Effect of L-carnitine on quality of life in covert hepatic encephalopathy: a randomized, double-blind, placebo-controlled study

Eileen L. Yoon1,2,*, Sang Bong Ahn3,*, Dae Won Jun2, Yong Kyun Cho4, Do Seon Song5, Jae Yoon Jeong6, Hee Yeon Kim7,8, Young Kul Jung9, Myeong Jun Song10, Sung Eun Kim11, Hyoung Su Kim12, Soung Won Jeong13, Sang Gyune Kim14, and Tae Hee Lee15

Department of Internal Medicine, 1Inje University Sanggye Paik Hospital, Seoul; 2Hanyang University Seoul Hospital, Hanyang University College of Medicine, Seoul; 3Nowon Eulji Medical Center, Eulji University School of Medicine, Seoul; 4Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul; 5St. Vincent’s Hospital, College of Medicine, The Catholic University of Korea, Suwon; 6National Medical Center, Seoul; 7Uijeongbu St. Mary’s Hospital, College of Medicine, The Catholic University of Korea, Uijeongbu; 8Bucheon St. Mary’s Hospital, College of Medicine, The Catholic University of Korea, Bucheon; 9Korea University Ansan Hospital, Korea University College of Medicine, Ansan; 10Daejeon St. Mary’s Hospital, College of Medicine, The Catholic University of Korea, Daejeon; 11Hallym University Sacred Heart Hospital, Hallym University College of Medicine, Anyang; 12Hallym University Kangdong Sacred Heart Hospital, Hallym University College of Medicine, Seoul; 13Soonchunhyang University Seoul Hospital, Soonchunhyang University College of Medicine, Seoul; 14Soonchunhyang University Bucheon Hospital, Soonchunhyang University College of Medicine, Bucheon; 15Konyang University College of Medicine, Daejeon, Korea

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| Covert Hepatic encephalopathy | L-carnitine group | Control group |
|------------------------------|-------------------|--------------|
| n = 70                       | Improved          | No change    |
| Quality of life (Δ Total SF-36 score: 12weeks-baseline) | No significant difference | No change |
| Change of liver function (Δ MELD score: 12weeks-baseline) | Improved          | Worsen       |
| Change of cognitive function (Δ Stroop inhibition test: 12weeks-baseline) | Improved          | No change    |
|                              | Significant difference | No change |

*These authors contributed equally to this work.
Background/Aims: L-carnitine is potentially beneficial in patients with hepatic encephalopathy (HE). We aimed to evaluate the impact of L-carnitine on the quality of life and liver function in patients with liver cirrhosis and covert HE.

Methods: We conducted an investigator-initiated, prospective, multi-center, double-blind, randomized phase III trial in patients with covert HE. A total of 150 patients were randomized 1:1 to L-carnitine (2 g/day) or placebo for 24 weeks. Changes in quality of life and liver function were assessed at 6 months. The model for end-stage liver disease (MELD), the 36-Item Short Form Survey (SF-36), the psychometric hepatic encephalopathy score (PHES), and the Stroop Test were evaluated in all patients.

Results: The total SF-36 score significantly improved in the L-carnitine group after 24 weeks (difference: median, 2; interquartile range, 0 to 11; \( p < 0.001 \)); however, these values were comparable between the two groups. Furthermore, there was a significant ordinal improvement in PHES scores among patients with minimal HE who were in the L-carnitine group (\( p = 0.007 \)). Changes in the total carnitine level also positively correlated with improvements in the Stroop test in the L-carnitine group (color test, \( r = 0.3 \); word test, \( r = 0.4 \); inhibition test, \( r = 0.5 \); inhibition/switching test, \( r = 0.3 \); all \( p < 0.05 \)). Nevertheless, the MELD scores at week 24 did not differ between the groups.

Conclusions: Twenty-four weeks of L-carnitine supplementation was safe but ineffective in improving quality of life and liver function.

Keywords: Carnitine; Liver cirrhosis; Hepatic encephalopathy; Randomized controlled trials as topic; Stroop test
severity of liver disease (Child-Pugh A vs. B or C). Participant allocation was concealed from both the investigator and the participant.

**Inclusion criteria**
Thirteen academic centers in the Republic of Korea participated in this study. The inclusion criteria were as follows: (1) patients with liver cirrhosis aged 19 to 65 years and (2) diagnosed with covert HE. Liver cirrhosis was diagnosed through either liver biopsy or clinical findings, meeting one or more of the following criteria: (1) presence of surface nodularity of the liver and one or more signs of portal hypertension (ascites, splenomegaly, or portosystemic shunt) on abdominal imaging; (2) esophageal or gastric varices on endoscopy; (3) thrombocytopenia (platelet count ≤ 100,000/mm³); (4) hypoalbuminemia (albumin ≤ 3.5 g/dL); and (5) prolongation of prothrombin time (PT) (international normalized ratio ≥ 1.3). Minimal HE was diagnosed when the psychometric hepatic encephalopathy score (PHES) was < –4. Covert HE was defined as either grade 1 in the West Haven classification or grade 0 in the same classification while meeting the minimal HE definition described above.

**Exclusion criteria**
Patients were excluded if they met any of the following criteria: (1) previously diagnosed with overt HE; (2) prescribed and treated with medications affecting the natural course of HE, such as neomycin, lactulose, lactitol, branched-chain amino acids, probiotics, and rifaximin in the 2 weeks before enrollment; (3) had been or is currently being treated for a neurological or psychiatric disease; (4) is being treated with viable hepatocellular carcinoma or other malignancies; (5) had developed an infection or gastrointestinal bleeding within 6 weeks before enrollment; (6) has a serum alanine aminotransferase level > 400 IU/L; (7) has a serum creatinine level > 1.5 mg/dL; or (8) has alcohol dependence or a history of alcohol abuse.

**Intervention**
At the baseline visit (Visit 1), each patient was provided with
2 g (three tablets of 333 mg to be taken twice a day) of either L-carnitine or placebo drugs orally, to be repeatedly taken for 24 weeks.

**Study endpoints**
The primary endpoint was to assess the effect of L-carnitine on the improvement of quality of life compared to that of the placebo. This assessment was performed using the 36-Item Short Form Survey (SF-36) questionnaire at 24 weeks. The secondary endpoints were to assess the additional effects of L-carnitine administration for 24 weeks on the improvement of the model for end-stage liver disease (MELD), serum ammonia, and normalization of covert HE compared to the placebo.

**Study follow-up and measurements**
After the baseline visit, the patients were followed up every 3 months. The West Haven criteria, SF-36, PHES, and Stroop test were performed on all patients [17]. The PHES consisted of five tests: the digit symbol test, number connection test (NCT)-A, NCT-B, serial dotting, and line tracing. Assessments were based on normative Korean data [18]. Minimal HE was diagnosed when PHES scores were < –4. The Stroop test was developed to screen minimal/covert HE in both easier and more objective ways by using a web-based smartphone method. The diagnostic performance of minimal HE was excellent when using the Stroop test (area under the receiver operating characteristic curve, 0.75; 95% confidence interval, 0.67 to 0.84; \( p < 0.001 \)) [17].

**Sample size and rationale**
The sample size was based on a previous study assessing the effects of acetyl-L-carnitine administration on the improvement of SF-36 in patients with minimal HE [16]. The difference in SF-36 score changes from the score measured at the baseline to that at 90 days between the acetyl-L-carnitine group and placebo group was 4.85, and the standard deviation was presumed to be 10 based on these results. We maintained a statistical power of 80% with a 2.5% one-sided significance level. In addition, we allowed a rate of withdrawal or loss to follow-up of up to 10%. The final sample size was estimated to be 150 participants.

**Handling of dropouts or missing data**
For the efficacy endpoints, the last observation carried forward method was used for missing data imputation. The SF-36 is expected to improve over time, hence it is more conservative to replace the missing data using this method. However, the available data set underwent safety analysis without imputation of missing data.

**Statistical analysis**
All analyses were performed using the full analysis set according to the intention-to-treat principle, which included all patients who received at least one dose of the investigational product. Demographic and baseline characteristics were summarized by the intervention group and were tested statistically to identify any imbalance between the groups. For continuous variables, group comparisons of efficacy endpoints were tested using an independent two-sample \( t \) test or Wilcoxon rank-sum test, whereas within-group comparisons were tested using the paired \( t \) test or Wilcoxon signed test. These tests were also performed depending on the results of the normality test. The generalized estimating equations logit model was used for categorical variables to test the time effect within a group and the interaction effect of time \( \times \) group.

**Ethics approval and informed consent**
This study was approved by the Institutional Review Boards of all participating centers (HYUH 2015-10-003, SGPAIK 2015-11-010) and was performed in accordance with relevant guidelines and regulations. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki. Informed consent was obtained from all the participants enrolled in this study.

**RESULTS**

**Basic characteristics**
A total of 238 patients with liver cirrhosis were screened between June 2015 and December 2017. Among them, 150 patients with covert HE evaluated using PHES underwent randomization. Among them, 72 and 70 patients were assigned to the placebo group and the L-carnitine group, respectively (Fig. 1, full analysis dataset). Among them, 21 patients in the placebo group and 12 in the L-carnitine group were dropped out because of consent withdrawal (16 patients in the placebo group and eight in the L-carnitine group), loss to follow-up (two patients in the placebo group), discontinuation due to adverse events (two patients...
Table 1. Baseline characteristics of patients

| Characteristic                          | Total (n = 142) | Placebo (n = 72) | L-carnitine (n = 70) | p value<sup>a</sup> |
|----------------------------------------|-----------------|------------------|----------------------|-------------------|
| Age, yr                                | 54 (49.0 to 59.0) | 55 (49.0 to 59.0) | 54 (49.0 to 59.0) | 0.325            |
| Male ex                                | 92 (64.8)       | 46 (63.9)        | 46 (65.7)           | 0.325            |
| Body mass index                        | 25.3 (23.0 to 27.2) | 25.0 (22.2 to 26.5) | 25.6 (23.0 to 27.5) | 0.273            |
| Current alcohol drinker                | 38 (26.8)       | 16 (22.2)        | 22 (31.4)           | 0.470            |
| Etiologies of liver cirrhosis          |                 |                  |                     | 0.698            |
| Alcohol                                | 14 (9.9)        | 9 (12.5)         | 5 (7.1)             |                  |
| Hepatitis B                            | 126 (88.7)      | 62 (86.1)        | 64 (91.4)           |                  |
| On antiviral treatment                 | 117 (82.3)      | 58 (80.6)        | 59 (84.3)           |                  |
| Others                                 | 2 (1.4)         | 1 (1.4)          | 1 (1.4)             |                  |
| Child-Pugh Class                       |                 |                  |                     | 0.824            |
| A                                      | 117 (82.4)      | 59 (81.9)        | 58 (82.9)           |                  |
| B                                      | 24 (16.9)       | 13 (18.1)        | 11 (15.7)           |                  |
| C                                      | 1 (0.7)         | 0                | 1 (1.4)             |                  |
| MELD                                   | 8 (7 to 10)     | 8 (7 to 10)      | 8 (7 to 10)         | 0.868            |
| Platelets, × 1,000/mm<sup>3</sup>      | 121 (79 to 157) | 118 (67 to 162)  | 125 (83 to 153)     | 0.450            |
| Prothrombin time, INR                  | 1.1 (1.1 to 1.2) | 1.1 (1.1 to 1.2) | 1.1 (1.1 to 1.2)    | 0.648            |
| Albumin, g/dL                          | 4.3 (3.8 to 4.5) | 4.2 (3.8 to 4.5) | 4.3 (3.9 to 4.6)    | 0.550            |
| Total bilirubin, mg/dL                 | 0.9 (0.7 to 1.4) | 0.9 (0.7 to 1.4) | 0.9 (0.7 to 1.3)    | 0.989            |
| Cholesterol, mg/dL                     | 155 (126 to 179) | 152 (122 to 175) | 156 (127 to 183)    | 0.350            |
| ALT, U/L                               | 26 (19 to 39)   | 24 (16 to 38)    | 26 (20 to 41)       | 0.304            |
| Glucose, mg/dL                         | 107 (97 to 123) | 105 (96 to 120)  | 109 (100 to 129)    | 0.133            |
| Creatinine, mg/dL                      | 0.8 (0.7 to 1.0) | 0.8 (0.7 to 1.0) | 0.8 (0.7 to 1.0)    | 0.799            |
| Ascites                                |                 |                  |                     | 0.668            |
| No                                     | 120 (84.5)      | 63 (87.5)        | 57 (81.4)           |                  |
| Controlled                             | 20 (14.1)       | 8 (11.1)         | 12 (17.1)           |                  |
| Uncontrolled                           | 2 (1.4)         | 1 (1.4)          | 1 (1.4)             |                  |
| SF-36                                   | 71.9 (59.4 to 81.6) | 72.4 (60.1 to 80.8) | 71.7 (59.1 to 81.7) | 0.998            |
| West Haven Criteria                    |                 |                  |                     | 0.852            |
| MHE                                     | 103 (72.5)      | 53 (73.6)        | 50 (71.4)           |                  |
| Grade 1                                 | 39 (27.5)       | 19 (26.4)        | 20 (28.6)           |                  |
| PHES (Z-score)                          |                 |                  |                     |                  |
| NCT-A                                   | –6.0 (–1.5 to 0.1) | –0.7 (–1.6 to 0)  | –0.6 (–1.5 to 0.1)  | 0.509            |
| NCT-B                                   | –0.9 (–2.3 to 0.4) | –0.9 (–2.1 to 0.2) | –1.0 (–2.4 to 0.7)  | 0.890            |
| Digit symbol test                       | –0.6 (–1.2 to 0.2) | –0.6 (–1.2 to 0.1) | –0.5 (–1.1 to 0.3)  | 0.320            |
| Serial dotting test                     | 0.9 (0.3 to 1.4) | 0.9 (0.3 to 1.4) | 0.9 (0.3 to 1.5)    | 0.797            |
| Line tracing test (time)                | –0.8 (–1.6 to 0.3) | –0.6 (–1.6 to 0.2) | –0.8 (–1.6 to 0.3)  | 0.842            |
| Line tracing test (error)               | –0.7 (–3 to 0.5) | –0.7 (–3 to 0.6) | –0.6 (–2.7 to 0.3)  | 0.912            |
| Total score                             | –3.0 (–5.0 to –1.0) | –3.0 (–5.0 to –1.0) | –3.0 (–5.0 to 0.0)  | 0.980            |
| Stroop test                             |                 |                  |                     |                  |
| Color to RCS                            | 2.9 (2.1 to 3.4) | 2.8 (2.1 to 3.3) | 3 (2.1 to 3.6)      | 0.265            |
| Word to RCS                             | 3.6 (3.1 to 4.0) | 3.5 (3.1 to 4.0) | 3.6 (3.1 to 4.0)    | 0.408            |
| Inhibition to RCS                       | 2.3 (1.5 to 3.3) | 2.5 (1.5 to 3.3) | 2.2 (1.6 to 3.1)    | 0.782            |
in the placebo group and three in the L-carnitine group),
and discontinuation at the investigator’s discretion (one pa-
tient from each group). Fifty-one and 58 patients completed
the study at week 24 in each group. The most common eti-
ology for liver cirrhosis was chronic hepatitis B (88.7%), and
the proportion of patients with chronic hepatitis B receiving
antiviral treatment did not differ between the groups (Table
1). The median MELD score was 8.0 points. The compliance
of the patients in the placebo and L-carnitine groups was
90.5% ± 11.5% and 85.1% ± 17.2%, respectively, which
was not significantly different.

Effects on quality of life
There was a significant improvement in SF-36 values within
the L-carnitine group after 24 weeks (p < 0.001), but the
median SF-36 values of both groups were comparable at
week 24 (Table 2). Both physical and mental component
scores were improved in the L-carnitine group, but the men-
tal component score was improved in the placebo group as
well, resulting in no difference between both groups at 24
weeks.

Effects on liver chemistry and MELD score
Aspartate aminotransferase levels were decreased in the
L-carnitine group after 24 weeks of treatment compared
to that at the baseline (p = 0.014) (Supplementary Table
1), PT also improved in the L-carnitine group, whereas total
bilirubin concentration worsened in the placebo group after
24 weeks. The MELD scores were increased in the place-
bo group (p = 0.047) and were significantly decreased in
the L-carnitine group (p = 0.008). Hence, the gaps in the
change of MELD scores were significantly different between
the two groups (p = 0.003). However, the MELD scores of
both groups at week 24 were comparable (Fig. 2). Further-
more, the serum ammonia levels did not exhibit significant
differences between or within each group after 24 weeks of treatment.

Effects on cognitive function
The changes in PHES scores and the normalization rates of
minimal and covert HE at week 24 were compared between
the groups (Supplementary Table 2). Both groups exhibited
improved PHES scores, with no difference in values between
groups at week 24. However, the ordinal association of the
change in PHES scores during sequential visits (e.g., base-
line, week 12, and week 24) among patients with minimal
HE diagnosed at the baseline was significantly improved
within the L-carnitine group (p = 0.007) (Fig. 3). The inhi-
bition test, which is one of the subtests in the Stroop test,
also showed significant improvement within the L-carnitine
group after 24 weeks (2.3 ± 1.1 at the baseline vs. 2.7 ±
1.1 at 24 weeks, p < 0.001), but not in the placebo group
(Fig. 4A). Additionally, this difference between the baseline
level and the level at week 24 was significantly higher in
the L-carnitine group (0.0 ± 0.8 in the placebo group vs.
0.3 ± 0.7 in the L-carnitine group, p = 0.038). However, the
rate-correct scores of each subtest in the Stroop test were
comparable for both groups at 24 weeks.

Correlation of serum carnitine level and
cognitive function/quality of life
Serum levels of total carnitine and free carnitine were ele-
vated in the L-carnitine group and were significantly differ-
ent between the two groups at week 24 (reference values:
42–81 µmol/L [males] and 31–67 µmol/L [females] for total
carnitine; 35–67 µmol/L [males] and 25–55 µmol/L [females]
for free carnitine; 3.8–19 µmol/L for acyl carnitine). Howev-
er, serum acylcarnitine levels did not significantly increase
in the L-carnitine group. Furthermore, the change in total
carnitine level between the baseline and at week 24 was
Table 2. The comparison of quality of life assessed by SF-36 between the groups and within the group during 24 weeks

| Variable                | Baseline | Week 24 | Change of values (24 weeks–baseline) |
|-------------------------|----------|---------|--------------------------------------|
|                         | Value    | p value | Value                                | p value | Within group difference | p value | p value |
| Physical functioning    |          |         |                                      |         |                        |         |
| Placebo                 | 85 (68–95) | 0.757   | 85 (68–93)                           | 0.519   | 0 (0 to 5)             | 0.330   |         |
| L-carnitine             | 80 (70–95) |          | 85 (70–95)                           |         | 0 (0 to 10)            |         | 0.135   |
| Role-physical           |          | 0.651   |                                      | 0.193   | 0 (0 to 3)             | 0.306   |         |
| Placebo                 | 75 (56–94) |          | 84 (63–100)                          | 0.416   | 0 (0 to 13)            | 0.153   |         |
| L-carnitine             | 81 (63–100) |         | 91 (75–100)                          | 0.135   | 0 (0 to 19)            | < 0.001 |         |
| Bodily pain             | 0.863    | 0.106   |                                      | 0.152   |                        |         |         |
| Placebo                 | 90 (70–100) |         | 89 (63–100)                          | 0.153   | 0 (–5 to 10)           | 0.617   |         |
| L-carnitine             | 90 (67.5–100) |       | 90 (78–100)                          |         | 0 (0 to 10)            |         | 0.112   |
| General health          | 0.310    |         |                                      | 0.677   | 0 (0 to 13)            | 0.398   |         |
| Placebo                 | 48 (35–60) |         | 50 (40–60)                           | 0.153   | 0 (–5 to 10)           | 0.398   |         |
| L-carnitine             | 50 (30–55) |         | 50 (35–65)                           | < 0.001 | 0 (–5 to 10)           | 0.038   |         |
| Vitality                | 0.739    |         |                                      | 0.944   | 0 (0 to 16)            | 0.006   |         |
| Placebo                 | 50 (31–72) |         | 50 (41–72)                           | 0.006   | 0 (0 to 16)            |         |         |
| L-carnitine             | 50 (38–69) |         | 56 (44–69)                           | 0.022   | 0 (0 to 13)            |         |         |
| Social functioning      | 0.878    |         |                                      | 0.513   | 0 (–5 to 10)           | 0.245   |         |
| Placebo                 | 88 (75–100) |        | 88 (75–100)                          | 0.285   | 0 (0 to 13)            |         |         |
| L-carnitine             | 88 (75–100) |       | 100 (75–100)                         | 0.058   | 0 (0 to 13)            |         |         |
| Role-emotional          | 0.593    |         |                                      | 0.262   | 0 (–8 to 17)           | 0.629   |         |
| Placebo                 | 83 (67–100) |         | 92 (67–100)                          | 0.169   | 0 (0 to 8)             |         |         |
| L-carnitine             | 92 (67–100) |         | 92 (75–100)                          | 0.148   | 0 (0 to 8)             |         |         |
| Mental health           | 0.577    |         |                                      | 0.796   | 0 (–5 to 10)           | 0.752   |         |
| Placebo                 | 68 (55–80) |         | 70 (58–80)                           | 0.213   | 0 (–5 to 10)           |         |         |
| L-carnitine             | 70 (55–80) |         | 70 (60–85)                           | 0.518   | 0 (–10 to 10)          |         |         |
| Physical component      | 0.789    |         |                                      | 0.216   | 0 (–4 to 5)            | 0.107   |         |
| Placebo                 | 73 (63–82) |         | 74 (61–84)                           | 0.400   | 0 (–4 to 5)            |         |         |
| L-carnitine             | 72 (58–83) |         | 79 (66–86)                           | 0.001   | 0 (–1 to 13)           |         |         |
| Mental component score  | 0.723    |         |                                      | 0.735   | 0 (–2 to 9)            | 0.546   |         |
| Placebo                 | 72 (58–80) |         | 74 (60–84)                           | 0.042   | 0 (–2 to 9)            |         |         |
| L-carnitine             | 72 (59–81) |         | 77 (64–86)                           | 0.010   | 1.7 (–1 to 11)         |         |         |
| Total score             | 0.998    |         |                                      | 0.342   | 0 (–2 to 7)            | 0.163   |         |
| Placebo                 | 72 (60–81) |         | 74 (60–82)                           | 0.059   | 0 (–2 to 7)            |         |         |
| L-carnitine             | 72 (59–82) |         | 78 (63–86)                           | < 0.001 | 0 (–2 to 7)            |         |         |

Values are presented as median (interquartile range).
SF-36, 36-Item Short Form Survey.

aComparison between the groups.
bComparison between within group differences from two groups.
cComparison within the groups.
positively correlated with the improvement of rate-correct scores of all four components in the Stroop test (color test, \( r = 0.3 \); word test, \( r = 0.4 \); inhibition test, \( r = 0.5 \); switching test, \( r = 0.3 \); all \( p \) values < 0.05) (Fig. 4B). However, the change in total carnitine level between the baseline and at week 24 was not significantly correlated with improvement in quality of life as assessed by the SF-36.

Safety analysis
Adverse events were observed in 25 out of 72 patients in the placebo group and 29 out of 70 patients in the L-carnitine group (34.7% vs. 41.4%, \( p = 0.490 \)). In addition, the rate of serious adverse events did not differ between the two groups (8% in the placebo group vs. 11% in the L-carnitine group). However, there were no serious adverse events related to the study drugs in either group. Overall, 21 patients out of the full analysis data set stopped the study drugs either transiently or permanently. There were 5.6% (four out of 72 patients) and 7.1% (five out of 70 patients) in the placebo and L-carnitine groups, respectively, who permanently discontinued the medication due to adverse events, and these numbers did not differ between the groups. Events leading to death were also not observed in either group.

Per-protocol analysis of the endpoints
Sixty-five patients were included in the per-protocol analysis (32 patients in the placebo group and 33 in the L-carnitine group) (Fig. 1). Nineteen patients in the placebo group and
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25 patients in the L-carnitine group were excluded from the per-protocol analysis due to one or more reasons such as inadequate compliance to the medications (< 80%), violation of the visiting windows, or not meeting the inclusion/exclusion criteria. The total SF-36 scores, especially the physical component scores, PHES scores, and the rate-correct scores of the inhibition test were improved within the L-carnitine group after 24 weeks of treatment (Supplementary Table 3). However, the SF-36 scores, PHES scores, normalization rate of minimal HE, and rate-correct scores on the Stroop test at week 24 did not differ between the two groups.

**DISCUSSION**

This is the first prospective, randomized, double-blind, placebo-controlled, multicenter clinical trial that evaluated the effects of carnitine on quality of life and liver function. The definition and diagnostic criteria of minimal HE were unclear in two previous clinical trials conducted in patients with minimal HE [15,16]. The patients included in those studies had liver cirrhosis but had no overt HE compared to patients with liver cirrhosis and only minimal HE. Moreover, their assessment of minimal HE had not been based on data normative to their population [16].

Our study has several strengths compared to previous ones. First, this study was based on the largest number of participants with the longest period of treatment (up to 24 weeks). Most previous studies have evaluated the effects of carnitine for only 4 to 12 weeks [19]. Secondly, this is the first study to evaluate the improvement of cognitive function by performing an assessment using the Stroop test as well as the PHES, which were based on normative data [17,18]. Stroop results and MELD scores are more objective than the PHES values in the evaluation of liver function among patients with covert HE. The difference in the median rate-correct scores of the Stroop inhibition test after 24 weeks was significantly higher in the L-carnitine group than in the placebo group. Additionally, liver function improved within the L-carnitine group based on MELD scores. However, the median rate-correct scores of the Stoop inhibition test and the MELD scores did not significantly differ between the placebo and L-carnitine groups at week 24. Therefore, we are cautious in drawing a conclusion regarding the beneficial effects of L-carnitine on the quality of life of patients with covert HE, which was the primary endpoint of this study.

Our study had some limitations. First, a quarter of the patients dropped before the completion of the study period. Missing data were handled using the last observation carried forward method in the analysis of the endpoints, except for the safety outcome. Therefore, the effects of L-carnitine may have been underestimated. Additionally, the possibility of a type II error should be considered in the interpretation of our findings, since the limited number of patients in
each arm could have led to the limited effect of L-carnitine on the quality of life. Nevertheless, we arrived at similar results when the per-protocol analysis was applied, despite half of the patients in each group not being included in the analyses. Additionally, the change in total carnitine levels after 24 weeks showed a positive correlation with the improvement in the Stroop test. Traditionally, serum carnitine levels are reportedly maintained at normal concentrations among patients with liver cirrhosis [20,21]. The disruption of mitochondrial permeability and the subsequent lowering of L-carnitine levels incorporated into the mitochondria in patients with cirrhosis reportedly lead to intrinsic insufficiency at the mitochondrial level, even with normal serum levels [22]. Therefore, we could assume that patients with liver cirrhosis and covert HE may benefit from L-carnitine supplementation even with normal serum concentrations. Second, the appropriate dose of L-carnitine required for the improvement of cognitive function and quality of life could not be determined in our study. Nevertheless, the little increase in serum acylcarnitine levels following 24 weeks of L-carnitine treatment suggests that 2 g of L-carnitine may not be sufficient to discriminate its positive effects. In previous studies, L-carnitine was administered at doses up to 4 to 6 g per day [23]. If we had administered higher doses of L-carnitine, the effects on cognitive function and quality of life could have been more remarkable than our present findings. Third, as 89% of our participants had chronic hepatitis B, we could not exclude the effect of antiviral treatment on the marginal improvement in the results of the inhibition test or the MELD scores in the L-carnitine group. However, the proportion of patients who were already on stable antiviral treatment did not differ between the groups. Therefore, the possible beneficial effects of antiviral treatment were minimal in this study. Fourth, following the improved results of PHES in both groups without significant change in serum ammonia levels, we could not exclude the possibility of learning effects that patients could have achieved during the repeated examinations throughout the study period.

In conclusion, 24 weeks of L-carnitine supplementation was safe but was not effective in improving the quality of life among patients with covert HE. However, their MELD scores were stabilized with L-carnitine supplementation, and the difference in total carnitine concentration exhibited a positive correlation with improvements in cognitive function among these patients.

**KEY MESSAGE**

1. Twenty-four weeks of L-carnitine supplementation (2 g/day) was ineffective in the improvement of quality of life in liver cirrhosis patients with covert hepatic encephalopathy (CHE).
2. Twenty-four weeks of L-carnitine supplementation (2 g/day) was safe in liver cirrhosis patients with CHE.
3. Further studies with higher doses of L-carnitine supplementation would be needed to confirm the possible beneficial effects on the improvement of covert hepatic encephalopathy and liver function.

**Conflict of interest**

This study was financially supported by the Ildong Pharmaceutical Company. The funding source had no role in the study design, implementation, data collection, analysis, and interpretation, or in the preparation, review, and approval of the manuscript.

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Supplementary Table 1. The comparison of biochemical tests between the groups and visits

| Variable                      | Screening | Week 24 | Change of values (24 weeks–baseline) |
|-------------------------------|-----------|---------|--------------------------------------|
|                               | Value     | p value | Value                                | p value |
| AST, IU/L                     | 33 (28–46)| 0.449c  | 31 (26–40)                           | 0.193c  |
| Placebo                      | 38 (27–56)| 0.520c  | 37 (27–44)                           | 0.449c  |
| L-carnitine                  |           |         |                                      |         |
| ALT, IU/L                    | 24 (18–35)| 0.520c  | 25 (19–36)                           | 0.988c  |
| Placebo                      | 26 (20–32)| 0.520c  | 23 (19–35)                           | 0.520c  |
| L-carnitine                  |           |         |                                      |         |
| Albumin, g/dL                | 4.2 (3.7–4.6) | 0.549c | 4.2 (3–4.6) | 0.794c |
| Placebo                      | 4.4 (3.8–4.7) | 0.520c | 4.4 (3.9–4.5) | 0.243c |
| L-carnitine                  |           |         |                                      |         |
| Total bilirubin, mg/dL       | 1 (0.7–1.6)| 0.989c | 1 (0.8–1.5) | 0.116c |
| Placebo                      | 0.9 (0.8–1.2) | 0.549c | 0.9 (0.7–1.2) | 0.520c |
| L-carnitine                  |           |         |                                      |         |
| Prothrombin time, INR        | 1.2 (1.1–1.2) | 0.647c | 1.1 (1.1–1.2) | 0.693c |
| Placebo                      | 1.2 (1.1–1.2) | 0.520c | 1.1 (1.1–1.2) | 0.100c |
| L-carnitine                  |           |         |                                      |         |
| Creatinine, mg/dL            | 0.8 (0.7–1) | 0.799c | 0.8 (0.7–0.9) | 0.829c |
| Placebo                      | 0.8 (0.6–0.9) | 0.544c | 0.9 (0.7–1) | 0.951c |
| L-carnitine                  |           |         |                                      |         |
| MELD                         | 8 (7–10)  | 0.868c  | 8 (7–11)                            | 0.409c  |
| Placebo                      | 8 (7–10)  | 0.544c  | 8 (7–9)                             | 0.003c  |
| L-carnitine                  |           |         |                                      |         |
| Sodium, mEq/L                | 140 (138–142) | 0.544c | 141 (139–142) | 0.544c |
| Placebo                      | 140 (138–142) | 0.544c | 140 (138–141) | 0.867f |
| L-carnitine                  |           |         |                                      |         |
| Ammonia, µmol/L              | 85 (65–118) | 0.567c | 74 (57–118) | 0.567c |
| Placebo                      | 79 (58–113) | 0.567c | 75 (60–96) | 0.567c |
| L-carnitine                  |           |         |                                      |         |
| Total carnitine, µmol/L      | 67.7 (56.8–73.5) | 0.676c | 62.9 (54.4–70.2) | <0.0001e |
| Placebo                      | 66.2 (57.9–74.8) | 0.676c | 74.9 (66.2–90.2) | 0.676c |
| L-carnitine                  |           |         |                                      |         |
| Acyl carnitine, µmol/L       | 12.4 (7.1–15.1) | 0.215c | 8.5 (6.6–15.1) | 0.046c |
| Placebo                      | 13.1 (7.7–18.1) | 0.215c | 12 (8.2–20.5) | 0.215c |
| L-carnitine                  |           |         |                                      |         |
| Free carnitine, µmol/L       | 52.8 (45.7–63.4) | 0.953c | 50.5 (44.8–59.2) | <0.0001e |
| Placebo                      | 52.5 (45.3–62.3) | 0.953c | 65.6 (53.3–78.1) | 0.953c |
| L-carnitine                  |           |         |                                      |         |
| LPS, EU/mL                   | 1,000 (365.1–1,000) | 0.527f | 1,000 (378.6–1,000) | 0.545f |
| Placebo                      | 1,000 (274.6–1,000) | 0.527f | 972.3 (310.8–1,000) | 0.527f |

Values are presented as median (interquartile range).

AST, aspartate aminotransferase; ALT, alanine aminotransferase; INR, international normalized ratio; MELD, model for end-stage liver disease; LPS, lipopolysaccharides.

aComparison between the groups.
bComparison within the groups.
cWilcoxon’s rank sum test.
dWilcoxon Signed rank test.
eTwo sample t test.
fPaired t test.
**Supplementary Table 2. The comparison of cognitive function assessed by PHES between the groups and visits**

| Variable   | Baseline Value | Baseline p value<sup>a</sup> | Week 24 Value | Week 24 p value<sup>a</sup> | Change of values (24 weeks–baseline) p value<sup>b</sup> | p value<sup>c</sup> |
|------------|----------------|------------------------------|---------------|----------------------------|------------------------------------------------------|-------------------|
| PHES score | 0.951<sup>c</sup> | 0.131<sup>c</sup> | 0.129<sup>c</sup> |                           |                                                     |                   |
| Placebo    | −3 (−5 to −1)  | 0 (0 to 2)                  | 0.038<sup>d</sup> |                           |                                                     |                   |
| L-carnitine| −3 (−5 to 0)   | 0 (0 to 2)                  | < 0.001<sup>d</sup> |                           |                                                     |                   |
| MHE        | 0.830<sup>e</sup> | 0.454<sup>e</sup> | 0.463<sup>f</sup> |                           |                                                     |                   |
| Placebo    | 21/72 (29.2)   | 15/72 (20.8)                | 7/21 (33.3)    | 0.030<sup>g</sup>        |                                                     |                   |
| L-carnitine| 19/69 (27.5)   | 11/69 (15.9)                | 9/19 (47.4)    | 0.009<sup>g</sup>        |                                                     |                   |
| CHE        | 0.211<sup>e</sup> | 0.272<sup>e</sup> | 0.678<sup>f</sup> |                           |                                                     |                   |
| Placebo    | 64/72 (88.9)   | 29/72 (40.3)                | 35/64 (54.7)   | < 0.001<sup>g</sup>      |                                                     |                   |
| L-carnitine| 57/70 (81.4)   | 22/70 (31.4)                | 36/57 (63.2)   | < 0.001<sup>g</sup>      |                                                     |                   |

Values are presented as median (interquartile range) or number (%).

PHES, psychometric hepatic encephalopathy score; MHE, minimal hepatic encephalopathy; CHE, covert hepatic encephalopathy.

<sup>a</sup>Comparison between the groups.

<sup>b</sup>Comparison within the groups.

<sup>c</sup>Independent t test or Wilcoxon rank sum test.

<sup>d</sup>Paired t test or Wilcoxon signed rank test.

<sup>e</sup>Chi-square test.

<sup>f</sup>Generalized Estimating Equations for the interaction effect of time × group.

<sup>g</sup>Generalized Estimating Equations for the time effect.
### Supplementary Table 3. The comparison of SF-36, PHES, and the rate correct scores in the Stroop test based on per-protocol analysis

| Variable                  | Baseline Value | Baseline p value<sup>a</sup> | Week 24 Value | Week 24 p value<sup>a</sup> | Week 24–Baseline Difference Value | Change of values (24 weeks–baseline) p value<sup>a</sup> | Within group difference p value<sup>a</sup> | p value<sup>b</sup> |
|---------------------------|----------------|-------------------------------|---------------|-------------------------------|-----------------------------------|------------------------------------------------|------------------------------------------------|-------------------|
| **SF-36**                 |                |                               |               |                               |                                   |                                                 |                                                 |                   |
| Physical component        |                |                               |               |                               |                                   |                                                 |                                                 |                   |
| Placebo                   | 75 (68 to 82)  | 0.460                         | 77 (63 to 86) | 0.380                         | 3 (–6 to 8)                      | 0.410                                          | 0.400                                          |                   |
| L-carnitine               | 71 (59 to 81)  | 0.430                         | 82 (68 to 86) | 0.380                         | 5 (–1 to 13)                     | 0.011                                          | 0.011                                          |                   |
| Mental component          |                |                               |               |                               |                                   |                                                 |                                                 |                   |
| Placebo                   | 73 (60 to 85)  | 0.840                         | 76 (65 to 90) | 0.850                         | 3 (–2 to 10)                     | 0.038                                          | 0.038                                          |                   |
| L-carnitine               | 76 (59 to 81)  | 0.750                         | 77 (68 to 82) | 0.750                         | 7 (–3 to 12)                     | 0.019                                          | 0.019                                          |                   |
| **Total score**           |                |                               |               |                               |                                   |                                                 |                                                 |                   |
| Placebo                   | 75 (63 to 82)  | 0.580                         | 76 (65 to 87) | 0.580                         | 4 (–3 to 9)                      | 0.058                                          | 0.058                                          |                   |
| L-carnitine               | 72 (59 to 81)  | 0.530                         | 79 (67 to 86) | 0.530                         | 4 (–1 to 12)                     | 0.004                                          | 0.004                                          |                   |
| **PHES**                  |                |                               |               |                               |                                   |                                                 |                                                 |                   |
| Total score               |                | 0.350<sup>c</sup>            | 0.760<sup>c</sup> | 0.340<sup>c</sup> |                                   |                                                 |                                                 |                   |
| Placebo                   | –2 (–5 to –1)  | 0.350                         | –1 (–3 to 1)  | 0.760                         | 1 (–1 to 3)                      | 0.068<sup>d</sup>                              | 0.068<sup>d</sup>                              |                   |
| L-carnitine               | –4 (–6 to 0)   | 0.340                         | –2 (–4 to 1)  | 0.780                         | 2 (–1 to 3)                      | < 0.001<sup>d</sup>                            | < 0.001<sup>d</sup>                             |                   |
| MHE                       | 0.430<sup>e</sup> | 0.780<sup>e</sup>         | 0.710         | 0.710<sup>f</sup>             |                                   |                                                 |                                                 |                   |
| Placebo                   | 9/32 (28.1)    | 0.430                         | 5/32 (15.6)   | 0.780                         | 5/9 (55.6)                       | 0.096<sup>g</sup>                              | 0.096<sup>g</sup>                              |                   |
| L-carnitine               | 12/32 (37.5)   | 0.710                         | 6/32 (18.8)   | 0.025<sup>g</sup>             | 7/12 (58.3)                      |                                                |                                                 |                   |
| CHE                       |                | 0.300<sup>e</sup>            | 1.000<sup>e</sup> | 0.210<sup>f</sup> |                                   |                                                 |                                                 |                   |
| Placebo                   | 29/32 (90.6)   | 0.300                         | 7/32 (21.9)   | 0.210<sup>f</sup>             | 22/29 (75.9)                     | < 0.0001<sup>h</sup>                           | < 0.0001<sup>h</sup>                            |                   |
| L-carnitine               | 26/33 (78.8)   | 0.210                         | 8/33 (24.2)   | 0.210<sup>f</sup>             | 19/26 (73.1)                     | < 0.0001<sup>h</sup>                           | < 0.0001<sup>h</sup>                            |                   |
| **Stroop test (rate correct score)** | | | | | | | | |
| Color                     |                | 0.950                         | 0.540         | 0.730                         |                                   |                                                 |                                                 |                   |
| Placebo                   | 2.8 (2.2 to 3.3)| 0.950             | 3.0 (2.2 to 3.6)| 0.540                         | 0.4 (–0.2 to 0.82)               | 0.046                                          | 0.046                                          |                   |
| L-carnitine               | 2.9 (2.0 to 3.6)| 0.540             | 3.0 (2.1 to 3.7)| 0.540                         | 0.2 (–0.2 to 0.6)               | 0.100                                          | 0.100                                          |                   |
| Word                      |                | 0.910                         | 0.540         | 0.860                         |                                   |                                                 |                                                 |                   |
| Placebo                   | 3.6 (3.2 to 4.0)| 0.910             | 3.6 (3.0 to 3.8)| 0.540                         | –0.1 (–0.5 to 0.3)              | 0.560                                          | 0.560                                          |                   |
| L-carnitine               | 3.6 (3.2 to 4.0)| 0.860             | 3.5 (2.9 to 4.0)| 0.860                         | –0.1 (–0.4 to 0.2)              | 0.230                                          | 0.230                                          |                   |
| Inhibition                |                | 0.860                         | 0.540         | 0.160                         |                                   |                                                 |                                                 |                   |
| Placebo                   | 2.4 (1.5 to 3.3)| 0.860             | 2.4 (1.4 to 3.2)| 0.540                         | 0.2 (–0.8 to 0.6)               | 0.940                                          | 0.940                                          |                   |
| L-carnitine               | 2.2 (1.5 to 3.1)| 0.860             | 2.6 (1.8 to 3.3)| 0.540                         | 0.3 (–0.2 to 0.5)               | 0.032                                          | 0.032                                          |                   |
| Inhibition/Switching      |                | 0.860                         | 0.540         | 0.610                         |                                   |                                                 |                                                 |                   |
| Placebo                   | 1.5 (1.0 to 2.1)| 0.860             | 1.6 (1.2 to 2.5)| 0.610                         | 0.2 (–0.3 to 0.8)               | 0.110                                          | 0.110                                          |                   |
| L-carnitine               | 1.5 (1.0 to 2.1)| 0.610             | 1.7 (1.5 to 2.1)| 0.610                         | 0.1 (–0.3 to 0.6)               | 0.320                                          | 0.320                                          |                   |

Values are presented as median (interquartile range) or number (%).
SF-36, 36-Item Short Form Survey; PHES, psychometric hepatic encephalopathy score; MHE, minimal hepatic encephalopathy; CHE, covert hepatic encephalopathy.

<sup>a</sup>Comparison between the groups.
<sup>b</sup>Comparison within the groups.
<sup>c</sup>Independent <i>t</i> test or Wilcoxon rank sum test.
<sup>d</sup>Paired <i>t</i> test or Wilcoxon signed rank test.
<sup>e</sup>Chi-square test.
<sup>f</sup>Generalized Estimating Equations for the interaction effect of time × group.
<sup>g</sup>Generalized Estimating Equations for the time effect.