrosis</b>						
F0-1	Ref.		Ref.		Ref.	
F2	1.087(0.751-1.574)	0.657	1.006(0.692-1.462)	0.975	0.691(0.420-1.135)	0.145
F≥3	1.777(1.291-2.447)	<0.001	1.608(1.160-2.226)	0.004	1.371(0.897-2.096)	0.144

Note: Model 1 adjusted for age and sex; Model 2 was adjusted for model 1 plus body mass index hypertension, type 2 diabetes mellitus, alanine aminotransferase, aspartate aminotransferase, gamma-glutamyl-transferase and disease classification.

Abbreviations: OR,odds ratio; CI,confidence intervals.



**Table 4.** Sensitivity analysis in the presence of risk factors for fatigue in chronic liver disease

Variables	No.of Participants	OR(95%CI)	P Value
<b>Age</b>			
≥60 years	107		
G0-1	37	Ref.	
G2	45	1.813(0.668-4.919)	0.632
G≥3	25	2.848(0.937-8.659)	0.870
<60 years	1267		
G0-1	556	Ref.	
G2	517	1.566(1.134-2.163)	0.006
G≥3	194	1.989(1.324-2.988)	0.001
<b>Elevated GGT</b>			
Yes	451		
G0-1	141	Ref.	
G2	191	1.919(1.077-3.420)	0.027
G≥3	119	2.420(1.304-4.490)	0.005
No	923		
G0-1	452	Ref.	
G2	371	1.458(1.011-2.105)	0.019
G≥3	100	1.880(1.108-3.190)	0.044
<b>AILDs</b>			
Yes	43		
G0-1	9	Ref.	
G2	13	1.714(0.294-9.999)	0.549
G≥3	21	1.818(0.357-9.272)	0.472
No	1331		
G0-1	584	Ref.	
G2	549	1.587(1.161-2.167)	0.004
G≥3	198	1.959(1.313-2.923)	0.001

Abbreviations: AILDs, autoimmune liver diseases; GGT, gamma-glutamyl-transferase; OR, odds ratio; CI, confidence intervals.

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3 **Figure 1.** Comparison of the histopathological characteristics of chronic liver disease patients  
4 with and without fatigue. **(A)** Comparison of the inflammation grades of patients with CLD  
5 stratified according to the presence or absence of fatigue. **(B)** Comparison of the fibrosis  
6 stages of patients with CLD stratified according to the presence or absence of fatigue. **(C)**  
7 Comparison of hepatic steatosis scores of patients with CLD stratified according to the  
8 presence or absence of fatigue. **(D)** Comparison of the ballooning scores of the patients with  
9 CLD stratified according to the presence or absence of fatigue.  
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3 **Figure 2.** Prevalence of fatigue in different chronic liver disease populations. (A) Prevalence  
4 of fatigue stratified according to age. (B) Prevalence of fatigue stratified according to body  
5 mass index. (C) Prevalence of fatigue stratified according to sex. (D) Prevalence of fatigue  
6 stratified according to CLD classification. (E) Prevalence of fatigue stratified according to  
7 inflammation grade. (F) Prevalence of fatigue stratified according to fibrosis stage.

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14 **Abbreviations:** CHB, chronic hepatitis B; NAFLD, non-alcoholic fatty liver disease; AFLD,  
15 alcoholic fatty liver disease; AILD, autoimmune liver diseases.  
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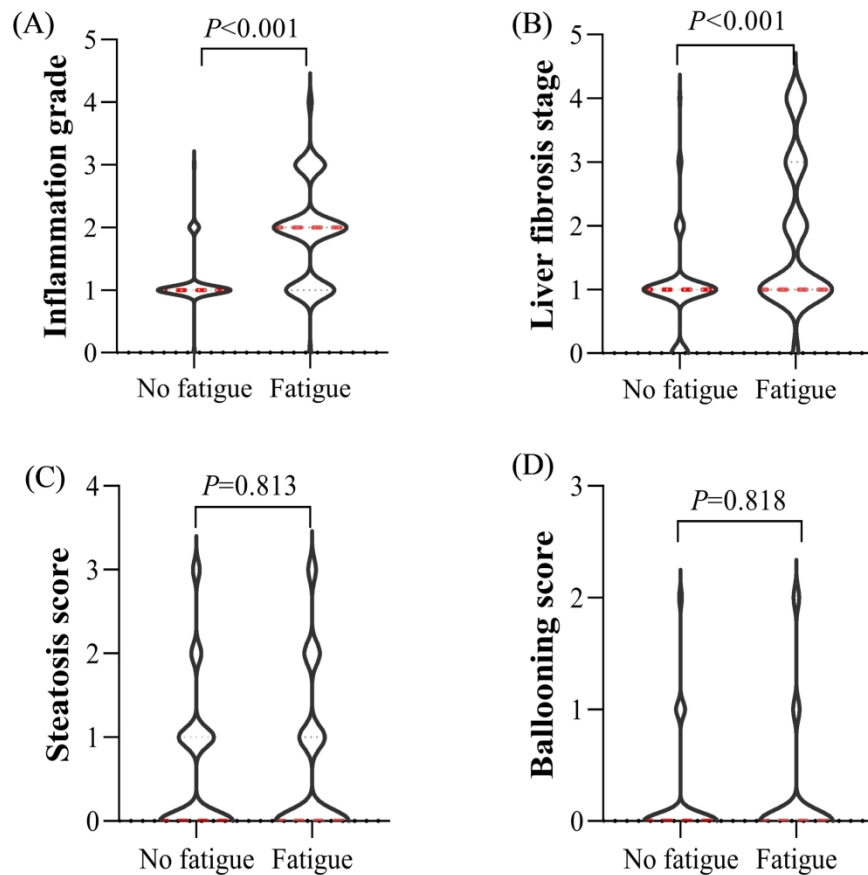


Figure 1. Comparison of the histopathological characteristics of chronic liver disease patients with and without fatigue. (A) Comparison of the inflammation grades of patients with CLD stratified according to the presence or absence of fatigue. (B) Comparison of the fibrosis stages of patients with CLD stratified according to the presence or absence of fatigue. (C) Comparison of hepatic steatosis scores of patients with CLD stratified according to the presence or absence of fatigue. (D) Comparison of the ballooning scores of the patients with CLD stratified according to the presence or absence of fatigue.

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Figure 2. Prevalence of fatigue in different chronic liver disease populations. (A) Prevalence of fatigue stratified according to age. (B) Prevalence of fatigue stratified according to body mass index. (C) Prevalence of fatigue stratified according to sex. (D) Prevalence of fatigue stratified according to CLD classification. (E) Prevalence of fatigue stratified according to inflammation grade. (F) Prevalence of fatigue stratified according to fibrosis stage. Abbreviations: CHB, chronic hepatitis B; NAFLD, non-alcoholic fatty liver disease; AFLD, alcoholic fatty liver disease; AILD, autoimmune liver diseases.

STROBE Statement—Checklist of items that should be included in reports of *cross-sectional studies*

	Item No	Recommendation	Page No
<b>Title and abstract</b>	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	1
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	3
<b>Introduction</b>			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
<b>Methods</b>			
Study design	4	Present key elements of study design early in the paper	5-6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5-7
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants	5-6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6-7
Bias	9	Describe any efforts to address potential sources of bias	6-7
Study size	10	Explain how the study size was arrived at	5-6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	7
		(b) Describe any methods used to examine subgroups and interactions	7
		(c) Explain how missing data were addressed	7
		(d) If applicable, describe analytical methods taking account of sampling strategy	7
		(e) Describe any sensitivity analyses	7
<b>Results</b>			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8
		(b) Give reasons for non-participation at each stage	8
		(c) Consider use of a flow diagram	0
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8-9
		(b) Indicate number of participants with missing data for each variable of interest	0
Outcome data	15*	Report numbers of outcome events or summary measures	8

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Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	9-10
		(b) Report category boundaries when continuous variables were categorized	7
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	9-10
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	10
<b>Discussion</b>			
Key results	18	Summarise key results with reference to study objectives	10
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	12
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	10-12
Generalisability	21	Discuss the generalisability (external validity) of the study results	12
<b>Other information</b>			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	2

\*Give information separately for exposed and unexposed groups.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at [www.strobe-statement.org](http://www.strobe-statement.org).

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## Is fatigue related to the severity of liver inflammation in patients with chronic liver disease? A cross-sectional study.

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## Is fatigue related to the severity of liver inflammation in patients with chronic liver disease? A cross-sectional study

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**Word count:** 2959

**Figures:** 2; **Tables:** 4.

**Abbreviations:** AFLD, alcoholic liver disease; AIH, autoimmune hepatitis; AILDs, autoimmune liver diseases; AKP, alkaline phosphatase; ALB, albumin; ALD, alcoholic liver disease; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CHB, chronic hepatitis B; CI, confidence interval; CLD, chronic liver disease; CP, child Pugh; DBP, diastolic blood pressure; FPG, fasting plasma glucose; GGT, gamma-glutamyl-

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3 transferase; HbA1c, glycated hemoglobin; HDL-c/LDL-c, high/low-density lipoprotein  
4 cholesterol; HRQL, health-related quality of life; NAFLD, non-alcoholic fatty liver disease;  
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7 OR, odds ratio; PBC, primary biliary cholangitis; PSC, primary sclerosing cholangitis; PSM,  
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9 propensity score matching; SBP, systolic blood pressure; STB, serum total bilirubin; TC, total  
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11 cholesterol; TG, triglycerides.  
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18  
19 interest to disclose.  
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22  
23 Health project (grant number 2020KY715).  
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28 available from the corresponding author upon reasonable request.  
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30 **Ethics Approval Statement:** This study was performed according to the ethical guidelines of  
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32 the Declaration of Helsinki and was approved by the Ethics Committee of the Affiliated  
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34 Hospital of Hangzhou Normal University (approval number: 2020(02)-KS-022).  
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37 **Patient Consent Statement:** As this was an observational retrospective study, the requirement  
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39 for informed consent was waived by the Ethics Committee.  
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## Abstract

**Objectives:** Fatigue is common in patients with chronic liver disease; however, its pathogenesis is unclear. This study aimed to provide insights into the pathogenesis of chronic liver disease-related fatigue by assessing the relationship between fatigue and the degree of inflammation in chronic liver disease.

**Design:** We performed a cross-sectional study of 1,374 patients with pathologically proven chronic liver disease diagnosed at the Affiliated Hospital of Hangzhou Normal University in Hangzhou, China.

**Setting:** Primary single-center study

**Participants:** One thousand three hundred and seventy-four patients with liver biopsy-proven chronic liver disease.

**Interventions:** The patients were divided into fatigue and non-fatigue groups according to the Chronic Liver Disease Questionnaire. Propensity score matching was used to match the baseline features of the patients in the two groups.

**Primary and secondary outcome measures:** Liver steatosis, ballooning, inflammation, and fibrosis were measured according to the pathological results of liver biopsy. Fatigue was measured using the Chronic Liver Disease Questionnaire.

**Results:** Of the 1,374 patients, 262 (19.67%) experienced fatigue. There were 242 and 482 patients with and without fatigue, respectively, who were successfully matched for sex, age, and classification of chronic liver disease by propensity score matching. After matching, the fatigue group showed higher liver enzyme levels, inflammation grades, and fibrosis stages than the non-fatigue group ( $P<0.05$ ). Multivariate analysis showed that age (odds ratio: 2.026;  $P=0.003$ ), autoimmune liver disease (OR: 2.749;  $P=0.002$ ), and active inflammation (odds ratio: 1.587;  $P=0.003$ ) were independent risk factors for fatigue after adjusting for confounders. The odds ratio of the risk for fatigue increased in a stepwise manner with increasing inflammation

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3 grade in young and middle-aged patients ( $P<0.05$ ). This tendency was not observed in elderly  
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5 patients ( $P>0.05$ ).  
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8 **Conclusion:** Chronic liver disease patients were burdened by fatigue, which increased  
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10 progressively with rising liver inflammation severity in young and middle-aged rather than  
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12 elderly patients.  
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### 14 15 16 17 **Strengths and limitations of this study**

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19 • This study was the first comprehensive assessment of the relationship between fatigue  
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21 and the severity of liver inflammation in a large sample of liver biopsy-proven chronic  
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23 liver disease.  
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26 • Propensity score matching was used to exclude the influence of gender, age, blood  
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28 pressure, blood glucose, liver function, and composition ratio of patients with chronic  
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30 liver disease.  
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33 • Since this is a retrospective study, some data that could contribute to the development  
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35 of fatigue, namely plasma iron level, markers of thyroid gland function, and blood  
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37 oxygen tension, are missing.  
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40 • An important limitation is the dichotomic division of the chronic liver diseases  
41  
42 population into suffering and not-suffering from fatigue with no self-assessment of  
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44 fatigue severity.  
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47 • Due to the cross-sectional study design, we have not been able determine the causal  
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49 relationship between the severity of inflammation and fatigue.  
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54 **Keywords:** hepatology, histopathology, health management  
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## 58 59 **Introduction** 60

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Chronic liver disease (CLD) affects approximately 1.5 billion people worldwide. The prevalence of CLD is rising rapidly owing to the ongoing impact of viral hepatitis and the rapidly increasing incidence of non-alcoholic fatty liver disease (NAFLD).[1-3] Fatigue is commonly experienced by patients with CLD and significantly impairs their quality of life.[4] The findings of previous studies suggest that the impact of fatigue on patients with CLD can be substantial,[5] with patients reporting that it interferes with several aspects of their lives, including physical activities, family life, and job performance.[6] These issues add to the personal and societal burdens associated with CLD and indirectly contribute to financial costs. In addition to affecting quality of life, CLD-related fatigue has a negative impact on survival. In a 4-year follow-up study of patients with primary biliary cholangitis (PBC), fatigue was associated with poor outcomes, as patients with higher fatigue scores at the start of the study period had significantly lower survival rates.[7]

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It is difficult to characterize, define, and treat fatigue because it encompasses a complex interaction between biological, psychosocial, and behavioral processes.[8,9] Our understanding of CLD-related fatigue is still incomplete and its pathogenesis remains unclear. The most common view is that there are peripheral pathways between the liver and the brain that, when activated, lead to changes in neurotransmission within the brain and the development of disease-related behaviors, including fatigue.[10-12] Better understanding of the relationship between fatigue and liver histology features in different CLD populations may provide further evidence of the mechanism underlying liver disease-related fatigue and facilitate the development of specific and appropriate treatment for it.

In this study, we explored the risk factors for fatigue in CLD by comparing the clinical and histological features of patients with and without fatigue using a large cohort of patients with biopsy-proven CLD. In addition, we analyzed the correlation between the severity of liver histology features and CLD-related fatigue in different CLD populations.

## Methods

### Patients and Study Design

This was a cross-sectional study of patients with pathologically proven CLD, including NAFLD, alcoholic liver disease (ALD), PBC, primary sclerosing cholangitis (PSC), autoimmune hepatitis (AIH), chronic hepatitis B (CHB), and CHB with fatty liver, diagnosed at the Affiliated Hospital of Hangzhou Normal University in Hangzhou, China between 2011 and 2021. Patients with the following conditions were excluded: psychiatric or mental disorders, or cognitive difficulties that could hinder reliable description of symptoms; CLD combined with any other chronic disorders that may affect fatigue; causes of CLD other than NAFLD, ALD, autoimmune liver diseases (AILDs) (including PBC, PSC, AIH), and CHB; and past COVID-19 infection. The included patients were divided into fatigue and non-fatigue groups according to the presence or absence of fatigue.

### Clinical Examination and Biochemical Analysis

The clinical examination consisted of a physical examination and a health habit assessment, which were performed by professional physicians. Diastolic blood pressure (DBP), systolic blood pressure (SBP), height, and body weight were measured according to standard protocols. Body mass index (BMI) was calculated as weight (kg) divided by height (m) squared ( $\text{kg}/\text{m}^2$ ). Blood samples were collected after 8 h of fasting within 1 week before liver biopsy, and the biochemical tests performed included measurement of fasting plasma glucose (FPG), triglyceride (TG), total cholesterol (TC), high/low-density lipoprotein cholesterol (HDL-c/LDL-c), alanine aminotransferase (ALT), gamma-glutamyl-transferase (GGT), aspartate aminotransferase (AST), alkaline phosphatase (AKP), serum total bilirubin (STB), albumin (ALB), and glycated hemoglobin (HbA1c) levels. The biochemical tests were performed using

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3 an automated biochemical analyzer according to the manufacturer's instructions (OLYMPUS,  
4 Japan AU5821+ISE; OLYMPUS).  
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### 10 **Histological Analysis**

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12 All liver biopsies were reassessed by three professional histopathologists who were blinded to  
13 patient details. The steatosis score (positive if >5%, according to the Brunt classification [S0-  
14 S3]), fibrosis stage (based on a meta-analysis of histological data on viral hepatitis score [S0-  
15 S4]), ballooning score (S0-S2), and inflammation grades (G0-G4) of the patients were  
16 evaluated.[12-14]. Fibrosis stage  $\geq 2$ , inflammation grade  $\geq 2$ , and steatosis score  $\geq 2$  were  
17 defined as indicative of significant liver fibrosis, active inflammation, and severe steatosis,  
18 respectively.  
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### 30 **Fatigue Assessment**

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32 Fatigue was assessed by a professional physician within 1 week prior to liver biopsy using the  
33 Chronic Liver Disease Questionnaire (CLDQ), which defined fatigue as a score of less than 20  
34 according to the items 2, 4, 8, 11, and 13.[15]  
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### 42 **Statistical Analysis**

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44 Continuous variables were compared between the two groups using Student's *t*-test or the  
45 Mann–Whitney *U* test. Categorical variables were compared using the Chi-square test.  
46 Propensity score matching (PSM) was performed in a ratio of 1:2 and with a caliper value of  
47 0.2 to balance age, sex, and CLD classification between the two patient groups. Univariate and  
48 multivariate logistic regression analysis was conducted to analyze the factors that contribute to  
49 fatigue. We estimated adjusted odds ratios (ORs) and relevant 95% confidence intervals (CIs)  
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3 using a parametric proportional hazard model. SPSS 26.0 (IBM, Armonk, NY, USA) was used  
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5 for statistical analyses. Statistical significance was set at  $P<0.05$ .  
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### 10 **Ethical Considerations**

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12 This study was performed according to the ethical guidelines of the Declaration of Helsinki  
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14 and was approved by the Ethics Committee of the Affiliated Hospital of Hangzhou Normal  
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16 University (approval number: 2020(02)-KS-022). As this was an observational retrospective  
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18 study, the requirement for informed consent was waived by the Ethics Committee.  
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### 24 **Patient and public involvement**

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26 Patients or the public were not involved in the design, or conduct, or reporting, or dissemination  
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28 plans of the current work.  
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## 35 **Results**

### 36 37 38 39 **Comparison of the Clinical and Histological Features of Chronic Liver Disease Patients** 40 41 **with and without Fatigue**

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43 A total of 1,374 patients with biopsy-proven CLD were included in this study. Of these,  
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45 262 (19.07%) patients had symptoms of fatigue, while 1,112 (80.93%) had no fatigue. The  
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47 patients with fatigue were older, had lower BMI and higher HDL-c and GGT levels than the  
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49 patients without fatigue ( $P<0.05$ ). There were significant differences between the proportions  
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51 of patients with NAFLD, CHB with fatty liver, CHB, AFLD, and AILDs in the two groups  
52  
53 ( $P<0.05$ ) (Table 1).  
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57 After PSM, 242 patients with fatigue and 482 patients without fatigue were successfully  
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59 matched, and there were no statistically significant differences between the two groups in terms  
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3 of sex, age, BMI, blood pressure, fasting blood glucose, lipid profile, and liver function ( $P>0.05$ )  
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5 (Table 1). The fatigue group had higher ALT, AST, and GGT levels than the non-fatigue group.  
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7 Further comparison of the histological features of the two groups is shown in Figure 1. The  
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9 inflammation grades and liver fibrosis stages of the patients with fatigue were significantly  
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11 higher than those of the patients without fatigue ( $P<0.05$ ). There was no difference in hepatic  
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13 steatosis and ballooning scores between the two groups ( $P>0.05$ ) (Figure 1, A-D).  
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### 19 **Distribution and Risk Factors of Fatigue in Patients with Chronic Liver Disease**

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21 The prevalence of fatigue significantly increased with age ( $R=0.087$ ,  $P=0.001$ ) (Figure  
22  
23 2a). There was no correlation between fatigue and BMI and sex ( $P>0.05$ ) (Figures 2b and c).  
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25 The prevalence of fatigue among patients with different types of CLD varied. For patients with  
26  
27 AILDs, the prevalence of fatigue was 44.19%, which is more than twice that of patients with  
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29 other CLDs ( $P<0.001$ ) (Figure 2d). The prevalence of fatigue significantly increased with the  
30  
31 degree of liver inflammation and fibrosis stage ( $P<0.001$ ) (Figures 2e and f).  
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36 Univariate and multivariate analyses were performed to define the association between  
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38 fatigue using clinical and histological features (Table 2). Univariate analysis showed that old  
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40 age (OR=2.122, 95% CI: 1.379-3.267,  $P=0.001$ ), AILDs (OR=3.545, 95% CI: 1.911-6.574,  
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42  $P<0.001$ ), elevated GGT level (OR=1.356, 95%CI: 1.012-1.816,  $P=0.042$ ), active  
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44 inflammation (OR=1.768, 95%CI: 1.329-2.353,  $P<0.001$ ), and advanced fibrosis stage  
45  
46 (OR=1.743, 95%CI: 1.282-2.370,  $P<0.001$ ) were risk factors for fatigue in CLD. Further  
47  
48 multivariate analysis indicated that old age (OR= 2.026, 95% CI: 1.274-3.221,  $P=0.003$ ),  
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50 AILDs (OR=2.749, 95% CI: 1.446-5.226,  $P=0.002$ ), and active inflammation (OR= 1.587, 95%  
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52 CI: 1.164-2.164,  $P=0.003$ ) were independent risk factors for fatigue.  
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## Analysis of the Correlation between Histological Features and Fatigue in Chronic Liver Disease

Multivariate analysis was performed to explore the correlation between fatigue and the severity of histological features. Two different models were utilized to estimate the ORs for different outcomes. After adjusting for age, sex, BMI, hypertension, type 2 diabetes mellitus, disease classification, ALT level, AST level, and GGT level, the OR for the risk of fatigue increased in a stepwise manner from inflammation grades G0-G1 (as a reference) and G2 (OR=1.609, 95% CI: 1.085-2.386,  $P=0.018$ ) to G3 (OR=1.745, 95% CI: 1.019-2.986,  $P=0.042$ ) (Table 3). The severity of steatosis, ballooning, and fibrosis were not associated with fatigue ( $P>0.05$ ).

### Sensitivity Analysis

Subgroup analysis of the risk of fatigue in CLD showed a significant association between fatigue and increasing severity of liver inflammation among patients aged < 60 years old without AILDs ( $P<0.05$ ). However, the severity of inflammation was not associated with fatigue among patients > 60 years old or with AILDs ( $P>0.05$ ) (Table 4).

## Discussion

Fatigue is a critical component of CLD.[11] The findings of the present study indicate an association between fatigue and liver inflammation. In the present study, CLD patients with fatigue had significantly higher inflammation grades and liver fibrosis stages than patients without fatigue. In addition, multivariate analysis showed that age, AILDs, and active inflammation were independent risk factors for fatigue, and that the severity of liver inflammation was strongly associated with fatigue after adjustment for confounders. Further

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3 sensitivity analysis showed that this association was present in the young and middle-aged  
4 population of the present study but not in the elderly population.  
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7 The clinical features of CLD-related fatigue have not been uniformly demonstrated.[16,17]  
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9 In the present study, the CLD patients with fatigue were older, had lower BMI, and higher  
10 HDL-c and GGT levels than patients without fatigue. In addition, the fatigue group showed  
11 significantly higher inflammation grades and liver fibrosis stages than the non-fatigue group  
12 after PSM for age and sex (Table 1, Figure 1). The results of the present study are in line with  
13 those of most studies that showed that old age, AILDs, and active inflammation are  
14 independent risk factors for fatigue (Table 2).[18-21] Notably, our research suggested that liver  
15 inflammation caused by elevated GGT, and not elevated ALT or AST, was implicated in  
16 fatigue. Elevated GGT is usually a sign of cholestasis, and animal studies in bile duct-ligated  
17 rats have demonstrated cholestasis-disordered neurotransmission and the development of  
18 fatigue. This is suggested to be due to central nervous system damage caused by manganese  
19 accumulation. However, further studies are needed to understand the exact mechanism. [22]  
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35 The results of the present study showed that the risk of fatigue increased with the severity  
36 of inflammation, but not with the severity of hepatic steatosis, ballooning, and liver fibrosis  
37 (Table 3). Although the issue of fatigue in patients with CLD, including PBC, PSC, CHB,  
38 CHC, and NAFLD, has been extensively studied, the relationship between fatigue and the  
39 histological features of CLD remains controversial. Fatigue in NAFLD has been associated  
40 with inactivity and excessive daytime sleepiness but not with the severity of liver disease or  
41 insulin resistance.[16] However, a recent study indicated that the detection of lobular  
42 inflammation in biopsies is correlated with lower health-related quality of life (HRQL) in  
43 patients with NAFLD.[17] Data from clinical trials on chronic hepatitis B or C virus infection  
44 also support the dominant role of inflammation in fatigue. In these trials, viral elimination or  
45 suppression after antiviral therapy was associated with improved HRQL, which suggests an  
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3 effect of inflammation on fatigue, whereas improvement of fibrosis did not affect HRQL.[23-  
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8 Further subgroup analysis in the present study revealed a significant association between  
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10 fatigue and the severity of liver inflammation in patients <60 years old, but not in patients ≥60  
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12 years old (Table 4). Our findings suggest that the severity of liver inflammation may play a  
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14 dominant role in fatigue in young and middle-aged patients with CLD, whereas age-related  
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16 factors may play dominant roles in fatigue in elderly patients. Previous studies have shown that  
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18 fatigue is a significant component of the clinical presentation of patients with AIH, often  
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20 paralleling hepatic inflammation.[26] In line with previous research, the data of the present  
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22 study showed that patients with AILDs had the highest prevalence of fatigue, and that AILDs  
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24 was an independent risk factor for CLD-related fatigue. Though fatigue was associated with an  
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26 AILD diagnosis, it was not correlated with the severity of liver inflammation in patients with  
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28 AILDs. This may be related to the relatively small number of AILD cases in the present study.  
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30 Thus, studies with larger samples are needed to confirm this finding.  
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35 The strength of this study is that it is the first study, to the best of our knowledge, in which  
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37 the relationship between fatigue and the severity of liver inflammation in different CLD  
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39 populations was explored using liver histopathology features. However, the limitations of this  
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41 study should be noted as well. First, since this was a retrospective study, PSM was used to  
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43 minimize the influence of available factors. However, some of the retrieved data that could  
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45 contribute to the development of fatigue, namely plasma iron level, markers of thyroid gland  
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47 function, and blood oxygen tension, were unavailable. Second, although we diagnosed fatigue  
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49 based on responses to the CLDQ, an important limitation is the dichotomic division of the CLD  
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51 population into suffering and not-suffering from fatigue with no self-assessment of fatigue  
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53 severity. Therefore, we could only assess the relationship between the severity of inflammation  
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55 and the presence or absence of fatigue, but could not clarify the relationship between the  
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3 severity of liver inflammation and the severity of fatigue. Third, since the study was based on  
4 the liver biopsy, there was no control group composed of sex and aged-matched people with  
5 healthy livers, which is especially important in the older population. Fourth, since only 43  
6 patients in this study had AILDs, it is difficult to perform statistical analysis after subdividing.  
7  
8 Therefore, the AILDs were grouped together irrespective of whether they were parenchymatic  
9 or cholestatic, even though it is known that the pathophysiology of fatigue is different in  
10 primary biliary cholangitis, and autoimmune hepatitis may affect the results of AILDs to some  
11 extent. Fifth, as this was a cross-sectional study, we could not determine the causal relationship  
12 between the severity of inflammation and fatigue. Further studies with longitudinal cohorts are  
13 needed to confirm the effects of the severity of inflammation on fatigue in patients with CLD.  
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26 In conclusion, the impact of fatigue on the perceived quality of life can be profound for  
27 patients with CLD. Since the pathophysiology of fatigue is complex and poorly understood,  
28 developing therapeutic trials of symptom-directed therapies is challenging. For fatigue in CLD,  
29 the 'TrACE' method of Treating the treatable (co-morbid causes), Ameliorate the ameliorable  
30 causes (sleep, autonomic, and mood disorders), Coping strategies (lifestyle changes such as  
31 pacing the day, avoiding shift work) and Empathizing is generally suggested.[4,27] The present  
32 study demonstrates that fatigue is correlated with the severity of liver inflammation in young  
33 and middle-aged patients with CLD. However, this correlation was not observed in elderly  
34 patients. These findings contradict the perception that fatigue is not associated with the severity  
35 of liver disease. Since age is an important factor that influences fatigue, our findings highlight  
36 the need for age stratification during the evaluation and treatment of CLD patients with fatigue,  
37 which will provide new evidence for the management and treatment of fatigue in patients with  
38 CLD.  
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#### 55 **Author contributions**

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3 Research idea and study design: Junping Shi; data acquisition: Jing Liu, Xiying Gong, Shiyi  
4 Liu, Yanming Jiang, Geli Zhu, Xiaojie Ma, Jie Wang, Xiaoping Ye, Yidan Gao, Dian Wang,  
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6 Gongying Chen; data analysis/interpretation: Jing Liu, Haifeng Lv; statistical analysis: Jing  
7  
8 Liu, Haifeng Lv; supervision or mentorship: Junping Shi. Each author contributed important  
9  
10 intellectual content during manuscript drafting and revision, agreed to be personally  
11  
12 accountable for the individual's contributions, and ensured questions about the accuracy or  
13  
14 integrity of any portion of the work, even one in which the author was not directly involved,  
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16 are appropriately investigated and resolved.  
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TABLE 1 Comparison of clinical and laboratory characteristics between patients with and without fatigue in CLD

Variables	Before propensity score matching			After propensity score matching(1:2)		
	Fatigue	No fatigue	P Value	Fatigue	No fatigue	P Value
n	262	1112		242	484	
Male(%)	175(66.79)	785(70.59)	0.228‡	167(69.01)	337(69.63)	0.527‡
Age (year)	45.30 ±11.12	41.36 ±11.33	<0.001	44.02 ± 10.48	42.46 ± 11.26	0.071
BMI(kg/m <sup>2</sup> )	24.05 ±3.86	24.82 ±4.62	0.032	24.26 ± 3.88	24.18 ±4.02	0.840
BP(S)(mmHg)	124.33 ±15.26	125.70 ±15.52	0.204	123.86 ± 15.43	125.96 ± 16.01	0.098
FPG (mmol/L)	5.56 ± 1.66	5.65 ±1.54	0.493	5.56 ± 1.65	5.61 ± 1.40	0.718
HbA1c(%)	6.18 ± 1.54	6.12 ± 1.52	0.823	6.24 ±1.61	6.09 ± 1.52	0.639
TG (mmol/L)	1.23(0.95-1.85)	1.08(1.55-2.18)	0.793†	1.19(0.93-1.84)	1.31(0.90-2.00)	0.543
TC (mmol/L)	4.74 ± 1.20	4.68 ± 1.11	0.504	4.67 ± 1.16	4.63 ± 0.95	0.733
LDL-c (mmol/L)	2.76 ± 0.88	2.75 ± 0.82	0.875	2.72 ± 0.88	2.70 ± 0.75	0.788
HDL-c(mmol/L)	1.30 ± 0.36	1.24 ± 0.33	0.035	1.28 ± 0.35	1.25 ± 0.35	0.298
STB(μmmol/l)	16.65(12.82-22.45)	16.20(12.90-21.10)	0.511†	16.60(12.85-22.00)	15.50(12.50-20.80)	0.153†
ALT (U/L)	51.00(32.00-83.00)	49.00(30.00-80.00)	0.432†	51.00 (32.00-82.00)	41.00(26.00-66.00)	<0.001†
AST (U/L)	35.00(26.00-52.00)	33.00(25.00-49.00)	0.093†	34.00 (26.00-51.00)	28.00(23.00-41.00)	<0.001†
GGT(U/L)	37.00(23.00-77.00)	33.00(20.00-60.00)	0.005†	35.00(21.00-66.00)	27.00(17.00-49.00)	<0.001†
AKP(U/L)	110.00(88.00-	108.00(87.00-	0.650†	107.00(87.0-	106.00(83.00-133.00)	0.797†
ALB (g/L)	137.00	136.00)	0.297	129.00)	44.70 ± 5.77	0.460
<b>CLD Category</b>	44.08 ± 4.15	44.51 ± 5.85		44.37 ± 3.95		
NAFLD n(%)			<0.001‡		70(14.46)	0.190‡
CHB with fatty liver n(%)	42(16.03)	205(18.44)		42(17.36)	103(21.28)	
CHB n(%)	47(17.94)	283(25.45)		47(19.42)	254(52.78)	
AFLD n(%)	138(52.67)	531(47.75)		137(56.61)	46(9.51)	
AILDs n(%)	16(6.11)	69(6.20)		12(4.96)	11(2.27)	
	19(7.25)	24(2.16)		4(1.65)		

\*P-value calculated using the  $\chi^2$  test.

†P-value calculated using the Mann–Whitney U-test.

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3 Abbreviations: Data are expressed as mean  $\pm$  standard deviation or median (interquartile range).  
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5 Abbreviations: AFLD, alcoholic fatty liver disease; AILD, autoimmune liver disease; ALB, albumin; AKP, alkaline phosphatase; ALT, alanine  
6 aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; BP, blood pressure; CHB, chronic hepatitis B; CLD, chronic liver  
7 disease; DBP, diastolic blood pressure; FPG, fasting plasma glucose; GGT, gamma-glutamyl-transferase; HDL-c, high-density lipoprotein  
8 cholesterol; LDL-c, low-density lipoprotein cholesterol; SBP, systolic blood pressure; STB, serum total bilirubin; SUA, serum uric acid; TC, total  
9 cholesterol; TG, triglycerides.  
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**Table 2.** Univariate and multivariable regression analysis of risk factors for fatigue in chronic liver disease

Variables	Univariate Analysis		Multivariate Analysis	
	OR (95% CI)	P Value	OR (95% CI)	P Value
Old Age				
No	Ref.		Ref.	
Yes	2.122(1.379-3.267)	0.001	2.026(1.274-3.221)	0.003
Male				
No	Ref.			
Yes	0.838(0.628-1.117)	0.228	--	--
AILDs				
No	Ref.			
Yes	3.545(1.911-6.574)	<0.001	2.749(1.446-5.226)	0.002
<b>Metabolic factors</b>				
Obesity				
No	Ref.			
Yes	0.813(0.591-1.121)	0.207	--	--
Hypertension				
No	Ref.			
Yes	0.735(0.536-1.008)	0.056	--	--
T2DM				
No	Ref.			
Yes	0.694(0.436-1.103)	0.122	--	--
Hypertriglyceridemia				
No	Ref.			
Yes	0.804(0.577-1.121)	0.198	--	--
Hypercholesterolemia				
No	Ref.			
Yes	1.448(0.974-2.153)	0.068	--	--
Hyperuricemia				
No	Ref.			
Yes	0.835(0.570-1.222)	0.353	--	--
High LDL-c				
No	Ref.			
Yes	0.943(0.675-1.316)	0.728	--	--
Low HDL-c				
No	Ref.			
Yes	1.104(0.764-1.569)	0.599	--	--
<b>Liver enzymes</b>				
Elevated ALT				
No	Ref.			
Yes	1.164(0.662-2.441)	0.306	--	--
Elevated AST				
No	Ref.			
Yes	1.205(0.906-1.602)	0.199	--	--
Elevated GGT				
No	Ref.			

Yes	1.356(1.012-1.816)	0.042	--	--
<b>Histopathology</b>				
Severe ballooning				
No	Ref			
Yes	1.049(0.606-1.815)	0.865	--	--
Severe steatosis				
No	Ref			
Yes	0.850(0.488-1.482)	0.567	--	--
Active inflammation				
No	Ref.			
Yes	1.768(1.329-2.353)	<0.001	1.587(1.164-2.164)	0.003
Advanced fibrosis				
No	Ref			
Yes	1.743(1.282-2.370)	<0.001	--	--

Abbreviations: AILDs, autoimmune liver diseases; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol; T2DM, type 2 diabetes mellitus; OR, odds ratio; CI, confidence intervals.

Table 3 Odds ratio of liver histological severity for fatigue in chronic liver disease

	Crude		Model 1		Model 2	
	OR(95% CI)	P Value	OR(95% CI)	P Value	OR(95% CI)	P Value
<b>Steatosis score</b>						
S0	Ref.		Ref.		Ref.	
S1-2	1.205(0.793-1.833)	0.383	1.204(0.787-1.841)	0.392	1.360(0.761-2.428)	0.299
S3	0.870(0.498-1.519)	0.624	0.918(0.522-1.615)	0.767	1.328(0.648-2.724)	0.493
<b>Ballooning score</b>						
S0	Ref.		Ref.		Ref.	
S1	0.665(0.405-1.090)	0.979	0.620(0.376-1.023)		0.942(0.521-1.703)	0.468
S2	1.007(0.581-1.747)	0.106	0.871(0.498-1.525)		1.310(0.632-2.716)	0.843
<b>Inflammation grade</b>						
G0-1	Ref.		Ref.		Ref.	
G2	1.618(1.190-2.200)	0.002	1.570(1.152-2.140)	0.004	1.609(1.085-2.386)	0.018
G≥3	2.170(1.486-3.169)	<0.001	2.014(1.372-2.056)	<0.001	1.745(1.019-2.986)	0.042
<b>Liver fibrosis</b>						
S0-1	Ref.		Ref.		Ref.	
S2	1.087(0.751-1.574)	0.657	1.006(0.692-1.462)	0.975	0.691(0.420-1.135)	0.145
S≥3	1.777(1.291-2.447)	<0.001	1.608(1.160-2.226)	0.004	1.371(0.897-2.096)	0.144

Note: Model 1 adjusted for age and sex; Model 2 was adjusted for model 1 plus body mass index hypertension, type 2 diabetes mellitus, alanine aminotransferase, aspartate aminotransferase, gamma-glutamyl-transferase and disease classification.

Abbreviations: OR, odds ratio; CI, confidence intervals.

**Table 4.** Sensitivity analysis in the presence of risk factors for fatigue in chronic liver disease

Variables	No. of Participants	OR(95%CI)	P Value
<b>Age</b>			
≥60 years	107		
G0-1	37	Ref.	
G2	45	1.813(0.668-4.919)	0.632
G≥3	25	2.848(0.937-8.659)	0.870
<60 years	1267		
G0-1	556	Ref.	
G2	517	1.566(1.134-2.163)	0.006
G≥3	194	1.989(1.324-2.988)	0.001
<b>Elevated GGT</b>			
Yes	451		
G0-1	141	Ref.	
G2	191	1.919(1.077-3.420)	0.027
G≥3	119	2.420(1.304-4.490)	0.005
No	923		
G0-1	452	Ref.	
G2	371	1.458(1.011-2.105)	0.019
G≥3	100	1.880(1.108-3.190)	0.044
<b>AILDs</b>			
Yes	43		
G0-1	9	Ref.	
G2	13	1.714(0.294-9.999)	0.549
G≥3	21	1.818(0.357-9.272)	0.472
No	1331		
G0-1	584	Ref.	
G2	549	1.587(1.161-2.167)	0.004
G≥3	198	1.959(1.313-2.923)	0.001

Abbreviations: AILDs, autoimmune liver diseases; GGT, gamma-glutamyl-transferase; OR, odds ratio; CI, confidence intervals.



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3 **Figure 1.** Comparison of the histopathological characteristics of chronic liver disease patients  
4 with and without fatigue. **(A)** Comparison of the inflammation grades of patients with CLD  
5 stratified according to the presence or absence of fatigue. **(B)** Comparison of the fibrosis stages  
6 of patients with CLD stratified according to the presence or absence of fatigue. **(C)** Comparison  
7 of hepatic steatosis scores of patients with CLD stratified according to the presence or absence  
8 of fatigue. **(D)** Comparison of the ballooning scores of the patients with CLD stratified  
9 according to the presence or absence of fatigue.  
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3 **Figure 2.** Prevalence of fatigue in different chronic liver disease populations. **(A)** Prevalence  
4 of fatigue stratified according to age. **(B)** Prevalence of fatigue stratified according to body  
5 mass index. **(C)** Prevalence of fatigue stratified according to sex. **(D)** Prevalence of fatigue  
6 stratified according to CLD classification. **(E)** Prevalence of fatigue stratified according to  
7 inflammation grade. **(F)** Prevalence of fatigue stratified according to fibrosis stage.

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14 **Abbreviations:** CHB, chronic hepatitis B; NAFLD, non-alcoholic fatty liver disease; AFLD,  
15 alcoholic fatty liver disease; AILD, autoimmune liver diseases.  
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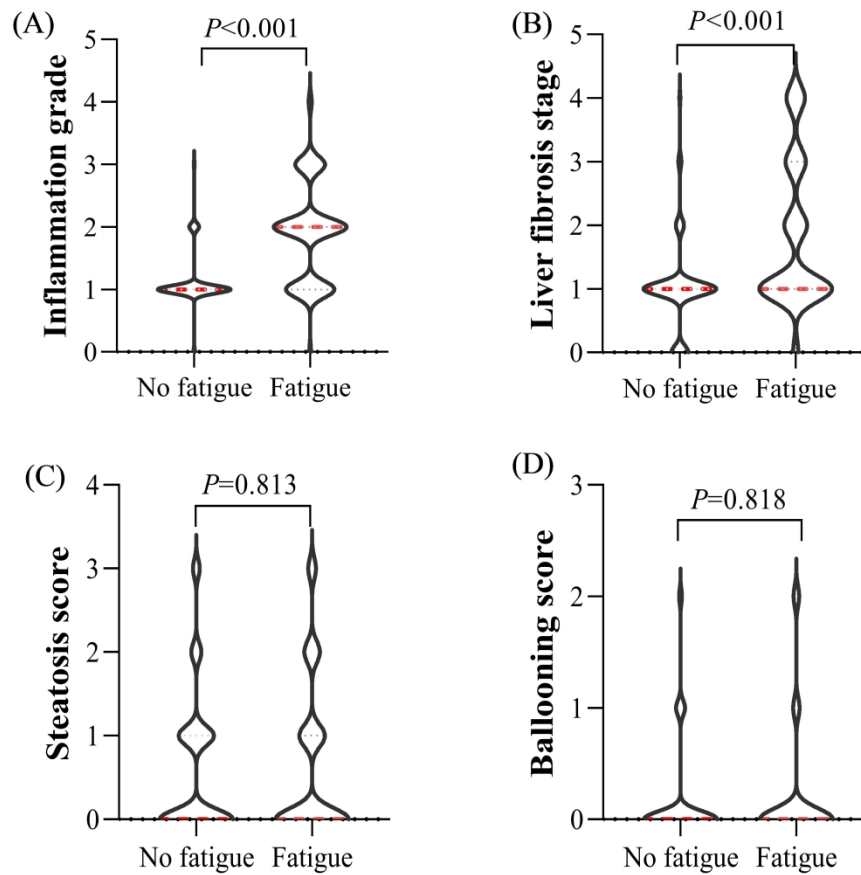
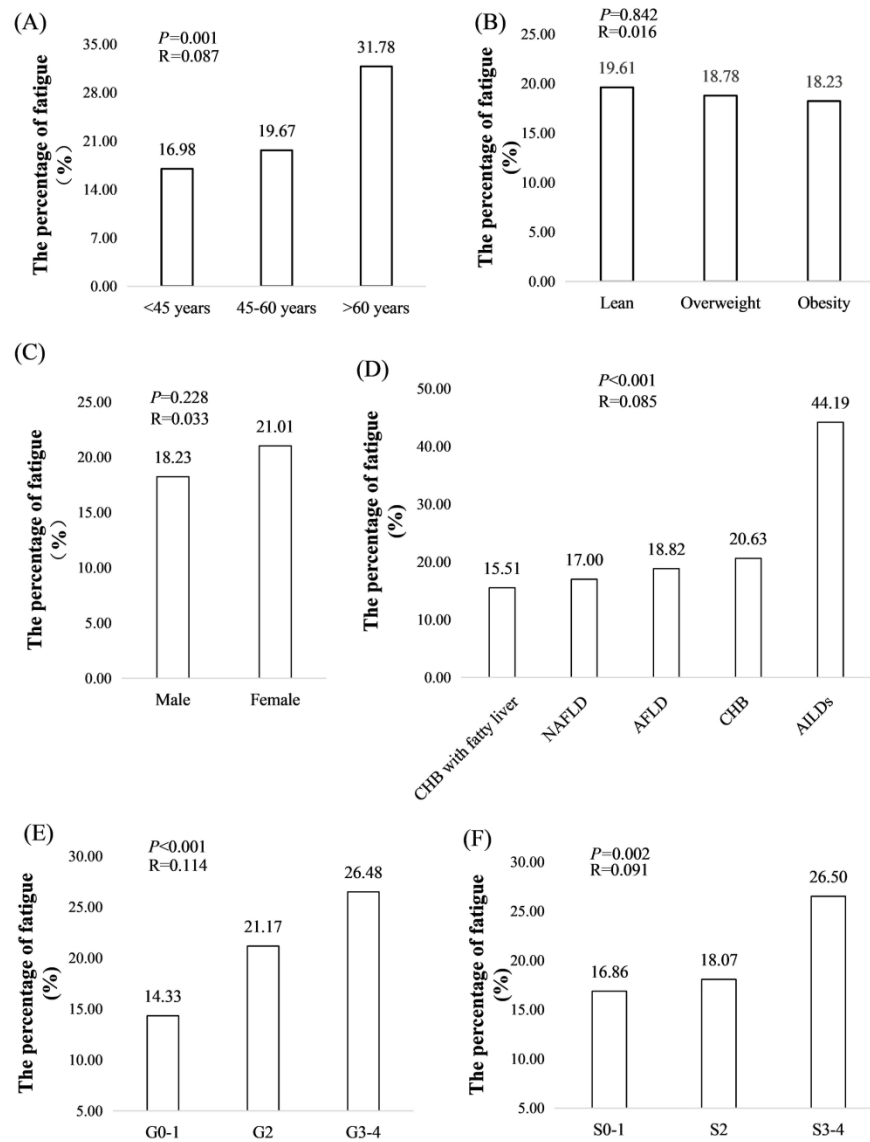


Figure 1. Comparison of the histopathological characteristics of chronic liver disease patients with and without fatigue. (A) Comparison of the inflammation grades of patients with CLD stratified according to the presence or absence of fatigue. (B) Comparison of the fibrosis stages of patients with CLD stratified according to the presence or absence of fatigue. (C) Comparison of hepatic steatosis scores of patients with CLD stratified according to the presence or absence of fatigue. (D) Comparison of the ballooning scores of the patients with CLD stratified according to the presence or absence of fatigue.

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Prevalence of fatigue in different chronic liver disease populations. (A) Prevalence of fatigue stratified according to age. (B) Prevalence of fatigue stratified according to body mass index. (C) Prevalence of fatigue stratified according to sex. (D) Prevalence of fatigue stratified according to CLD classification. (E) Prevalence of fatigue stratified according to inflammation grade. (F) Prevalence of fatigue stratified according to fibrosis stage.

Abbreviations: CHB, chronic hepatitis B; NAFLD, non-alcoholic fatty liver disease; AFLD, alcoholic fatty liver disease; AILD, autoimmune liver diseases.

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STROBE Statement—Checklist of items that should be included in reports of *cross-sectional studies*

	Item No	Recommendation	Page No
<b>Title and abstract</b>	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	1
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	3
<b>Introduction</b>			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
<b>Methods</b>			
Study design	4	Present key elements of study design early in the paper	5-6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5-7
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants	5-6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6-7
Bias	9	Describe any efforts to address potential sources of bias	6-7
Study size	10	Explain how the study size was arrived at	5-6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	7
		(b) Describe any methods used to examine subgroups and interactions	7
		(c) Explain how missing data were addressed	7
		(d) If applicable, describe analytical methods taking account of sampling strategy	7
		(e) Describe any sensitivity analyses	7
<b>Results</b>			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8
		(b) Give reasons for non-participation at each stage	8
		(c) Consider use of a flow diagram	0
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8-9
		(b) Indicate number of participants with missing data for each variable of interest	0
Outcome data	15*	Report numbers of outcome events or summary measures	8

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2	Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
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11	Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
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14	<b>Discussion</b>		
15	Key results	18	Summarise key results with reference to study objectives
16	Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
17			12
18			
19			
20	Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
21			10-12
22			
23			
24	Generalisability	21	Discuss the generalisability (external validity) of the study results
25			12
26	<b>Other information</b>		
27	Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based
28			2
29			
30			

\*Give information separately for exposed and unexposed groups.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at [www.strobe-statement.org](http://www.strobe-statement.org).