【 ORIGINAL ARTICLE 】

# The Efficacy of Levocarnitine Treatment in Relieving Fatigue in Patients with Cirrhosis but without Overt Hepatic Encephalopathy

Kazumichi Abe, Masashi Fujita, Manabu Hayashi, Atsushi Takahashi and Hiromasa Ohira

## Abstract:

**Objective**   In the present study, we prospectively examined the efficacy of levocarnitine in relieving symptoms of fatigue in patients with cirrhosis but without overt hepatic encephalopathy.

**Methods**   Twenty-one cirrhotic patients who were able to undergo fatigue symptom evaluations at our institution were enrolled. A total of 12 cirrhotic patients underwent levocarnitine treatment (1,200-1,800 mg/day), while 9 did not undergo levocarnitine treatment. As primary endpoints, we investigated whether or not levocarnitine treatment exerted any beneficial effects by assessing the symptoms of fatigue [8-item Short-Form Health Survey (SF-8) and Fisk Fatigue Severity Score (FFSS)] at baseline and three months after treatment. Furthermore, as exploratory secondary endpoints, we investigated whether or not levocarnitine treatment exerted ameliorative effects on oxidative stress by assessing the serum thioredoxin (TRX) and urinary 8-hydroxydeoxyguanosine (8-OHdG) levels.

**Results**   The median age of the patients was 73 years old. Three men and 18 women were categorized by their Child-Pugh class (A and B in 14 and 7 patients, respectively). There were no significant differences in the clinical laboratory values between the two groups. The FFSS and SF-8 scores were significantly improved in the patients with cirrhosis who underwent levocarnitine treatment ($p<0.01$) but not in those who did not undergo levocarnitine treatment. Furthermore, three months after levocarnitine treatment, the serum carnitine concentrations were significantly increased, and the serum thioredoxin levels were decreased in the patients with cirrhosis who underwent levocarnitine treatment ($p<0.05$).

**Conclusion**   These results suggest that levocarnitine treatment may relieve symptoms of fatigue in cirrhotic patients by reducing oxidative stress.

**Key words:** liver cirrhosis, fatigue, levocarnitine, thioredoxin

## Introduction

Fatigue, which is characterized as a persistent sense of exhaustion that prevents individuals from performing their usual tasks and decreases their capacity for physical and mental work, is one of the most common symptoms reported by patients in general medical practice (1, 2). Fatigue is also considered to be common in individuals with chronic liver disease (CLD). However, because it is difficult to define and treat fatigue, this symptom is often overlooked or minimized by physicians caring for patients with CLD. Although reports on fatigue in patients with cholestatic liver disease (3-5), chronic hepatitis C (6, 7), and nonalcoholic fatty liver disease (8) have been published, few of the patients in these studies were diagnosed with overt cirrhosis. Thus, published data on fatigue and its possible association with the health-related quality of life (HRQOL) in individuals with cirrhosis are scarce, and our understanding of fatigue in patients with cirrhosis remains limited (9).

Regarding fatigue assessment tools, the Fisk Fatigue Severity Score (FFSS) is a highly acceptable, internally consis-

tent and reproducible measure of fatigue severity in individuals with primary biliary cholangitis (PBC) (10). For the global function and QOL scoring, measures such as the 36- or 8-item Short-Form Health Survey (SF-36 and SF-8) have been used and, perhaps unsurprisingly, show that fatigue is one of the major contributing factors to life quality impairment in individuals with CLD. Furthermore, the global function can be very poor in individuals with CLD (11-13). In a study that used the SF-8 to evaluate the HRQOL in 300 patients with compensated cirrhosis, the median SF-8 score was 70 [interquartile range (IQR), 54-86] (14).

A previous study revealed the important role of oxidative stress in chronic fatigue (15). Biomarkers of oxidative stress include biological molecules whose chemical structures have been modified by free radicals (16). The thioredoxin (TRX) system exists in all living cells and, according to its evolutionary history, is considered to comprise genetic material linked to DNA and to serve as a defense against oxidative damage. Furthermore, oxidative stress-related urinary biomarkers, such as 8-hydroxydeoxyguanosine (8-OHdG), have been used to assess psychological distress. The urinary 8-OHdG level is a putative biomarker of total oxidative stress.

Levocarnitine transports long-chain fatty acids from the cytosol into the mitochondrial matrix for subsequent β-oxidation. According to previous studies, levocarnitine supplementation exerts positive effects on oxidative stress, inflammation, fatigue, the QOL, the nutritional status, and sarcopenia (17).

The present study evaluated the efficacy of exogenous levocarnitine in relieving physical and mental fatigue in patients with cirrhosis but without overt hepatic encephalopathy.

## Materials and Methods

### Study design

This study was conducted at Fukushima Medical University (Fukushima, Japan) between February 2013 and January 2018. We prospectively evaluated the symptoms of fatigue in 21 patients with liver cirrhosis undergoing levocarnitine treatment using the SF-8 and FFSS. A dose of levocarnitine (1,200 mg or 1,800 mg) was given orally 3 times a day for 3 months to 12 patients; the remaining 9 patients were not given levocarnitine.

The protocol was conducted with the approval of the institutional review board of our institution and in accordance with the World Medical Association's Declaration of Helsinki. The final protocol was approved by the Ethics Committee of Fukushima Medical University in Fukushima, Japan. Written informed consent was obtained from all patients.

Liver cirrhosis was diagnosed based on the presence of morphologic changes in the liver, such as hypertrophy of the left lateral and caudate lobes or atrophy of the right poste-

rior haptic lobe, as identified by ultrasonography, computed tomography (CT), and/or magnetic resonance imaging (MRI); the presence of pseudolobule formation, as identified by histopathologic examination; or the presence of signs of portal hypertension, such as varices. Patients with severe liver dysfunction, such as decompensated cirrhosis with a Child-Pugh (C-P) score ≥10 or residual hepatocellular carcinoma (HCC), were excluded. Patients with cirrhosis presenting with overt hepatic encephalopathy were excluded. Overt hepatic encephalopathy was diagnosed according to the following criteria: 1) disturbed consciousness in the absence of other causes, such as intracranial disease, serious systemic infection, hypoglycemia, electrolyte disorders, and drug or alcohol abuse; 2) a blood ammonia concentration greater than the baseline value; and 3) the presence of asterixis.

### Instruments for the QOL assessment

A cross-sectional analysis of the general HRQOL was conducted using the Japanese version of the Medical Outcomes Study SF-8. The validity and reliability of the Japanese version of this questionnaire have been confirmed, as described previously (18). The SF-8 comprises 8 subscales (general health, GH; physical functioning, PH; role limitation due to physical problems, RP; body pain, BP; vitality, VT; social functioning, SF; mental health, MH; role limitation due to emotional problems, RE). In the present study, the scores for each of the 8 subscales, the physical health component summary score (PCS), and the mental health component summary score (MCS) were determined using the norm-based scoring method, which was based on a large-scale population study conducted in Japan (18).

Fatigue was assessed using the Japanese version of the FFSS (2). The FFSS includes three subscales to assess the perceived impact of fatigue on cognitive functioning (10 items), physical functioning (10 items), and psychosocial functioning (20 items). The FFSS is a self-report instrument, for which subjects are asked to rate the extent to which fatigue has caused problems for them in relation to example statements (0 = no problems to 4 = extreme problems; maximum FFSS = 160).

### Clinical and laboratory assessments

Detailed clinical and demographic information, including the patient's age, sex, and complications (diabetes mellitus [DM], varices, ascites, shunt, and HCC) as well as etiology of cirrhosis were collected. Laboratory data were evaluated before and three months after levocarnitine treatment and included the following measurements: aspartate aminotransferase (AST), alanine aminotransferase (ALT), albumin (ALB), total bilirubin (TB), hemoglobin, and $NH^3$ levels; prothrombin time; platelet (PLT) count and serum levels of carnitine fractions (total carnitine, free carnitine, and acylcarnitine). DM was defined as the presence of any of the following criteria: (i) a documented history of diabetes, (ii) use of a diabetes medication, or (iii) a fasting glucose level of ≥126 mg/dl or HbA1c level ≥6.5 on two separate occa-

**Table.** **Cirrhotic Patients' Baseline Clinical and Biochemical Characteristics.**

| | All | Without levocarnitine treatment (n=9) | With levocarnitine treatment (n=12) | p values |
|---|---|---|---|---|
| Age (year), median (IQR) | 73 (64-78) | 67 (63-75) | 76 (66-79) | 0.0984 |
| Sex (male/female) | 3/18 | 2/7 | 1/11 | 0.3681 |
| Etiology (HCV/PBC/NASH/ Alcohol/HCV+PBC/HCV+HBV) | 10/3/4/2/1/1 | 4/0/3/2/0/0 | 6/3/1/0/1/1 | 0.7980 |
| Child-Pugh class (A/B) | 14/7 | 6/3 | 8/4 | 1.0000 |
| HCC yes/no (yes %) | 3/18 (14.3) | 1/8 (11.1) | 2/10 (16.7) | 0.7188 |
| Ascites yes/no (yes %) | 6/15 (28.6) | 3/6 (33.3) | 3/9 (25.0) | 0.6757 |
| Varices yes/no (yes %) | 4/17 (19.0) | 2/7 (22.2) | 2/10 (16.7) | 0.7483 |
| Diabetes Mellitus yes/no (yes %) | 6/15 (28.6) | 4/5 (44.4) | 2/10 (16.7) | 0.1632 |
| Shunt yes/no (yes %) | 3/18 (14.3) | 1/8 (11.1) | 2/10 (16.7) | 0.7188 |
| ALB (g/dL), median (IQR) | 3.8 (3.2-4.0) | 3.9 (3.8-4.0) | 3.7 (3.1-4.0) | 0.3691 |
| TB (mg/dL), median (IQR) | 1.0 (0.8-1.3) | 1.2 (1.0-1.6) | 1.0 (0.8-1.1) | 0.1966 |
| $NH_3$ (μg/dL), median (IQR) | 39 (33-55) | 40 (35-48) | 37 (33-61) | 0.8482 |
| Levocarnitine dose 1200/1800 (mg) | 6/6 | - | 6/6 | |

IQR: interquartile range, HCV: hepatitis C virus, HBV: hepatitis B virus, PBC: primary biliary cholangitis, NASH: non-alcoholic steatohepatitis, HCC: hepatocellular carcinoma, ALB: albumin, TB: bilirubin, $NH_3$: ammonia. *p<0.05 was considered significant.

sions.

### Measurement of TRX and 8-OHdG

The levels of TRX and 8-OHdG were measured in serum samples and urine samples, respectively, with enzyme-linked immunosorbent assay (ELISA) kits in accordance with the manufacturer's instructions. The following kits were used for all measurements: a serum TRX kit (Human TRX ELISA kit; CUSABIO, Hubei, China) and a urinary 8-OHdG kit (New 8-OHdG Check; Nikken Zeil, Fukuroi, Japan).

### Primary and secondary endpoints

As primary endpoints, we investigated whether levocarnitine treatment exerted any beneficial effects on the symptoms of fatigue (SF-8 and FFSS) at baseline and three months after treatment.

As exploratory secondary endpoints, we investigated whether or not levocarnitine treatment helped ameliorate oxidative stress by measuring the serum TRX and urinary 8-OHdG levels.

### Statistical analyses

Continuous variables are described as the medians (IQRs). Differences were compared using the Mann-Whitney U-test and Wilcoxon's matched-pairs signed-rank test. Correlations between variables were assessed using Spearman's rank correlation coefficient. All statistical analyses were performed using the Prism 6.0 (GraphPad Software, San Diego, USA) and JMP Pro 13.1 (SAS Institute, Cary, USA) software programs. p<0.05 indicated statistical significance.

## Results

### Patient characteristics

The patients' baseline characteristics are shown in Table. A total of 3 men and 18 women were enrolled. The median age of the patients at the start of treatment was 73 years old. The etiology of cirrhosis was the hepatitis C virus in 10 patients, nonalcoholic steatohepatitis in 4 patients, PBC in 3 patients, alcoholic liver dysfunction in 2 patients, and other causes in 2 patients. The C-P classification was A in 14 cases and B in 7 cases. A total of 3 patients had previously undergone HCC treatment (14.3%), 6 patients had DM (28.6%), 6 patients had ascites (28.6%), 4 patients had varices (19.0%), and 3 patients had shunts (14.3%). No patients had muscle cramps during this study. No significant differences in the baseline characteristics were observed between the cirrhotic patients who underwent levocarnitine treatment and those who did not.

The laboratory data recorded for patients with cirrhosis before and after levocarnitine treatment are compared in Supplementary material 1. No significant differences in the clinical laboratory results, including the ammonia level, were observed before and after levocarnitine treatment in either group. Although the serum levels of carnitine fractions in the patients with cirrhosis who did not undergo levocarnitine treatment were within the standard ranges, these levels were significantly increased in the patients with cirrhosis who underwent levocarnitine treatment (Fig. 1).

### Clinical effects of levocarnitine treatment on symptoms of fatigue in cirrhotic patients

Significant differences in the mental HRQOL, as measured by the SF-8 MCS, were not observed between the pa-
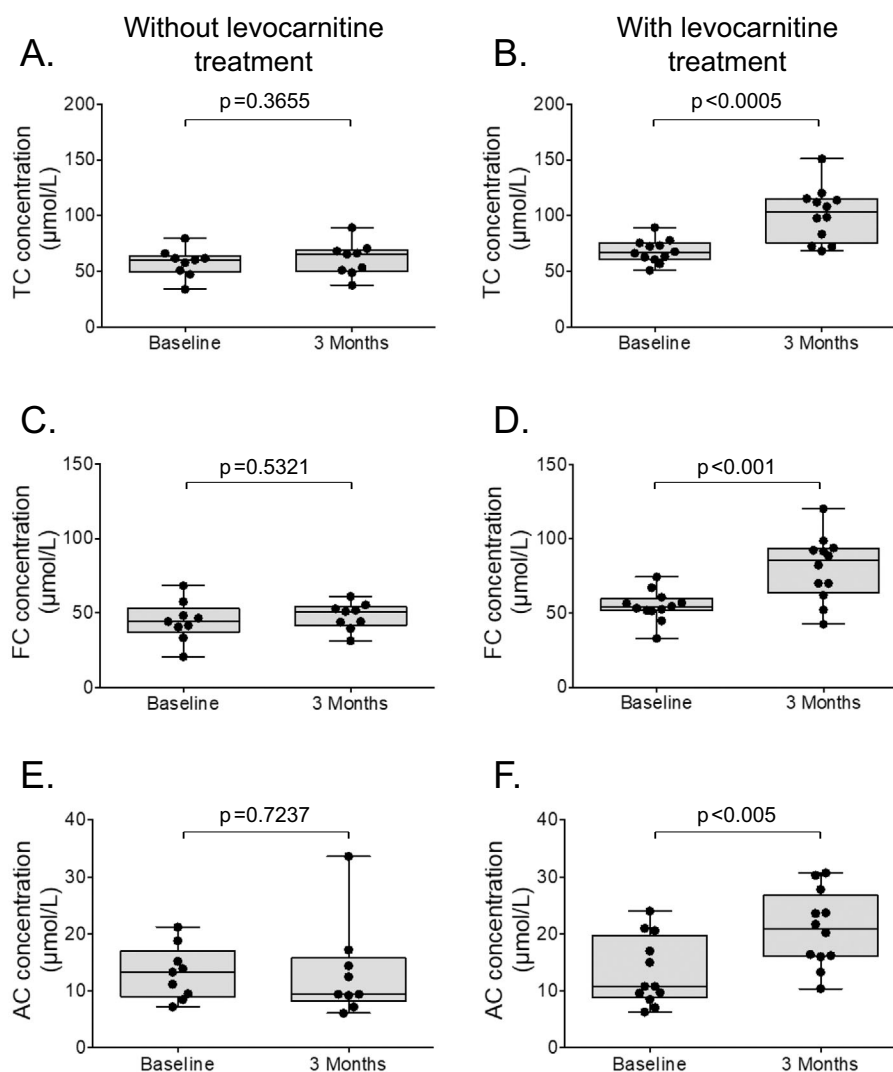
**Figure 1.** Serum levels of carnitine fractions in the patients with cirrhosis who did or did not undergo levocarnitine treatment. (A) A comparison of the serum levels of total carnitine in cirrhotic patients who did not undergo levocarnitine treatment from baseline to three months after treatment. (B) A comparison of the serum levels of total carnitine in cirrhotic patients who underwent levocarnitine treatment from baseline to three months after treatment. (C) A comparison of the serum levels of free carnitine in cirrhotic patients who did not undergo levocarnitine treatment from baseline to three months after treatment. (D) A comparison of the serum levels of free carnitine in cirrhotic patients who underwent levocarnitine treatment from baseline to three months after treatment. (E) A comparison of the serum levels of acylcarnitine in cirrhotic patients who did not undergo levocarnitine treatment from baseline to three months after treatment. (F) A comparison of the serum levels of acylcarnitine in cirrhotic patients who underwent levocarnitine treatment from baseline to three months after treatment. P<0.05 indicates a statistically significant difference.

tients with cirrhosis treated with or without levocarnitine at 3 months after levocarnitine treatment compared with before treatment (patients who underwent levocarnitine treatment: p =0.8501, patients who did not undergo levocarnitine treatment: p=0.8438) (Fig. 2A, B). Conversely, patients with cirrhosis who underwent levocarnitine treatment were more likely to report a significantly impaired physical HRQOL, as measured by the SF-8 PCS (patients who underwent levocarnitine treatment: p<0.01, patients who did not undergo levocarnitine treatment: p=0.3828) (Fig. 2C, D).

Furthermore, the FFSS for fatigue was significantly im-

proved in patients who underwent levocarnitine treatment (p <0.01) but did not improve in patients who did not undergo levocarnitine treatment (p=0.4922) (Fig. 2E, F).

### Levocarnitine treatment reduces serum thioredoxin levels in patients with cirrhosis

In patients who underwent levocarnitine treatment, we observed a significant decrease in the serum TRX levels (Fig. 3A, B). In contrast, there were no significant differences in the urinary 8-OHdG levels, which is thought to be an oxidative stress marker, in cirrhotic patients who under-
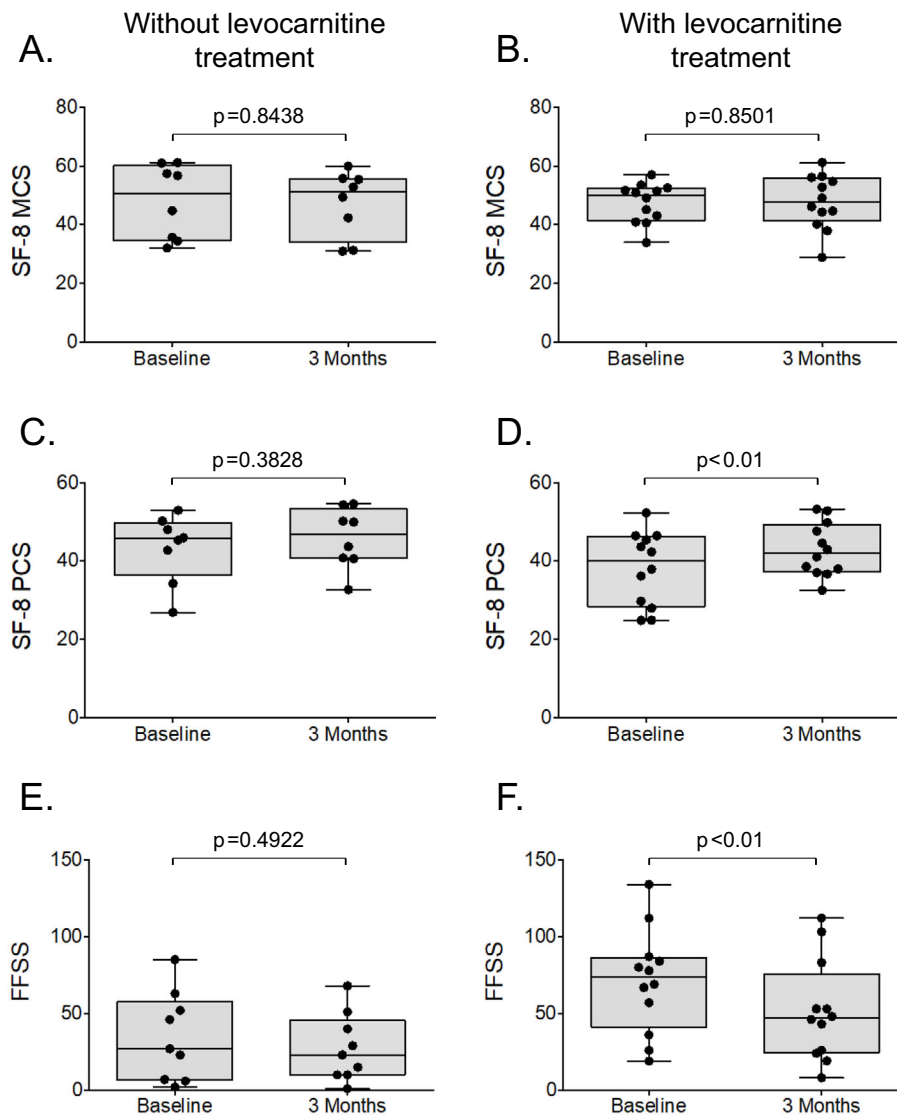
**Figure 2.** Results from the Japanese version of the Medical Outcomes Study Short-Form 8-Item Health Survey (SF-8) and the total score of the Japanese version of the Fisk Fatigue Severity Score (FFSS) in cirrhotic patients who did and did not undergo levocarnitine treatment. (A) A comparison of the mental health component summary score (MCS) in cirrhotic patients who did not undergo levocarnitine treatment from baseline to three months after treatment. (B) A comparison of the MCS in cirrhotic patients who underwent levocarnitine treatment from baseline to three months after treatment. (C) A comparison of the physical health component summary score (PCS) in patients who did not undergo levocarnitine treatment from baseline to three months after treatment. (D) A comparison of the PCS in patients who underwent levocarnitine treatment from baseline to three months after treatment. (E) A comparison of the FFSS in cirrhotic patients who did not undergo levocarnitine treatment from baseline to three months after treatment. (F) A comparison of the FFSS in cirrhotic patients who underwent levocarnitine treatment from baseline to three months after treatment. P<0.05 indicates a statistically significant difference.

went levocarnitine treatment (Fig. 3C, D).

**Relationship between the ΔFFSS and laboratory data in cirrhotic patients who did and did not undergo levocarnitine treatment**

The results of the Spearman's rank correlation analysis are shown in Fig. 4. The ΔFFSS [calculated as (FFSS after 3 months) - (FFSS at baseline)] was significantly negatively correlated with the serum ALB levels at baseline and after 3 months and with the free carnitine concentration after 3 months and was positively correlated with the serum TB level at baseline in cirrhotic patients who underwent levocarnitine treatment. However, no significant correlations were observed in those who did not undergo levocarnitine treatment (ALB level at baseline: r=-0.5972, p<0.05; TB level at baseline: r=0.6324, p<0.05; ALB level after 3 months: r=-0.7356, p<0.01; free carnitine concentration after 3 months: r=-0.6923, p<0.05). No significant correlations between the
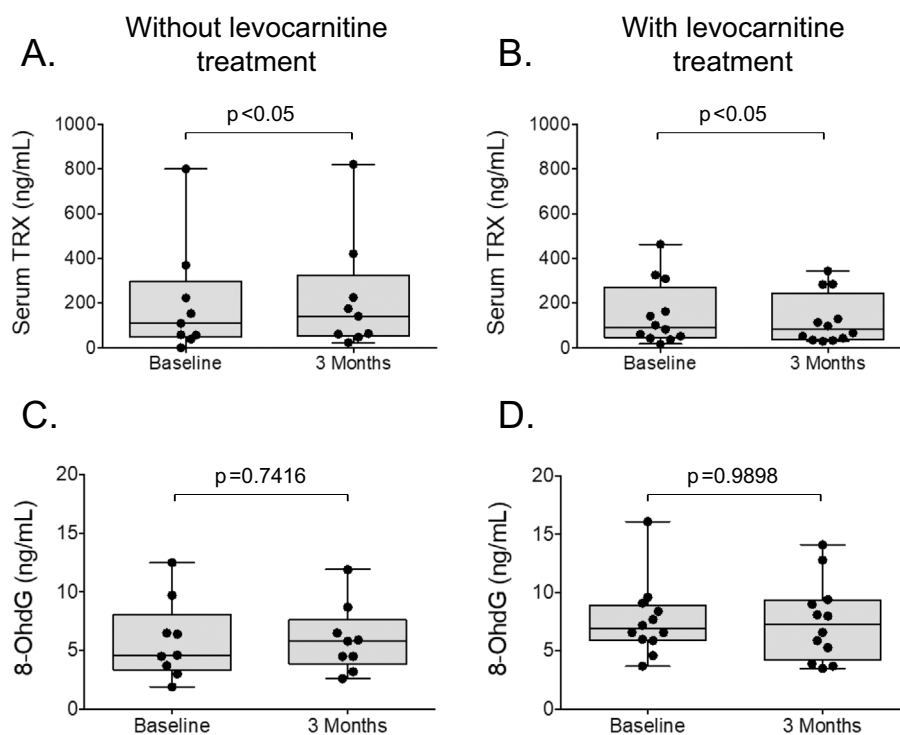
**Figure 3.** Serum thioredoxin (TRX) levels and urinary 8-hydroxydeoxyguanosine (8-OHdG) levels in cirrhotic patients who did and did not undergo levocarnitine treatment. (A) A comparison of the urinary 8-OHdG levels in cirrhotic patients who did not undergo levocarnitine treatment from baseline to three months after treatment. (B) A comparison of the urinary 8-OHdG levels in cirrhotic patients who underwent levocarnitine treatment from baseline to three months after treatment. (C) A comparison of the serum TRX levels in cirrhotic patients who did not undergo levocarnitine treatment from baseline to three months later. (D) A comparison of the serum TRX levels in cirrhotic patients who underwent levocarnitine treatment from baseline to three months after treatment. p<0.05 indicates a statistically significant difference.

ΔFFSS and the other clinical laboratory results, including the ammonia level, serum TRX level, and urinary 8-OHdG level, were observed before or after levocarnitine treatment in either group (Supplementary material 2). Furthermore, the ΔMCS [calculated as (MCS after 3 months) - (MCS at baseline)] was negatively correlated with the serum ALB levels at baseline and after 3 months and was positively correlated with the serum TB levels at baseline and after 3 months and with the serum ammonia levels at baseline and after 3 months in cirrhotic patients who underwent levocarnitine treatment (Supplementary material 3). However, no significant correlations between the ΔPCS and the clinical laboratory parameters were observed (Supplementary material 4).

## Discussion

In the present study, we investigated the efficacy of levocarnitine treatment in relieving symptoms of fatigue in patients with cirrhosis. Levocarnitine is critical for mitochondrial fatty acid oxidation, and levocarnitine supplementation has been shown to improve the QOL and relieve symptoms of fatigue in patients with chronic kidney disease, cancer, and chronic hepatitis (19-22). To our knowledge, this report is the first to show that levocarnitine treatment improves the

physical symptoms of fatigue in patients with cirrhosis but without overt hepatic encephalopathy by reducing oxidative stress. As fatigue is considered common in patients with cirrhosis, we believe that the results of our study have important implications for these patients.

Several reports have described the effects of levocarnitine supplementation on hepatic encephalopathy and muscle cramps in patients with cirrhosis (23-27). According to a previous study, patients with cirrhosis presenting with hepatic encephalopathy who were treated with acetyl-levocarnitine showed a decrease in the severity of both mental and physical fatigue and an increase in physical activity (28). Furthermore, a significant decrease in serum ammonia concentrations and a significant improvement in the mental function in patients treated with acetyl-levocarnitine were observed. Acetyl-levocarnitine is an endogenous molecule synthesized in mitochondria by the enzyme acetyl-levocarnitine transferase and is the predominant type of acylcarnitine in normal tissue. The relationship between serum acylcarnitine and free carnitine is highly sensitive to intramitochondrial metabolic changes. Fatigue may manifest as either a peripheral organ or central nervous system phenomenon or as a combination of both. A useful paradigm is to consider fatigue as two separate entities: peripheral fa-
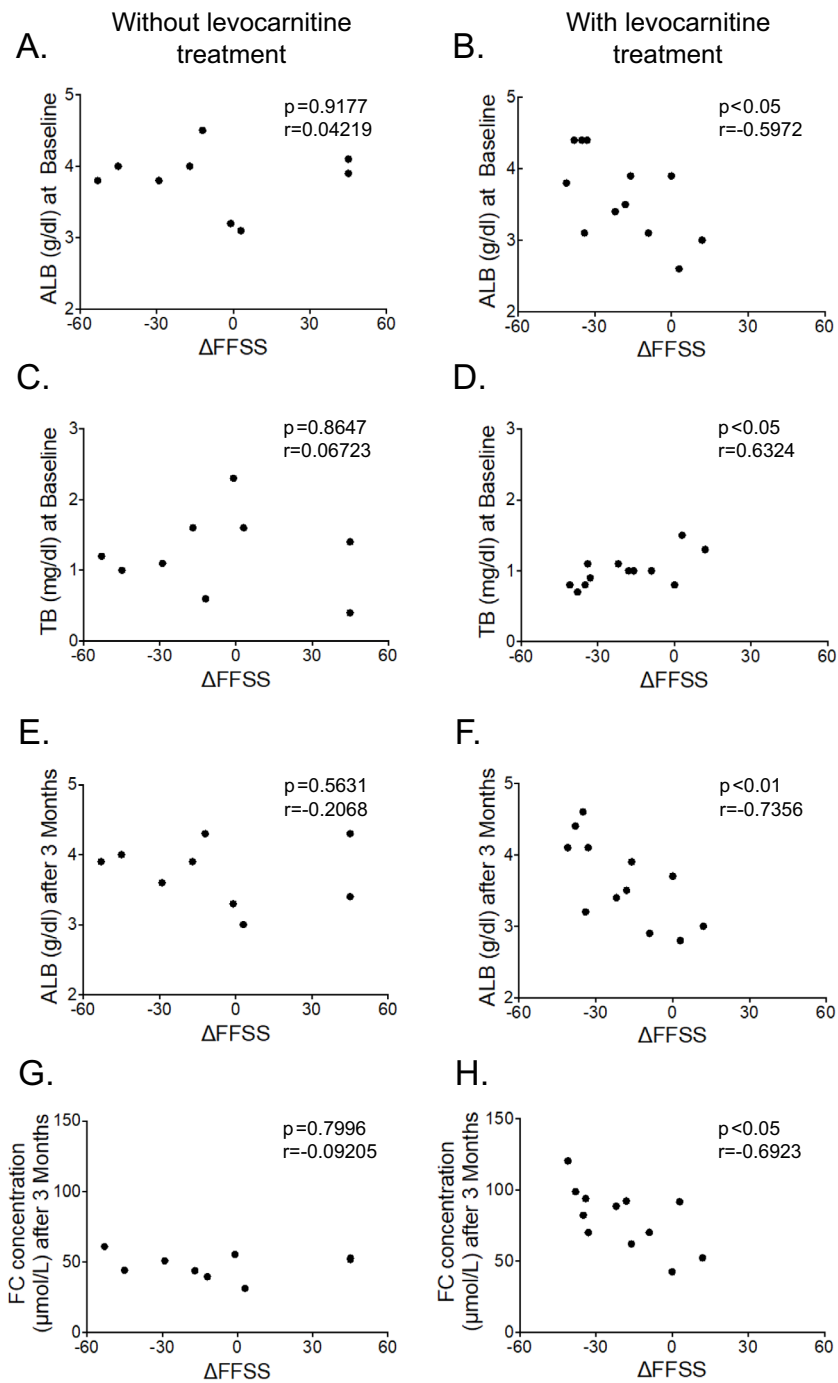
**Figure 4.** Relationship between the ΔFisk Fatigue Severity Score (ΔFFSS) and the laboratory parameters in cirrhotic patients who did and did not undergo levocarnitine treatment. (A) Relationship between the serum albumin (ALB) level at baseline and the ΔFFSS in cirrhotic patients who did not undergo levocarnitine treatment. (B) Relationship between the serum ALB level at baseline and the ΔFFSS in cirrhotic patients who underwent levocarnitine treatment. (C) Relationship between the serum total bilirubin (TB) level at baseline and the ΔFFSS in cirrhotic patients who did not undergo levocarnitine treatment. (D) Relationship between the serum TB level at baseline and the ΔFFSS in cirrhotic patients who underwent levocarnitine treatment. (E) Relationship between the serum ALB level after three months and the ΔFFSS in cirrhotic patients who did not undergo levocarnitine treatment. (F) Relationship between the serum ALB level after three months and the ΔFFSS in cirrhotic patients who underwent levocarnitine treatment. (G) Relationship between the free carnitine (FC) concentration after three months and the ΔFFSS in cirrhotic patients who did not undergo levocarnitine treatment. (H) Relationship between the FC concentration after three months and the ΔFFSS in cirrhotic patients who underwent levocarnitine treatment. The p values were calculated with Spearman's rank correlation test. p<0.05 indicates a statistically significant difference.

tigue and central fatigue (29). Peripheral fatigue results from neuromuscular dysfunction, originating from non-central nervous system mechanisms, and most commonly manifests as weakness in clinical examinations (30-32). Although changes in the muscle metabolism have been identified in patients with CLD, cirrhosis and liver failure are often associated with muscle wasting and sarcopenia (30). In contrast, central fatigue results from altered neurotransmission within the brain and is often closely associated with other neuropsychiatric complaints that are presumed to be secondary to altered central neurotransmission, namely depression and anxiety (30, 33, 34). In the present study, there were no significant differences in the mental HRQOL, as measured by the SF-8 MCS, in cirrhotic patients who did and did not undergo levocarnitine treatment from baseline to three months after levocarnitine treatment. High brain ammonia levels can lead to deleterious alterations in astrocyte morphology, cerebral energy metabolism, and neurotransmission, which may in turn impact the functioning of important signaling pathways within neurons (35). The cirrhotic patients in the present study did not have hepatic encephalopathy before they underwent levocarnitine treatment, and there were no significant differences in ammonia levels from baseline and three months after levocarnitine treatment.

Under normal conditions, 80% of the total serum carnitine is free carnitine, and 20% is acylcarnitine, with a normal acylcarnitine-to-free carnitine ratio of 0.25 (36, 37). In the present study, although the serum total carnitine, free carnitine, and acylcarnitine concentrations were all within the standard ranges in the majority of cirrhotic patients, these concentrations were significantly increased in the patients who underwent levocarnitine treatment.

There is evidence from both animal and clinical studies showing that levocarnitine supplementation improves the balance of nitrogen, either due to increased protein synthesis or reduced protein degradation, the inhibition of apoptosis, and the abrogation of inflammatory processes under pathologic conditions. Furthermore, animal studies have provided strong evidence that levocarnitine supplementation prevents oxidative stress and ameliorates mitochondrial dysfunction (38). TRX is a small, versatile protein that functions as a free radical scavenger to eliminate hydrogen peroxide and protect cells from oxidative injury (39). Elevated serum TRX levels have been associated with many diseases, including diabetes, chronic kidney disease, severe brain injury, coronary disease, and HCC (40-44). Levocarnitine protects cells from oxidative damage because it functions as a free radical scavenger and in lipid metabolism by transporting fatty acids across the inner mitochondrial membrane (45). In the present study, we observed a significant decrease in serum TRX levels in cirrhotic patients who underwent levocarnitine treatment. The dose of levocarnitine was not significantly associated with the percentage of patients with alleviated symptoms of fatigue and a decreased serum TRX level after three months (data not shown). The urinary 8-OHdG level is a putative biomarker of total sys-

temic oxidative stress, and psychological distress is associated with oxidative stress. In the present study, there were no significant differences in the urinary 8-OHdG levels or mental HRQOL in the cirrhotic patients who underwent levocarnitine treatment. The current study indicates that serum TRX is a more sensitive biomarker of the chronic oxidative response associated with cirrhotic patients with or without levocarnitine treatment than is urinary 8-OHdG. One report indicated that smoking increases the TRX level and that TRX is a more sensitive biomarker than 8-OHdG (46). 8-OHdG, which is produced by oxidative damage to DNA bases, is an oxidative stress marker. The urinary 8-OHdG level is dependent on the age and sex. In previous reports, the hepatic expression of TRX in individuals with chronic viral hepatitis was higher than that in individuals without liver damage. However, urinary excretion of 8-OHdG was not changed in individuals with chronic viral hepatitis (47). Furthermore, although we found reports related to 8-OHdG as an oxidative stress marker for the mental HRQOL (48), we did not find reports related to TRX as an oxidative stress marker for the mental HRQOL. In the present study, no significant improvement was found in the mental HRQOL. Therefore, it is possible that there was no significant difference in the urinary 8-OHdG levels between the cirrhotic patients who underwent levocarnitine treatment and those who did not.

Several limitations associated with the present study warrant mention. First, the sample population was relatively small. In the future, we would like to increase the number of cases by performing this study as a multicenter study. Second, we measured TRX levels in serum, not in histologic specimens. Whether or not serum and peripheral TRX levels reflect similar changes in the liver and muscle tissue remains unclear. The relationship between the peripheral and tissue TRX levels should be investigated further. Third, our intervention study conducted in patients with cirrhosis did not include a randomized design. Additional studies are required to increase the level of evidence. Fourth, most of the participants in the current study were women. Previous studies have revealed that in both normal control and chronic hepatitis groups, women are more likely to have fatigue than men (49, 50). Predisposing vulnerabilities for women, such as endocrine and stress-related factors and social-contextual determinants, have been proposed to explain this phenomenon; however, this association remains commonly observed but poorly understood (51). Fatigue has been shown to result in high economic costs to society, especially because of its impact on employment and the need for families and friends to spend time caring for the individual (52, 53). Fatigue related to cirrhosis may be improved through levocarnitine treatment. Further research is necessary to explore the cost effectiveness and personalization of approaches to manage fatigue in patients with cirrhosis.

## Conclusion

Taken together, our findings indicated that levocarnitine exerted potentially favorable effects on symptoms of fatigue after three months of treatment in cirrhotic patients, specifically by reducing oxidative stress. Additional clinical studies with levocarnitine need to be conducted to determine the mechanism by which levocarnitine relieves fatigue.

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

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