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【 ORIGINAL ARTICLE 】

Factors Related to Sleeping Disorder Due to Pruritus in Patients with Chronic Liver Disease

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Abstract:

Objective This study evaluated cases of pruritus, which is known to be associated with sleep disorder, in chronic liver disease (CLD) patients.

Methods Questionnaires were given to 339 enrolled CLD outpatients in winter (November 2019 to March 2020) and again in summer (April to October 2020) (median interval: 104 days). Relative changes in symptoms shown by a visual analogue scale (VAS) and Kawashima's pruritus score between winter and summer were evaluated in Study 1 (n=199), while Study 2 examined the clinical features of patients with sleep disorder based on the results of the second questionnaire (n=235, median age 70 years old; 141 men, liver cirrhosis 37%).

Results Study 1. There was a significant relationship in VAS between daytime and nighttime for each season, as well as between winter and summer for each time period ($p<0.001$). A comparison of Kawashima's pruritus scores for the daytime and nighttime showed no significant seasonal differences ($p=0.436$ and 0.828, respectively). When Kawashima's score increased, so did the average VAS for both daytime (0:1:2:3:4=0.4±0.2:1.4±0.9:3.0±1.8:5.9±2.1:6.2±2.3) and nighttime (0:1:2:3:4=0.3±0.1:1.4±1.5:3.5±2.3:6.7±2.6:6.9±1.8) ($p<0.001$ for both). Study 2. Twenty subjects (8.5%) complained of sleep disorder. An elevated FIB-4 index (≥3.07) showed a good predictive value for sleep disorder ($p<0.01$). The cut-off for the daytime and nighttime VAS values for existing sleep disorder were 1.6 [area under the curve (AUC) 0.901] and 3.4 (AUC 0.931). The respective sensitivity, specificity, and positive and negative predictive values for sleep disorder based on Kawashima's score (≥2) were 0.85, 0.28, 0.10, and 0.95 for the daytime and 1.00, 0.29, 0.12, and 1.00 for the nighttime.

Conclusion Intervention against pruritus is recommended in CLD patients with a high Kawashima's score (≥2) in any season, especially with an elevated FIB-4 index.

Key words: pruritus, chronic liver disease, quality of life, nalfurafine hydrochloride, FIB-4 index

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Introduction

Pruritus is a complication commonly seen in end-stage renal disease (ESRD) patients treated with hemodialysis (ranging from 36% in France to 50% in the United Kingdom) (1), and the presence of a sleep disorder is known to be associated with a reduced quality of life (QOL) (2). To improve the prognosis of ESRD patients, the importance of an improved QOL in those affected by pruritus has become

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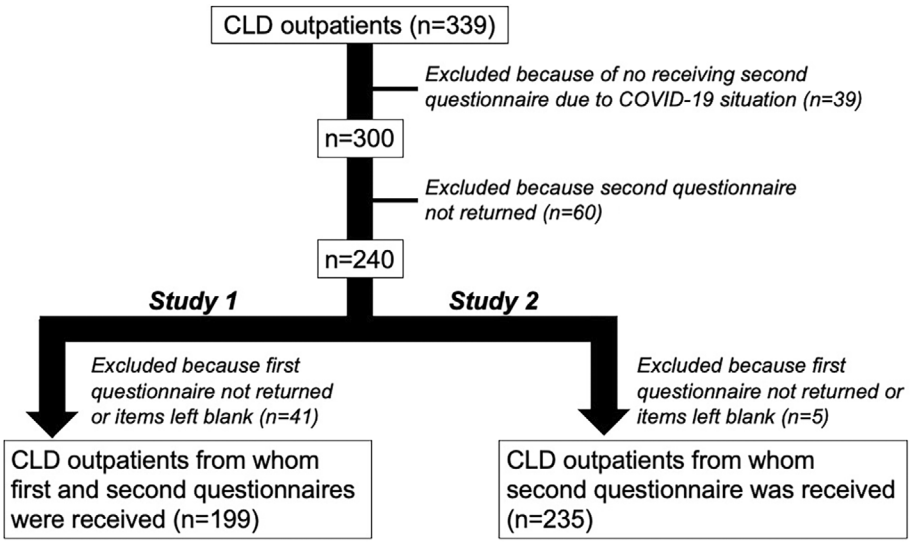

Figure 1. **Flow of the present study. CLD: chronic liver disease**

recognized as an important factor, with appropriate intervention to treat sleep disturbance shown to be effective (3). In addition, in chronic liver disease (CLD) patients, pruritus has been recognized as a common complication and found to be associated with the sleep quality and QOL (4).

Recently, nalfurafine hydrochloride (5), a selective κ-opioid receptor agonist, received approval for use in the treatment of pruritus in ESRD as well as CLD patients. However, specific information for clinicians is limited regarding the effects of sleep disorder-related pruritus, so establishing an objective assessment tool to identify patients at high risk for sleep disorder and who require intervention is considered important.

The present study was conducted to elucidate the characteristics of CLD patients complicated with a pruritus-associated sleep disorder.

Materials and Methods

This study was conducted at a single institution. From November 2019 to October 2020, a total of 339 CLD outpatients were enrolled and analyzed in a retrospective manner (Fig. 1). Questionnaires were given to the subjects at the time of their interview at the outpatient department in winter (from November 2019 to March 2020) and again in summer (from April to October 2020). The answers were noted, and two studies were performed. Study 1 was an analysis of the relative changes in symptoms between the winter and summer seasons, while Study 2 evaluated the presence of a sleep disorder related to pruritus in the CLD patients who returned the second (summer) questionnaire, which included a question asking about the presence of any sleep disorder. In addition, the humidity at the time of answering was recorded from a local temperature website (noon and midnight) (https://tenki.jp). None in the present cohort had received prior continuous treatment with nalfurafine hydrochloride.

Basal liver disease

CLD due to hepatitis C virus (HCV) was determined in subjects positive for anti-HCV, while CLD due to hepatitis B virus (HBV) was determined when the hepatitis B virus surface antigen was positive.

Tools for assessing the hepatic function

To assess the hepatic reserve function, the Child-Pugh classification (6) and modified albumin-bilirubin (ALBI) grade (mALBI) were used. The ALBI score was calculated with the serum albumin and total bilirubin values using the following formula: ALBI score=log10 bilirubin (μmol/L)×0.66+albumin (g/L)×-0.085 (≤-2.60, ALBI grade 1; >-2.60 to ≤-1.39, grade 2; and >-1.39, grade 3) (7-9). For a more detailed evaluation of subjects classified as the middle ALBI grade of 2, subjects were divided into 2 sub-grades (2a and 2b) (mALBI grade) based on an ALBI score of -2.27 as the cut-off value, which was previously developed based on the value for predicting 30% of indocyanine green retention after 15 minutes (10, 11). The degree of hepatic fibrosis was evaluated with the FIB-4 index (12).

Questionnaire regarding pruritus

During consultation, an outpatient unit nurse gave each subject a questionnaire. Itch severity was self-assessed using a visual analogue scale (VAS) (13) and Kawashima's pruritus score (14), which is based on a 5-point scale: 4 (intolerable itchiness, or little or no sleep due to itchiness), 3 (often feel itchiness and the urge to scratch even in public, or sleep disturbance due to itchiness), 2 (scratching occasionally, light itchiness, or can return to sleep after scratching), 1 (sometimes have a sense of itchiness but not enough to scratch, no sleep disturbance), 0 (little or no itchiness).

The questionnaire included the following questions: 1) When do you feel itchiness the most? (daytime, nighttime, both); 2) Are you currently taking medication for itchiness?

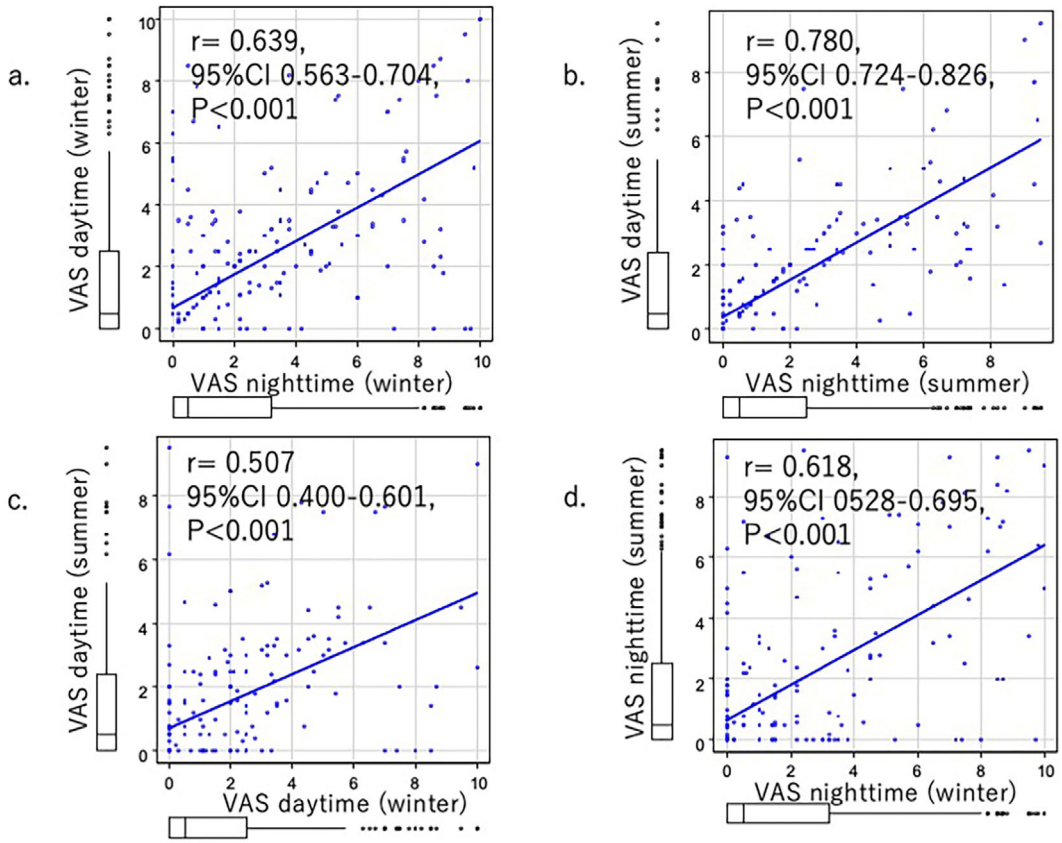

Figure 2. Correlations of VAS with time of day and seasons. The correlation between the daytime and nighttime VAS values in (a) winter and (b) summer, and between the winter and summer VAS values in (c) daytime and (d) nighttime. Each showed a significant relationship (p<0.001). VAS: visual analogue scale

(oral medicine, external medicine, other, none); 3) If you answered yes to the second question about taking medicine, has that improved the itchiness?; 4) How many times do you sense itchiness per day?; 5) How long does the itchiness last?; and 6) Where on your body do you feel itchiness? The second questionnaire had the same questions with one additional question: 7) Does itchiness cause you to wake up while sleeping? or to have sleep disorder due to itchiness?

The present investigation was conducted as a retrospective analysis of database records. The study protocol, based on the Guidelines for Clinical Research issued by the Ministry of Health and Welfare of Japan received approval from the Institutional Ethics Committee of our institution (IRB No. 31-50) and was conducted according to the Declaration of Helsinki.

Statistical analyses

Welch's *t*-test, Student's *t*-test, a paired *t*-test, Fischer's exact test, Pearson's test, Wilcoxon signed-rank test, and the Mann-Whitney's U test were used for the statistical analyses, as appropriate. When values are shown as the median, the interquartile range (IQR) is also shown. P values less than 0.05 were considered to indicate statistical significance. A receiver operating characteristic (ROC) curve and the area under the curve (AUC) were calculated for comparisons between VAS and sleep disorder due to pruritus.

All statistical analyses were performed using the Easy R (EZR) package, version 1.53 (Saitama Medical Center, Jichi Medical University, Saitama, Japan) (15), a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria).

Results

Of the 339 subjects, 39 did not receive the second questionnaire because of an inability to visit the hospital during the coronavirus disease 2019 (COVID-19) pandemic, and another 60 who received the second questionnaire did not return it. The median interval between the first and second questionnaire was 104 days (IQR: 84-175 days), and answers to the first and second questionnaire were received from 217 and 235 subjects, respectively. As a result, we analyzed seasonal changes in the VAS as a continuous variable using data obtained from 199 patients who completed both questionnaires (Fig. 1).

Study 1

Relationships between daytime and nighttime VAS values and the winter and summer VAS values are presented in

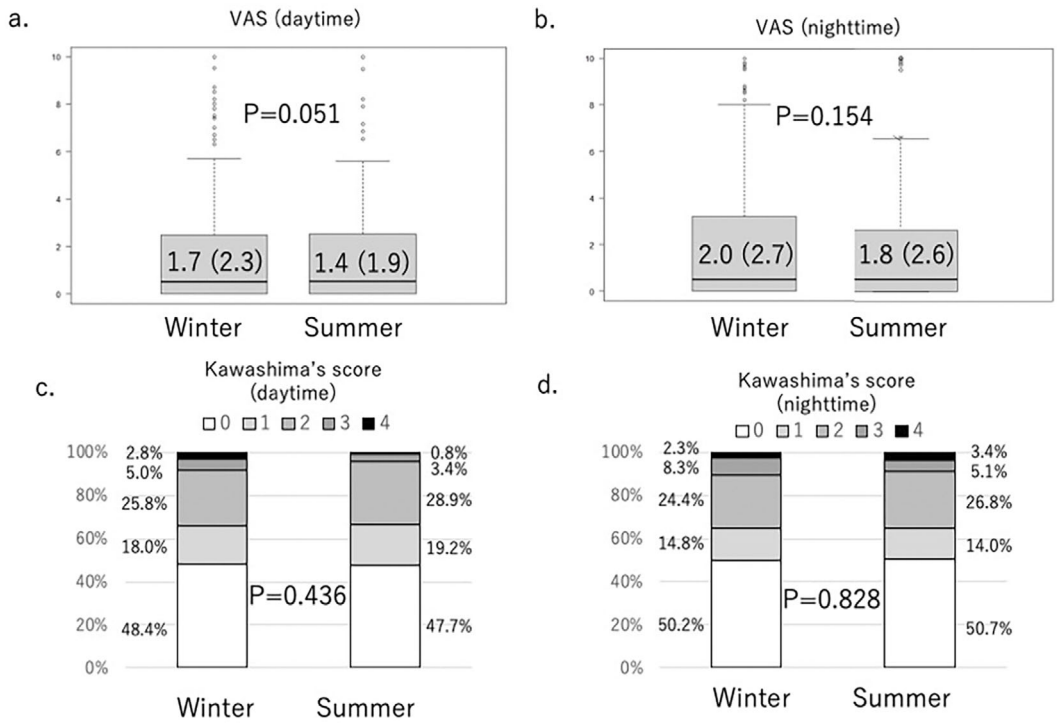

Figure 3. The comparison of the VAS values and Kawashima's pruritus score between seasons. There was no significant difference in the VAS value between winter and summer for (a) daytime or nighttime or between the (c) daytime and (d) nighttime Kawashma's pruritus scores. VAS: visual analogue scale

Fig. 2. There was a significant correlation in VAS between daytime and nighttime in winter [r=0.639, 95% confidence interval (CI) 0.563-0.704, p<0.001] (Fig. 2a) as well as in summer (r=0.780, 95% CI 0.724-0.826, p<0.001) (Fig. 2b). In addition, daytime VAS values in winter and summer showed a significant correlation (r=0.507, 95% CI 0.400-0.601, p<0.001) (Fig. 2c), which was also seen for nighttime VAS values between the seasons (r=0.618, 95% CI 0.528-0.695, p<0.001) (Fig. 2d). The average VAS value for daytime in winter was 1.7±2.3, and that in summer was 1.4±1.9 (p=0.051) (Fig. 3a), while those for nighttime were 2.0±2.7 and 1.8±2.6, respectively (p=0.154) (Fig. 3b). In addition, Kawashima's pruritus scores for daytime and nighttime were not significantly different between the winter and summer seasons (p=0.436 and 0.828, respectively) (Fig. 3c, d).

As Kawashima's pruritus score increased, so did the average VAS value for both daytime (0, 1, 2, 3, 4: 0.4±0.2, 1.4±0.9, 3.0±1.8, 5.9±2.1, 6.2±2.3, respectively) and nighttime (0, 1, 2, 3, 4: 0.3±0.1, 1.4±1.5, 3.5±2.3, 6.7±2.6, 6.9±1.8, respectively) (both p<0.001) (Supplementary material 1). In contrast, neither the age nor humidity showed a significant correlation with the VAS for daytime or nighttime in the winter or summer (Supplementary material 2, 3).

The patients with deteriorations of VAS (>0) from winter to summer did not show significant differences in their clinical features (e.g., the age, gender, basal liver diseases, hepatic function, FIB-4 index, etc.) (data not shown).

Study 2

Of the 235 CLD patients enrolled (Table 1), 20 (8.5%) complained of sleep disorder. In addition, an analysis showed that the patients with sleep disorder had a significantly lower platelet count, worse ALBI (mALBI grade)/Child-Pugh scores, higher FIB-4 index, higher rate of attempting treatment for pruritus, and higher frequency of a large number of itchiness incidents per day and itchiness duration than those without (Table 2). In the present study, there were no significant differences in sleep disorder (p=0.200) or daytime and nighttime VAS values between patients with and without chronic viral hepatitis infection (p=0.981 and p=0.939, respectively). The VAS values showed a significant relationship with the ALBI score for both daytime (r=0.209, 95% CI 0.083-0.328, p=0.001) (Fig. 4a) and nighttime (r=0.279, 95% CI 0.156-0.393, p<0.001) (Fig. 4b). Similar results were observed for the VAS values and FIB-4 index in daytime (r=0.252, 95% CI: 0.128-0.369, p<0.001) (Fig. 4c) and nighttime (r=0.268, 95% CI: 0.145-0.383, p<0.001) (Fig. 4d). The occurrence of frequent pruritus per day (≥3 times) was significantly greater in patients with sleep disorder than in those without (19.6% vs. 65.0%, p<0.001) (Fig. 4e), a trend also seen for the duration of pruritus (≥3 minutes) (38.6% vs. 90.0%, p<0.001) (Fig. 4f).

The VAS cut-off value for predicting sleep disorder in daytime was 1.6 (AUC 0.901, 95% CI 0.852-0.949) (sensitivity/specificity=0.722/1.000), while that for nighttime was 3.4 (AUC 0.931, 95% CI 0.894-0.968) (sensitivity/specificity

Table 1. Clinical Characteristics of Patients (n=235).

Age, years	70 (61-70)
Gender (male:female)	141:94
Basal liver disease (HCV:HBV:HBV&HCV:alcohol:others)	92:71:2:15:55
HCC (without:history of treatments:with)	149:72:14
Platelets, 10^4/μL	17.3 (12.2-21.5)
AST, U/L	26 (20-35)
ALT, U/L	21 (15-32)
Total bilirubin, mg/dL	0.7 (0.5-0.9)
Albumin, g/dL	4.2 (3.9-4.5)
Prothrombin time	94.0% (83.0-101.0%)
FIB-4 index	2.64 (1.44-4.14)
Liver cirrhosis	87 (37.0%)
ALBI score (mALBI grade 1:2a:2b:3)	-2.91 (-2.62 to -3.11) (181:27:25:2)
Child-Pugh score (5:6:7:8:9:≥10)	209:13:6:4:2:1

Values are shown as number (interquartile range), unless otherwise noted.
HCV: hepatitis C virus, HBV: hepatitis B virus, AST: aspartate aminotransferase, ALT: alanine aminotransferase, ALBI score: albumin-bilirubin, mALBI grade: modified ALBI grade

Table 2. Clinical Features of Patients with and without Sleep Disorder.

	Without (n=215)	With (n=20)	p value
Age, years	70 (61-77)	71 (63-80)	0.404
Gender (male:female)	128:87	13:7	0.812
Basal liver disease (HCV:HBV:HBV&HCV:alcohol:others)	79:67:1:14:53	12:4:1:1:2	0.065
HCC (without:history of treatments:with)	140:64:11	9:8:3	0.072
Platelets (10^4/μL)	17.6 (12.6-21.6)	15.1 (7.8-17.6)	0.015
ALBI score, mALBI grade 1:2a:2b:3	-2.91 (-2.65- -3.12), 170:25:18:2	-2.63 (-2.13- -2.96), 11:2:7:0	0.006 (0.011)
Child-Pugh score, 5:6:7:8:9:≥10	197:8:3:4:2:1	12:5:3:0	<0.001
FIB-4 index	2.55 (1.38-4.01)	4.64 (3.16-7.65)	<0.001
Medication for itching (none:external:oral:combined:other)	170:38:2:4:1	8:9:1:2:0	0.001
Therapeutic effect, (improved:slightly improved:no improvement)	19:27:0 (n=46)	3:8:1 (n=12)	<0.001
Number of itching incidents per day, none:1:2:3-5:>5	103:34:36:41:1	0:2:5:7:6	<0.001
Itching duration, min, 0 or <1:1:2:3-5:>5	103:22:7:42:41	0:1:1:4:14	<0.001
Kawashima's pruritus score (daytime), 0:1:2:3:4	112:42:59:2:0	0:3:9:6:2	<0.001
Kawashima's pruritus score (nighttime), 0:1:2:3:4	119:33:59:3:1	0:0:4:9:7	<0.001

Values are shown as number (interquartile range), unless otherwise noted.
HCV: hepatitis C virus, HBV: hepatitis B virus, HCC: hepatocellular carcinoma, AST: aspartate aminotransferase, ALT: alanine aminotransferase, ALBI score: albumin-bilirubin, mALBI grade: modified ALBI grade

=0.854/0.900) (Fig. 5a, b). The predictive value of the ALBI score (-2.984) for sleep disorder was not good (AUC 0.524, 95% CI 0.408-0.640) (sensitivity/specificity=0.442/0.680), while that of the FIB-4 index (3.07) was good (AUC 0.748, 95% CI 0.634-0.860) (sensitivity/specificity=0.623/0.800) (Fig. 5c). In contrast, the frequency of a high Kawashima's pruritus score was significantly greater in patients with sleep disorder in daytime and nighttime as compared to those without a sleep disorder (both p<0.001) (Fig. 5d, e). The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for sleep disorder-shown by a Kawashima's pruritus score ≥2-in daytime were 0.85, 0.28, 0.10, and 0.95, respectively, while those in nighttime were 1.00, 0.29, 0.12, and 1.00, respectively. The body part most affected by itchiness was the back (45.6%), followed by the lower limbs (37.5%), with some overlap (Supplementary material 4). In the head and neck, back, and lower limbs, there were significant differences in the presence of itchiness between the winter and summer seasons (improved/worsened: 5.9%/1.8%, 4.1%/6.4%, and 4.6%/11.0%, p<0.05, respectively). In the 57 patients treated with antihistamine and/or external medicine, no significant improvement in itchiness was observed (data not shown).

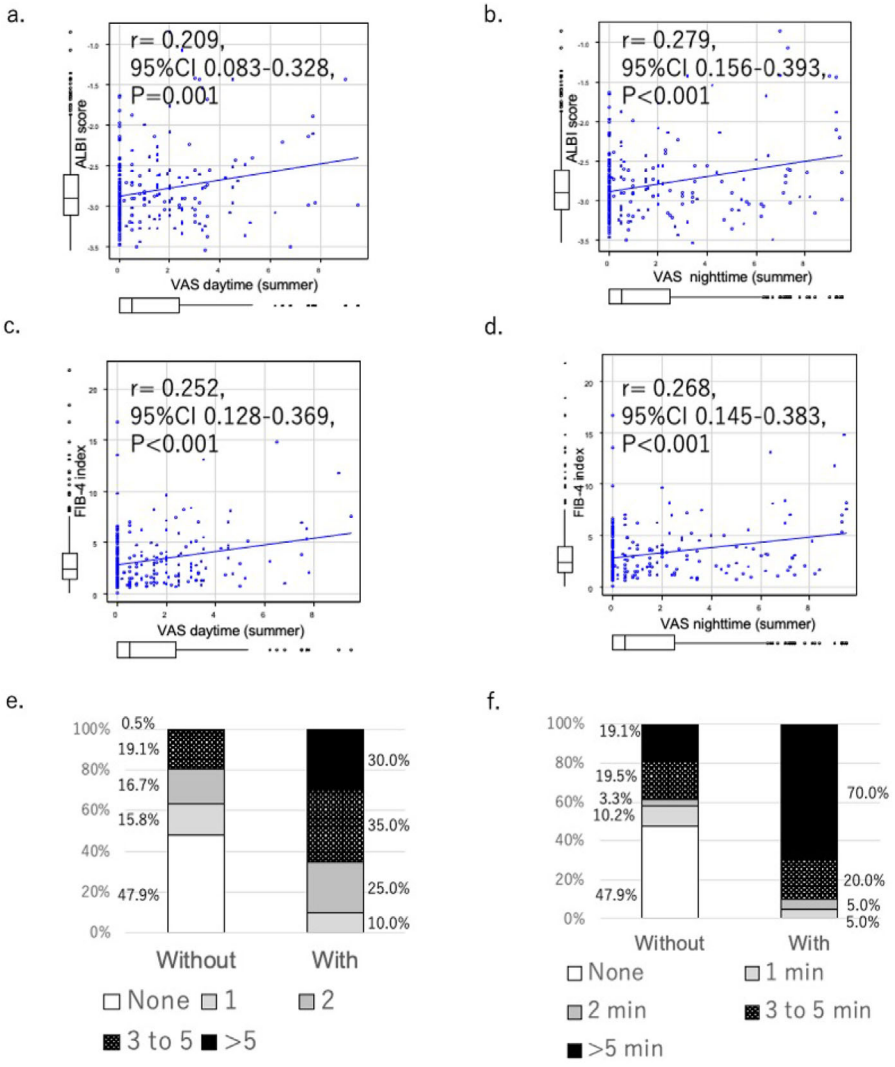

Figure 4. **The correlation between the hepatic function or FIB-4 index and visual analogue scale (VAS), and differences regarding pruritus between patients with and without sleep disorder. The albumin-bilirubin score showed a significant relationship with the VAS for summer (a) daytime and (b) nighttime. The FIB-4 index also showed a significant relationship with the VAS for summer (c) daytime and (d) nighttime. Patients with a sleep disorder showed a larger number of pruritus incidents each day (p<0.001) (e). Patients with a sleep disorder showed a greater frequency of longer duration pruritus than those without a disorder (p<0.001) (f).**

Discussion

Although there were a small number of decompensated liver cirrhosis patients classified as Child-Pugh B or C in the present cohort, our results showed a significant relationship between the ALBI score and FIB-4 index with the VAS. Akuta et al. (16) previously reported that negative HBsAg [odds ratio (OR) 4.61, p=0.012] and lower platelet count ($<10^4$/μL) (OR 2.39, p=0.017) were associated with a high Kawashima's pruritus score (≥3 points) (16). Furthermore, Tachi et al. presented results demonstrating that a history of HCC and high liver stiffness (on shear-wave elastography) were related, despite a sustained virological response (SVR) being achieved by direct-acting antiviral (DAA) administration in patients infected with HCV (17). Thus, patients with high liver stiffness are suggested to mainly be at high risk for pruritus. Interestingly, not only the ALBI score but also a high FIB-4 index (3.07) was a predictor of a sleep disorder in the present study. Of note, Rishe et al. reported that the rate of pruritus was 69% in primary biliary cirrhosis (PBC) patients (18), while it ranged from 5.1% to 20% in those infected with HCV (19-21) and was 8% in those with HBV (21). However, regarding the etiology of basal liver diseases and HCC, there were no significant differences in the rate of those conditions between patients with and without sleep disorder in the present study. Regardless of basal liver disease, interviews asking about pruritus and sleep disorder should be performed in CLD patients with an elevated FIB-4 index.

There was no significant difference in the frequency or severity of pruritus between winter and summer. Interest-

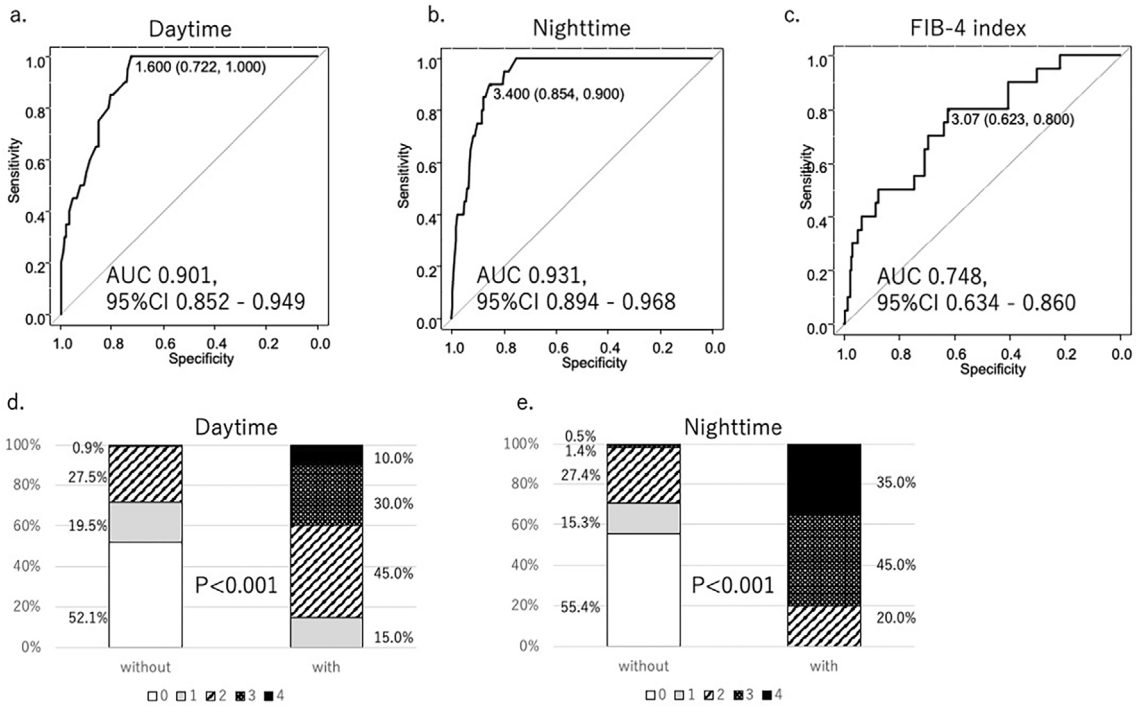

Figure 5. Predictive values of visual analogue scale (VAS) for the existence of a sleep disorder and the relationship between Kawashima's pruritus score and sleep disorder. The predictive values of VAS for the existence of sleep disorder in the (a) daytime were 1.6 [the area under curve (AUC) 0.901, 95% confidence interval (CI) 0.852-0.949], and those in the (b) nighttime were 3.4 (AUC 0.931, 95% CI 0.894-0.968). The predictive value of the FIB-4 index (3.07) was good (AUC 0.748, 95% CI 0.634-0.860) (sensitivity/specificity=0.623/0.800) (c). Patients with a sleep disorder showed a higher Kawashima's pruritus score in both (d) daytime and (e) nighttime than those without a disorder.

ingly, while neither age nor humidity showed a significant relationship with the VAS, in a previous study that examined itchiness in patients with PBC, 46% answered summer and 38% winter as the worst season (18). In contrast, Oeda et al. found that 45% of their subjects reported seasonal worsening, with 80.1% answering that it occurred in winter (22). The present results did not indicate a specific seasonal involvement. Differences related to ethnicity, severity of liver fibrosis, and geographic area where the studies were performed might have been factors causing these differences.

A previous report used Patient-Reported Outcomes Measurement Information System (PROMIS) scores and found that itchiness was similar to pain, constipation, sexual dysfunction, cough, and weight loss as factors affecting patient burden (23). In addition, a study that used the short-form health survey 36 item (SF-36) for primary sclerosing cholangitis (PSC) found more frequent pruritus to be associated with a considerable reduction in the QOL of patients in terms of physical and social functioning, general and mental health, bodily pain, vitality, and daily life roles (because of physical problems) ($p<0.01$) (24). These results indicate that pruritus worsens the QOL of affected CLD patients and suggest that an adequate intervention strategy should be established.

Although pruritus has been recognized as a common complication in CLD patients, the causative factors have not been elucidated. In general, existing medications (e.g., oral antihistamine, anti-allergy, external drugs) are used to treat itchiness, although improvement (vanishing symptom) was only noted in 36.5% of CLD patients thus treated in a previous study (22). Thornton et al. noted that plasma levels of Methionine enkephalin, an endogenous opioid peptide with μ-receptor agonist properties, were inversely correlated with the plasma albumin levels ($r=-0.434$, $p<0.002$) and suggested that pruritus might be expressed through the activation of opioid μ-receptors in the central nervous system (25). Nalfurafine hydrochloride, a selective κ-opioid receptor agonist (5), has been approved for the treatment of pruritus based on findings of good therapeutic efficacy (26). In a study conducted by Kumada et al. (26), changes in the VAS at week 4 were significantly greater in the nalfurafine hydrochloride groups that received 2.5 or 5 μg/day (28.56 and 27.46 mm, respectively) than in the placebo group (19.25 mm) (both $p<0.01$). Although this medication has shown favorable therapeutic effects, it is also important to keep in mind that its discontinuation was found to lead to pruritus recurrence in 100% of examined cases (27).

Answers to the questionnaire given by the present cohort revealed the existence of sleep disorder in CLD patients due to pruritus. These patients are likely to consider itchiness as a matter of course, so it is very important to confirm its presence and degree by an interview when considering inter-

vention. The same has been reported for sleep disorder and a decline in the QOL in CLD patients because of muscle cramping (28), and it is well known that a proper therapeutic diagnosis is important for relieving related symptoms by carnitine supplementation, as carnitine deficiency, a cause of muscle spasms, is serologically undiagnosable. Naturally, pruritus is also difficult to diagnose with a serological method, so it is necessary to clarify the symptoms by an interview in order to consider treatment intervention as well as possible carnitine deficiency. To improve the QOL in these patients, the first step for clinicians might be to suspect the existence of pruritus symptoms and then assess their improvement following intervention using a questionnaire, such as the VAS and/or Kawashima's pruritus score.

Several limitations associated with the present study warrant mention. First, this was a single-center study conducted in a retrospective manner. Second, although sleep disorder is often correlated with the average sleep duration, a neurotransmitter imbalance due to mild encephalopathy, skin moisturizing, and/or intake of caffeine, the questionnaire used in the present study and clinical background data did not include such information. Third, there were no data on the improvement in the Kawashima score, VAS, or sleep disturbance after administration of nalfurafine hydrochloride in the present cohort, as this study was a questionnaire survey. Furthermore, the present cohort was relatively small in number, and the population was not large enough to obtain concrete conclusions. A randomized trial with intervention by nalfurafine to assess improvements in sleep disorder in patients with a Kawashima's pruritus score of ≥2 should be performed in a greater number of patients in the near future.

In patients with significant liver stiffness (e.g., FIB-4 index ≥3.07), interviewing for pruritus and sleep disorder should be performed. Furthermore, intervention for pruritus in CLD patients should be considered because patients may have sleep disturbance if their Kawashima's pruritus score is ≥2 at any time or if their VAS is ≥1.6 in the daytime or ≥3.4 in the nighttime. When pruritus symptoms relapse or no improvement is seen with existing medications, nalfurafine hydrochloride should be considered.

The authors state that they have no Conflict of Interest (COI).

References

1. Pisoni RL, Wikström B, Elder SJ, et al. Pruritus in haemodialysis patients: International results from the Dialysis Outcomes and Practice Patterns Study (DOPPS). Nephrol Dial Transplant **21**: 3495-3505, 2006.
2. Elder SJ, Pisoni RL, Akizawa T, et al. Sleep quality predicts quality of life and mortality risk in haemodialysis patients: results from the Dialysis Outcomes and Practice Patterns Study (DOPPS). Nephrol Dial Transplant **23**: 998-1004, 2008.
3. Scherer JS, Combs SA, Brennan F. Sleep disorders, restless legs syndrome, and uremic pruritus: diagnosis and treatment of common symptoms in dialysis patients. Am J Kidney Dis **69**: 117-128, 2017.
4. Montagnese S, Nsemi LM, Cazzagon N, et al. Sleep-wake profiles in patients with primary biliary cirrhosis. Liver Int **33**: 203-209, 2013.
5. Seki T, Awamura S, Kimura C, et al. Pharmacological properties of TRK-820 on cloned mu-, delta- and kappa-opioid receptors and nociceptin receptor. Eur J Pharmacol **376**: 159-167, 1999.
6. Pugh RN, Murray-Lyon IM, Dawson JL, Pietroni MC, Williams R. Transection of the oesophagus for bleeding oesophageal varices. Bri J Surg **60**: 646-649, 1973.
7. Johnson PJ, Berhane S, Kagebayashi C, et al. Assessment of liver function in patients with hepatocellular carcinoma: a new evidence-based approach-the ALBI grade. J Clin Oncol **33**: 550-558, 2015.
8. Hiraoka A, Kumada T, Michitaka K, et al. Usefulness of albumin-bilirubin grade for evaluation of prognosis of 2584 Japanese patients with hepatocellular carcinoma. J Gastroenterol Hepatol **31**: 1031-1036, 2016.
9. Hiraoka A, Kumada T, Kudo M, et al. Albumin-bilirubin (ALBI) grade as part of the Evidence-Based Clinical Practice Guideline for HCC of the Japan Society of Hepatology: a comparison with the liver damage and Child-Pugh classifications. Liver Cancer **6**: 204-215, 2017.
10. Hiraoka A, Michitaka K, Kumada T, et al. Validation and potential of albumin-bilirubin grade and prognostication in a nationwide survey of 46,681 hepatocellular carcinoma patients in Japan: the need for a more detailed evaluation of hepatic function. Liver Cancer **6**: 325-336, 2017.
11. Hiraoka A, Kumada T, Tsuji K, et al. Validation of modified ALBI grade for more detailed assessment of hepatic function in hepatocellular carcinoma patients: a multicenter analysis. Liver Cancer **8**: 121-129, 2019.
12. Vallet-Pichard A, Mallet V, Nalpas B, et al. FIB-4: an inexpensive and accurate marker of fibrosis in HCV infection. comparison with liver biopsy and fibrotest. Hepatology **46**: 32-36, 2007.
13. Wahlgren CF, Ekblom A, Hägermark O. Some aspects of the experimental induction and measurement of itch. Acta Derm Venereol **69**: 185-189, 1989.
14. Kawashima M, Tango T, Noguchi T, Inagi M, Nakagawa H, Harada S. Addition of fexofenadine to a topical corticosteroid reduces the pruritus associated with atopic dermatitis in a 1-week randomized, multicentre, double-blind, placebo-controlled, parallel-group study. Br J Dermatol **148**: 1212-1221, 2003.
15. Kanda Y. Investigation of the freely available easy-to-use software 'EZR' for medical statistics. Bone Marrow Transplant **48**: 452-458, 2013.
16. Akuta N, Kumada H, Fujiyama S, et al. Predictors of pruritus in patients with chronic liver disease and usefulness of nalfurafine hydrochloride. Hepatol Res **48**: 45-50, 2018.
17. Tachi Y, Hirai T, Kojima Y, et al. Predictive ability of shear wave elastography for pruritus in chronic hepatitis C patients with sustained virological response. Eur J Gastroenterol Hepatol **30**: 1066-1072, 2018.
18. Rishe E, Azarm A, Bergasa NV. Itch in primary biliary cirrhosis: a patients' perspective. Acta Derm Venereol **88**: 34-37, 2008.
19. Lebovics E, Seif F, Kim D, et al. Pruritus in chronic hepatitis C: association with high serum bile acids, advanced pathology, and bile duct abnormalities. Dig Dis Sci **42**: 1094-1099, 1997.
20. Cacoub P, Poynard T, Ghillani P, et al. Extrahepatic manifestations of chronic hepatitis C. MULTIVIRC Group. Multidepartment Virus C. Arthritis Rheum **42**: 2204-2212, 1999.
21. Bonacini M. Pruritus in patients with chronic human immunodeficiency virus, hepatitis B and C virus infections. Dig Liver Dis **32**: 621-625, 2000.
22. Oeda S, Takahashi H, Yoshida H, et al. Prevalence of pruritus in patients with chronic liver disease: a multicenter study. Hepatol Res **48**: E252-e262, 2018.

23. Silverberg JI, Hinami K, Trick WE, Cella D. Itch in the general internal medicine setting: a cross-sectional study of prevalence and quality-of-life effects. Am J Clin Dermatol **17**: 681-690, 2016.

24. Gotthardt DN, Rupp C, Bruhin M, et al. Pruritus is associated with severely impaired quality of life in patients with primary sclerosing cholangitis. Eur J Gastroenterol Hepatol **26**: 1374-1379, 2014.

25. Thornton JR, Dean H, Losowsky MS. Is ascites caused by impaired hepatic inactivation of blood borne endogenous opioid peptides? Gut **29**: 1167-1172, 1988.

26. Kumada H, Miyakawa H, Muramatsu T, et al. Efficacy of nalfurafine hydrochloride in patients with chronic liver disease with refractory pruritus: a randomized, double-blind trial. Hepatol Res **47**: 972-982, 2017.

27. Akuta N, Kumada H, Fujiyama S, et al. Recurrence rates of pruritus after the stop of nalfurafine hydrochloride in chronic liver disease: Preliminary prospective confirmatory trial. Hepatol Res **48**: 810-813, 2018.

28. Iwasa M, Karino Y, Kawaguchi T, et al. Relationship of muscle cramps to quality of life and sleep disturbance in patients with chronic liver diseases: a nationwide study. Liver Int **38**: 2309-2316, 2018.