Decrease of Grip Strength is Associated with Progression of Sleep Disturbance in Chronic Liver Diseases

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Abstract

Background and aims: The causal relationship between sarcopenia and sleep disorder in patients with chronic liver disease (CLDs) is unclear. We aimed examine the influence of sarcopenia-related factors (grip strength (GS) and muscle mass) on the progression of sleep disorder in patients with chronic liver disease (n=182, 46 cirrhotic cases, median age=64 years).

Methods: Sleep quality was evaluated by the Japanese version of Pittsburgh Sleep Quality Index (PSQI-J). PSQI-J ≥6 points was defined as sleep disorder. In all analyzed patients, evaluation using PSQI-J questionnaire was performed twice or more during the follow-up period. Time interval from the date of baseline PSQI-J and the first confirmed date of elevation of PSQI-J score was calculated. Our primary endpoint was the elevation of PSQI-J score compared to the baseline PSQI-J score. GS decline was diagnosed with a GS of <26 kg for male and <18 kg for female. Loss of muscle mass was diagnosed by a skeletal muscle index of <7.0 kg/m^2 for male and <5.7 kg/m^2 for female on bioelectrical impedance analysis.

Results: The median PSQI-J score was 5. PSQI-J ≥6 points at baseline was found in 83 patients (45.6%). In patients with GS decline (n=48), the 3-year cumulative elevation rate of PSQI-J score was 82.4%, while in patients with GS non-decline, that was 36.2% (P<0.0001). In patients with SMI decline (n=64), the 3-year cumulative elevation rate of PSQI-J score was 60.6%, while in patients with SMI non-decline, that was 43.4% (P=0.1822). On the multivariate analysis of factors associated with the elevation of PSQI-J score, only GS decline (P=0.0002) was a significant factor.

Conclusions: Reduced GS rather than loss of muscle mass is independently associated with an elevated risk for the progression of sleep disorder in CLD patients.

Key words: Chronic liver disease, Sleep disorder, Muscle strength, Muscle mass

Running title: Grip strength and sleep disturbance in liver diseases

Abbreviations

CLD; chronic liver disease, PSQI; Pittsburgh Sleep Quality Index, PSQI-J; Japanese version of Pittsburgh Sleep Quality Index, GS; strength, BIA; bioelectrical impedance analysis, SMI; skeletal muscle index; JSH; Japanese Society of Hepatology, IQR; interquartile range, HR; hazard ratio, CI; confidence interval, HCV; hepatitis C virus, BMI; body mass index

What's already known about this topic?

1．Sleep is pivotal for the maintenance of mental and physical health.

2．Sarcopenia can result in decreased QOL and be associated with unfavorable outcomes in patients with chronic liver diseases.

What does this article add?

We elucidated the causal relationship between grip strength decline and sleep disorder in patients with chronic liver diseases.

Introduction

Sleep is pivotal for the maintenance of mental and physical health, and there is globally increasing research interest for sleep disorder. Some patients with chronic liver diseases (CLDs) complain of sleep disorders. Iwasa, et al. reported that out of 1788 CLD patients, 4.0% experienced severe sleep disorder, and 33.4% had moderate sleep disorder [1]. Ghabril, et al. reported that 81% of advanced cirrhotic patients have disturbed sleep [2]. One of the reasons for these is the disturbance of the sleep-regulating hormone (i.e., melatonin) and the appetite-regulating hormone (i.e., leptin) during the day. Itchy skin due to CLDs and anxiety about illness can also cause insomnia [3-5]. Kumashiro, et al. demonstrated that sleep disturbance is associated with fat accumulation in the liver and glucose intolerance in mice [6]. Thus, sleep disorder can be a critical issue for CLD patients. Pittsburgh Sleep Quality Index (PSQI) is a widely used and well validated patient-reported sleep questionnaire [7-9].

Skeletal muscle is also an endocrine organ that secretes myokines that regulate systemic glucose and lipid homeostasis and regulate protein synthesis in muscle tissue [10]. Sarcopenia is a condition accompanied by decrease of skeletal muscle mass and strength or physical function [11]. Primary sarcopenia is a condition in which skeletal muscle mass and strength or physical function decline with aging. Secondary sarcopenia is defined as a condition in which skeletal muscle mass and strength or physical function are impaired due to underlying diseases such as respiratory diseases, heart diseases, inflammatory diseases, malignancies, renal diseases, and liver diseases [12]. Regarding mechanisms of falling into sarcopenia in CLD patients, the involvement of various factors (aging, protein energy malnutrition, signal

transduction related to protein synthesis and degradation, myokines, and sex hormones, etc.) has been reported [13-15]. Sarcopenia can result in decreased QOL and be associated with unfavorable outcomes in CLD patients [13, 16-18].

In our previous cross-sectional study, we demonstrated the close relationship between sarcopenia and sleep disorder in CLD patients [19]. There are several reports regarding relationship between sarcopenia and sleep disorder [19-22]. However, the causal relationship between sarcopenia and sleep disorder in CLD patients is unclear. To clarify these problems, we sought to examine the influence of sarcopenia-related factors (i.e., muscle strength and muscle mass) on the progression of sleep disorder in CLD patients.

Patients and methods

Patients

Using a retrospective computerized database, a total of 182 CLD individuals who visited our hospital between December 2013 and April 2018 were analyzed. Clinical features, the Japanese version of PSQI (PSQI-J) scores and laboratory data recorded at baseline were collated. Diagnosis for cirrhosis was determined according to the current guidelines [23]. In all analyzed patients, evaluation using PSQI-J questionnaire was performed twice or more during follow-up period. Time interval from the date of baseline PSQI-J and the first confirmed date of elevation of PSQI-J score was calculated in each subject. The most suitable intervention for each underlying liver disease was performed [23-26]. The study protocol rigorously conformed to the 1975 Helsinki Declaration, and approval of ethics was obtained from the institutional review board in our hospital. An opt out method was employed.

PSQI-J score and our study

Sleep quality was evaluated by PSQI-J, which is a screening tool for sleep disorder [7-9]. PSQI-J consists of 7 categories (a total of 10 questions): (1) subjective sleep quality, (2) sleep latency, (3) sleep duration, (4) habitual sleep efficiency, (5) sleep disorders, (6) use of sleep medications and (7) daytime sleep disturbance. Each category was scored on a scale of 0 to 3, and the sum of PSQI-J scores for all categories was 21 points. Higher PSQI-J scores mean a poorer sleep quality. Favorable sensitivity and specificity were reported to be found when the sum of PSQI-J scores exceeded 6 points [8]. Our cohort were categorized as normal (0-5 points), mild sleep disorder (6-8 points), moderate mild sleep disorder (9-11 points) and severe mild sleep disorder (12 or more points) [7-9].

Muscle strength and muscle mass measurement

Muscle strength (grip strength (GS) in this study) measurement and muscle mass measurement were done based on the previous reports [12]. For the evaluation of muscle mass, bioelectrical impedance analysis (BIA) was performed using InBody 720 to calculate appendicular muscle mass. Skeletal muscle index (SMI) was calculated as sum of muscle mass in upper and lower extremities divided by height squared (kg/m^2). Based on the criteria of Japanese Society of Hepatology (JSH), muscle strength weakness was diagnosed with a GS of <26 kg for male and <18 kg for female. Likewise, loss of muscle mass was diagnosed by a SMI of <7.0 kg/m^2 for male and <5.7 kg/m^2 for female on BIA [12].

Statistics

Continuous variables were presented as median value (interquartile range (IQR)) and compared by Student's t test. Our primary endpoint was the elevation of PSQI-J score compared to the baseline PSQI-J score. Cumulative elevation rates of PSQI-J score were calculated by the Kaplan-Meier method and compared between groups by the log-rank test. Univariate and multivariate Cox proportional hazard models were employed for identifying significant factors associated with the elevation rates of PSQI-J score, and the results were presented as hazard ratios (HRs) and 95% confidence intervals (CIs) with corresponding *P* value. In the univariate analysis, the cohort was divided into two categories using each median value. Variables with *P* value below 0.1 were entered into the multivariate analysis. The JMP version 14.0 software (SAS Institute, Cary, NC, USA) was employed to analyze data statistically (significant level, *P*- value below 0.05).

Results

Patient characteristics

Of the 182 patients with CLDs, 82 (45.1%) were males, and the median (IQR) age was 64 (55, 71) years. There were 136 patients (74.7%) with non-cirrhosis and 46 patients (25.3%) with cirrhosis. There was no patient with overt hepatic encephalopathy. The main liver disease etiology was hepatitis C virus (HCV, 155 cases, 85.2%). The median (IQR) PSQI-J score was 5 (3, 7). PSQI-J score 0-5 (normal) was observed in 99 (54.4%), 6-8 (mild sleep disorder) in 53 (29.1%), 9-11 (moderate sleep disorder) in 19 (10.4%), 12 or more (severe sleep disorder) in 11

(6.0%). The median (IQR) PSQI-J scores in cirrhotic patients and non-cirrhotic patients were 6 (4, 9) and 5 (3, 7) (P=0.0662). GS decline as defined by the JSH criteria was observed in 9 male patients (11.0%) and 39 female patients (39.0%). SMI decline as defined by the JSH criteria was observed in 25 male patients (30.5%) and 39 female patients (39.0%). Sarcopenia as defined by the JSH criteria was observed in 25 patients (13.7%). In patients with any grade of sleep disorder at baseline (PSQI-J score ≥6, n=83), 24 (28.9%) had GS decline, and 28 (33.7%) had SMI decline. The baseline clinical characteristics and laboratory data of all analyzed patients are summarized in table 1.

Cumulative elevation rate of PSQI-J score for all cases (n=182)

During the follow-up period, 61 patients (33.5%) had the elevation of PSQI-J score. For all cases, the 1-, 2- and 3-year cumulative elevation rates of PSQI-J score were 26.4%, 35.2% and 49.3% (Figure 1).

Cumulative elevation rates of PSQI-J score according to the GS value and the SMI value

In patients with GS decline (n=48), the 1-, 2- and 3-year cumulative elevation rates of PSQI-J score were 46.0%, 67.1% and 82.4%, while in patients with GS non-decline (n=134), the 1-, 2- and 3-year cumulative elevation rates of PSQI-J score were 19.1%, 22.9% and 36.2% (P<0.0001, Figure 2A).

In patients with SMI decline (n=64), the 1-, 2- and 3-year cumulative elevation rates of PSQI-J score were 33.1%, 39.3% and 60.6%, while in patients with SMI non-

decline (n=118), the 1-, 2- and 3-year cumulative elevation rates of PSQI-J score were 22.7%, 33.0% and 43.4% (*P*=0.1822, Figure 2B).

Predictors of the elevation of BDI-II score in all patients by univariate and multivariate analyses

As per the univariate analyses, age ≥64 years (*P*=0.0095), gender (*P*=0.0292), and lower GS (*P*<0.0001) were found to be significantly associated with the elevation of PSQI-J score, while HCV or not (*P*=0.0632) and serum albumin ≤4.2 g/dl (*P*=0.0887) tended to be significant (table 2). As per the multivariate analyses, only lower GS (*P*=0.0002) was identified to be a significant factor associated with the elevation of PSQI-J score (table 3). HRs and 95% CIs of age ≥64 years, gender, lower GS, HCV or not, and serum albumin ≤4.2 g/dl were shown in table 3.

Cumulative elevation rates of PSQI-J score according to the GS value and the SMI value in cirrhotic patients and non-cirrhotic patients

Cirrhotic patients with GS decline (n=17) had significantly higher cumulative elevation rates of PSQI-J score compared to those with GS non-decline (n=29) (*P*=0.0210, Figure 3A). Cirrhotic patients with SMI decline (n=15) did not have significantly higher cumulative elevation rates of BDI-II score compared to those with SMI non-decline (n=31) (*P*=0.9373, Figure 3B).

Non-cirrhotic patients with GS decline (n=31) had significantly higher cumulative elevation rates of PSQI-J score compared to those with GS non-decline (n=105) (*P*<0.0001, Figure 3C). Non-cirrhotic patients with SMI decline (n=49) tended to have significantly higher cumulative elevation rates of PSQI-J score compared to those with SMI non-decline (n=87) (*P*=0.0683, Figure 3D).

Cumulative elevation rates of PSQI-J score according to the GS value and the SMI value in patients aged 64 years or more and patients aged less than 64 years

Patients aged 64 years (median age in this study) or more with GS decline (n=37) had significantly higher cumulative elevation rates of PSQI-J score compared to those with GS non-decline (n=61) (P<0.0001, Figure 4A). However, patients aged 64 years or more with SMI decline (n=43) did not have significantly higher cumulative elevation rates of BDI-II score compared to patients with SMI non-decline (n=55) (P=0.6912, Figure 4B).

Patients aged less than 64 years with GS decline (n=11) had significantly higher cumulative elevation rates of PSQI-J score compared to those with GS non-decline (n=73) (P=0.0168, Figure 4C). Patients aged less than 64 years with SMI decline (n=21) tended to have significantly higher cumulative elevation rates of PSQI score compared to patients with SMI non-decline (n=63) (P=0.0701, Figure 4D).

Cumulative elevation rates of PSQI-J score according to the GS value and the SMI value in male and female patients

Male patients with GS decline (n=9) had significantly higher cumulative elevation rates of PSQI-J score compared to those with GS non-decline (n=73) (P=0.0074, Figure 5A). Likewise, male patients with SMI decline (n=25) had significantly higher cumulative elevation rates of PSQI-J score compared to those with SMI non-decline (n=57) (P=0.0347, Figure 5B).

Female patients with GS decline (n=39) had significantly cumulative higher elevation rates of PSQI-J score compared to those with GS non-decline (n=61) (P<0.0001, Figure 5C). However, female patients with SMI decline (n=39) did not

have significantly higher cumulative elevation rates of PSQI-J score compared to those with SMI non-decline (n=61) (*P*=0.9312, Figure 5D).

Cumulative elevation rates of PSQI-J score according to the GS value and the SMI value in patients with baseline PSQI score ≥6 (baseline) and baseline PSQI score ≤5 (baseline)

Patients with baseline PSQI-J score ≥6 with GS decline (n=24) had significantly higher cumulative elevation rates of PSQI score compared to those with GS non-decline (n=59) (*P*=0.0014, Figure 6A). However, patients with baseline PSQI score ≥6 with SMI decline (n=28) did not have significantly higher cumulative elevation rates of PSQI-J score compared to those with SMI non-decline (n=55) (*P*=0.4948, Figure 6B).

Patients with baseline PSQI-J score ≤5 with GS decline (n=24) had significantly higher cumulative elevation rates of PSQI-J score compared to those with GS non-decline (n=75) (*P*<0.0001, Figure 6C). Likewise, patients with baseline PSQI-J score ≤5 with SMI decline (n=36) had significantly higher cumulative elevation rates of PSQI-J score compared to those with SMI non-decline (n=63) (*P*=0.0240, Figure 6D).

Discussion

The causal relationship between sleep disorder and sarcopenia-related factors in CLD patients is not fully examined. In the current study, comprehensive analyses regarding the influence of sarcopenia-related factors on the elevation of PSQI-J score in patients with CLDs were performed. The multivariate analysis identified only GS decline as a significant adverse predictor associated with the elevation of PSQI-J score. To conclude, reduced GS rather than muscle mass was associated with the elevation of PSQI-J score independent of age, cirrhosis status, gender and baseline sleep condition. The causal relationship between sleep disorder and sarcopenia-related factors in CLD patients was clarified to some extent through the present study. To the best of our knowledge, this is the first report demonstrating the impacts of sarcopenia-related factors on the progression of sleep disorder in patients with CLDs.

It is unclear why the weakness of muscle strength can better predict the exacerbation of sleep status in patients with CLDs compared to muscle mass loss. One possible reason for these is that muscle strength decline occurs 2-5 times faster than muscle mass loss, which can be linked to the QOL decline, resulting in the elevation of PSQI-J score [27]. GS is representative of whole−body muscle strength and has been shown to be an independent marker of nutrition [28]. However, in male patients and in patients with baseline PSQI-J score ≤5, the SMI decline group had significantly higher cumulative elevation rates of PSQI-J score compared to the SMI non-decline group. While the current study emphasizes the significance of GS on the progression of sleep disorder, it does not deny the significance of muscle mass on prognosis.

In the present study, 83 patients (45.6%) out of analyzed subjects had baseline PSQI-J score ≥6. In patients with cirrhosis (n=46), 27 patients (58.7%) had baseline PSQI-J score ≥6. Samanta J, et al. reported that 60 out of 100 cirrhotic patients (60%)

had PSQI score ≥6, which were in agreement with our data [29]. Clinicians should be aware of the high prevalence of sleep disorder in CLDs. During the follow-up period, 20 cirrhotic patients (43.5%) had the elevation of PSQI score, while 41 non-cirrhotic patients (30.1%) had the elevation of PSQI score, which was largely different from cirrhotic patients. In addition, the median baseline PSQI-J score in cirrhotic patients tended to be higher than that in non-cirrhotic patients in our data (P=0.0662). Longer liver disease duration in cirrhotic patients and anxiety about having cirrhosis may be linked to the current results.

HCV tended to be significant in our multivariate analysis (P=0.0902). In patients with HCV (n=155), 57 patients (36.8%) had the elevation of PSQI-J score during the follow-up period. Most of these 57 patients received antiviral therapies with sustained virological response (SVR). SVR does not eliminate the possibility of liver carcinogenesis [30]. Similarly, SVR does not solve the sleep problems in patients with HCV considering the current data. Clinicians should be fully aware of these, and post SVR surveillance in HCV patients will be needed. On the other hand, obstructive sleep apnea is frequently seen in patients with non-alcoholic fatty liver disease with obesity [31]. In the present study, the median body mass index (BMI) was 22.7 kg/m^2 and the number of patients with BMI ≥30 kg/m^2 was only 4 (2.2%). The PSQI-J score in these 4 obese patients were 0 or 1. Therefore, it is likely that obstructive sleep apnea is not included in the analyzed subjects, and sleep disorder shown in this study may be due to disease itself or other causes than obstructive sleep apnea.

PSQI-J question 8 is a question regarding the frequency of falling asleep while driving, eating and social activities. In our data, 19 patients (10.4%) had a scale of 1 or more (i.e., experience of drowsiness at least once a week) in the question 8 of

PSQI-J. Excessive drowsiness, especially while driving, can lead to major accidents, so caution should be exercised for such patients [32, 33].

The limitations of our study must be acknowledged. First, the retrospective nature of the study limits the evaluation of factors influencing the sleep condition such as life circumstances or sleep medications. Second, PSQI-J is a subjective assessment tool, and not objective one. Third, our data were derived from Japanese CLD patient data; further examinations on other cohorts will be required to extend the application. Finally, several interventions for CLD patients during the follow-up period have been done, making bias for the disease progression. Thus, interpretation with caution to the results will be needed.

In conclusion, we would like to emphasize the significance of muscle strength on the sleep condition in CLDs. Our study findings involve essential implications in clinical practice as they highlight that reduced GS rather than loss of muscle mass is independently associated with an elevated risk for the progression of sleep disorder. Appropriate interventions for CLD patients with GS decline will be necessary for improving patient QOL including sleep condition.

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Authors' Contribution

Data curation, H.N., K.Y., H.E., and T.N.; Formal analysis, H.N.; Supervision, S.N. and H.I.; Writing – original draft, H.N. and K.Y.; Writing – review & editing, H.E.

Conflicts of interest

Nothing to declare.

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Figure Legend

Figure 1. Cumulative elevation rate of PSQI-J score for all cases (n=182).

Figure 2. (A) Cumulative elevation rate of PSQI-J score according to the GS decline. (B) Cumulative elevation rate of PSQI-J score according to the SMI decline.

Figure 3. Cumulative elevation rate of PSQI-J score according to the GS decline (A) and the SMI decline (B) in cirrhotic patients. Cumulative elevation rate of PSQI-J score according to the GS decline (C) and the SMI decline (D) in non-cirrhotic patients.

Figure 4. Cumulative elevation rate of PSQI-J score according to the GS decline (A) and the SMI decline (B) in patients aged 64 years (median age) or more. Cumulative

elevation rate of PSQI-J score according to the GS decline (C) and the SMI decline (D) in patients less than 64 years.

Figure 5. Cumulative elevation rate of PSQI-J score according to the GS decline (A) and the SMI decline (B) in male patients. Cumulative elevation rate of PSQI-J score according to the GS decline (C) and the SMI decline (D) in female patients.

Figure 6. Cumulative elevation rate of PSQI-J score according to the GS decline (A) and the SMI decline (B) in patients with baseline PSQI-J score ≥6. Cumulative elevation rate of PSQI-J score according to the GS decline (C) and the SMI decline (D) in patients with baseline PSQI-J score ≤5.