The carnitine dynamics and their effects on hyperammonemia in cirrhotic Japanese patients

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Short Title: Dynamics of carnitine on encepalopathy

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Abstract

Aim: Supplementation with levocarnitine preparations has been reported to improve hepatic encephalopathy, but no detailed investigations have addressed dynamics of carnitine or its supplementation indication in cirrhosis patients. We studied carnitine dynamics in cirrhotic patients by measuring serum and liver tissue carnitine levels, also tested the effects of levocarnitine supplementation on concurrent hyperammonemia. Methods: In a pilot cohort of 7 cirrhotics and 5 non-cirrhotics, the serum and liver carnitine concentrations were measured. Then, in 70 liver cirrhosis patients, the serum carnitine fractions were analyzed. Among them, a levocarnitine preparation (1800 mg/day) was supplemented orally for 3 months to 27 patients with refractory hyperammonemia, and the effects were evaluated. Results: A

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significant correlation was observed between serum and liver tissue carnitine concentrations ($r = 0.69$, $p < 0.05$). The serum total carnitine concentration was 68.4±4.7 μmol/L, the free carnitine concentration was 53.2±2.6 μmol/L, and the acylcarnitine concentration was 13.2±1.1 μmol/L in 70 cirrhotics (Reference values are 45-91, 36-74, 6-23 μmol/L, respectively). There was no correlation between blood ammonia and serum carnitine concentrations. The serum carnitine concentration rose with levocarnitine supplementation reaching steady state after 1 month and, in parallel, refractory hyperammonemia was significantly improved. The cut-off level for a 20% decrease in blood ammonia was identified as 62.0 μmol/L total carnitine concentration by ROC curve analysis, with the area under the curve of 0.69. Conclusions: Serum carnitine concentrations were within standard levels in the majority of liver cirrhosis patients. In patients with concurrent hyperammonemia, the levocarnitine supplementation reduced blood ammonia levels.

Key Words : levocarnitine, hyperammonemia, liver cirrhosis, serum carnitine concentration, liver tissue carnitine concentration

Introduction

Hepatic encephalopathy is one of the most serious clinical complications in liver cirrhosis and is characterized by impaired mental function, neuromuscular disorders, and an altered level of consciousness [1, 2]. Although various factors have been postulated to induce hepatic encephalopathy in experimental models or in clinical studies, ammonia is still regarded as a major factor [3, 4, 5]. Possible mechanisms of ammonia toxicity for the pathogenesis of hepatic encephalopathy include astrocyte dysfunction, brain edema, neurotransmitter imbalance, and neuronal dysfunction. Candidate therapeutic interventions are protein (or nitrogen) restricted diets, non-absorbable antibiotics, oral disaccharides such as lactulose and lactitol, disaccharide enemas, intravenous L-ornithine-L-aspartate (LOLA), oral LOLA, levodopa, flumazenil, intravenous or oral branched-chain amino acids (BCAAs), zinc supplementation, portal-systemic shunt obliteration, artificial liver support, and liver transplantation [1,7, 8, 9].

L-carnitine is a vitamin-like biofactor involved in lipid metabolism. Pharmacologically, L-carnitine translocates acetyl-CoA into mitochondria, promotes the metabolic flux in the tricarboxylic acid cycle by sparing free CoA and activating the transport of adenine nucleotides across the inner mitochondrial

membrane, and prevents inhibition of the activity of pyruvate dehydrogenase by adenylate translocase. Thus, L-carnitine finally enhances the oxidative utilization of glucose [10, 11].

Previous studies have reported a protective effect of L-carnitine against hepatic encephalopathy in mice, rats and humans [12, 13, 14, 15, 16]. In fact, L-carnitine treatment is associated with significant reduction in blood and brain ammonia concentrations [14, 15, 16], but the dynamics of carnitine have not been examined in cirrhotic patients. We conducted the present study to analyze carnitine dynamics by measuring serum and liver tissue levels of carnitine in cirrhotic patients. Furthermore, to assess the clinical effects of carnitine on blood ammonia level, a levocarnitine (L-carnitine chloride) preparation was supplemented to patients with concurrent hyperammonemia.

Patients and Methods

Experimental design: This research involved three studies.

Study A: Measurement of serum carnitine concentration in cirrhosis patients

Patients: Seventy patients with liver cirrhosis (40 men, 30 women; mean age, 68.6 ± 9.3 years) were recruited from Gifu University Hospital. Liver cirrhosis was diagnosed by clinical and laboratory profiles and by histologic examination of liver biopsy specimens. The etiology of cirrhosis was hepatitis B virus in 8 patients, hepatitis C virus in 37, alcohol in 14, and others in 11. The Child-Pugh classification of disease severity was A in 26 cases, B in 28 cases, and C in 16 cases. Thirty-four patients had hepatocellular carcinoma (HCC). The patients' clinical profiles are presented in Table 1. Patients with fever, human immunodeficiency virus (HIV) infection, overt infectious disease (septicemia, pneumonia, urinary tract infection), renal insufficiency, or on immunomodulatory therapy were excluded.

Methods: Blood was drawn in the early morning, and serum albumin, total bilirubin, alanine aminotransferase, prothrombin activity, and blood ammonia were measured with a standard clinical analyzer at the central laboratory in Gifu University Hospital. Serum carnitine levels were determined by enzyme cycling methods as described previously [17].

Study B: Evaluation of relationship between serum and liver tissue concentrations of carnitine

Patients: Twelve patients (8 men, 4 women) were recruited from Gifu University Hospital. Seven patients had liver cirrhosis by hepatitis C virus, and 5 of them had HCC. The Child-Pugh classification was

A in 2 cases and C in 5 cases. The diagnosis of another five patients were cholangiocellular carcinoma in 2 cases, acute leukemia in 2 cases, and gallbladder cancer in 1 case.

Methods: Liver tissue was obtained by autopsy in 9 cases and by surgery in 3 cases. Serum and liver tissue carnitine levels were determined by enzyme cycling methods as described previously [17].

Study C: Clinical effects of carnitine on refractory hyperammonemia in cirrhosis patients

Patients: Twenty-seven patients with liver cirrhosis (9 men, 18 women; mean age, 66 ± 6.9 years) who had concurrent refractory hyperammonemia (>80 μg/dL) were enrolled from study A.
These patients received a protein-restricted diet, oral disaccharides such as lactulose and lactitol, oral branched-chain amino acids (BCAAs), and non-absorbable antibiotics, but their blood ammonia levels were resistant to such therapies. The etiology of cirrhosis was hepatitis B virus in 4 patients, hepatitis C virus in 13, and others in 10. The Child-Pugh classification was A in 13 cases, B in 13 cases, and C in 1 case. None of the patients had HCC (Table 2).

Methods: A levocarnitine preparation, 600 mg 3 times a day, was supplemented orally for 3 months to all 27 patients. The serum carnitine fractions and blood ammonia levels were measured every one month.

The study protocol was approved by the medical ethics committee of Gifu University Graduate School of Medicine (Approval No.24-129), and informed consent was obtained from all patients. The study protocol was in agreement with the 1975 Helsinki Declaration as revised in 1983.

Statistical Analysis

Continuous variables are presented as means with S.D., and Mann-Whitney *U*-test was used to evaluate the significance of difference in mean values. Categorical variables are shown as number of patients, and statistical analysis was done by χ^2–test. Changes in biochemical data by levocarnitine supplementation were tested by repeated measures of analysis of variance (ANOVA). The cut-off level for a 20% decrease in blood ammonia by supplementation with levocarnitine preparations was assessed by the receiver operator characteristics (ROC) curve analysis. All analyses were carried out using JMP version 9.0.2 software (SAS Institute, Cary, NC, USA). P-value < 0.05 was considered statistically significant.

Results

The results of Study A: Serum carnitine concentration in cirrhosis patients

The serum total carnitine concentration was 68.4±4.7 μmol/L, the free carnitine concentration was 53.2±2.6 μmol/L, and the acylcarnitine concentration was 13.2±1.1 μmol/L. These value were within standard ranges [18] in the majority of cirrhotic patients (Figure1). Serum total carnitine, free carnitine, or acylcarnitine levels did not correlate with increasing grade of disease severity as defined by the Child-Pugh classification (data not shown). There was neither significant correlation between serum carnitine and blood ammonia concentrations in cirrhosis patients (Figure2).

The results of Study B: Relationship between serum and liver tissue concentrations of carnitine

In patients with liver cirrhosis, the liver tissue total carnitine concentration was 2.1±0.4 μmol/g wet wt, the free carnitine concentration was 1.9±0.4μmol/g wet wt, and the acylcarnitine concentration was 0.17±0.1μmol/g wet wt, respectively. In patients with non-cirrhosis, the concentrations were 1.9±0.8 μmol/g wet wt, 1.7±0.7μmol/g wet wt, and 0.16±0.1μmol/g wet wt, respectively. There was no significant difference in each liver carnitine fraction level between patients with liver cirrhosis and those without cirrhosis. There was neither significant difference in serum carnitine level between patients with liver cirrhosis and those without cirrhosis.

A significant correlation was observed between serum and liver tissue total carnitine concentrations ($r = 0.69$, $p < 0.05$) (Figure3).

The results of Study C: Clinical effects of carnitine supplementation on refractory hyperammonemia in cirrhosis patients

After treatment with carnitine, serum total carnitine, free carnitine, and acylcarnitine concentrations rose significantly, while blood ammonia was reduced significantly by 20% in patients with refractory hyperammonemia (Table3). On the other hand, significant changes in liver function tests such as serum albumin, total bilirubin and alanine aminotransferase were not observed.

The cut-off level of pre-supplementation serum total carnitine concentration for a 20% decrease in blood ammonia by L-carnitine was 62.0 μmol/L on ROC analysis (the area under the ROC curve=0.69; sensitivity 0.71; specificity 0.73; positive predictive value 0.77; negative predictive value 0.67) (Figure4).

Discussion

This is the first study to demonstrate the significant correlation between serum and liver tissue concentrations of carnitine and also to reveal the indication of carnitine supplementation by baseline serum carnitine concentration on refractory hyperammonemia in cirrhosis patients.

One of the most common and serious complications in patients with cirrhosis is hepatic encephalopathy [1]. Those with hepatic encephalopathy can experience a spectrum of altered mental status that ranges from minimal encephalopathy to deep coma. Hepatic encephalopathy impairs quality of life, accompanies higher readmission rates, and brings poorer survival outcomes [16, 19]. Among various candidate factors that induce hepatic encephalopathy, ammonia is regarded as the most significant one [1, 2, 3, 5, 6].

L-carnitine is a biofactor involved in lipid metabolism. Several recent studies have also reported an important protective effect of carnitine against ammonia-related encephalopathy in cirrhotic patients [14, 15, 16, 20]. However, the dynamics of carnitine have not yet been examined in cirrhotic patients. We, therefore, first measured baseline serum and liver tissue carnitine levels in cirrhotic patients and, furthermore, investigated the clinical effects of levocarnitine supplementation on refractory hyperammonemia in cirrhotics.

Only a limited number of studies have reported the serum carnitine levels in patients with liver disease [20, 21]. In our study, serum total carnitine, free carnitine, and acylcarnitine concentrations were all within standard ranges in the majority of cirrhotic patients (Figure1). In addition, such carnitine fraction levels did not correlate with Child-Pugh grade. Because carnitine is distributed in various tissues including skeletal muscle, myocardium, liver, and brain, but only 1% present in blood [10], we measured liver tissue carnitine density. The liver carnitine content was approximately 10 fold higher than serum by tissue wet weight basis, but no significant difference was noted between cirrhotic liver and non-cirrhotic liver. Since a significant correlation was observed between serum and liver tissue carnitine concentrations (Figure3), we assume that the whole body carnitine status can be estimated by examining blood carnitine levels.

Several reports have already described the effects of carnitine supplementation on hepatic encephalopathy [14, 15, 16] and leg cramps [22] in liver cirrhosis, as well as on non-alcoholic steatohepatitis [23]. In

particular, Malaguarnera et al. reported a prominent effect of levocarnitine supplementation on refractory hepatic encephalopathy [15, 24], but the detailed carnitine dynamics were not examined. To address this concern in the present study, we measured the serum carnitine fractions and blood ammonia level every month during the levocarnitine supplementation period in patients with hyperammonemia. Significant increase in serum carnitine levels and a significant decrease in blood ammonia were obtained in the first month, and were maintained thereafter (Table3). In comparison with past reports [15, 24], where a levocarnitine preparation was used at 2000 mg 2 times a day, we showed a significant clinical effect with less than a half dose of levocarnitine preparation at 600 mg 3 times a day in this study.

The cut-off level of the pre-supplementation serum total carnitine for a 20% decrease in blood ammonia by L-carnitine was 62.0μmol/L on ROC analysis (Figure4). Because this value is in the standard range, cirrhosis patients might be starved in carnitine even at this serum level. Thus, we suggest levocarnitine supplementation as a new therapeutic option for refractory hyperammonemia that are resistant to other interventions including a protein-restricted diet, oral disaccharides such as lactulose, oral BCAAs, and non-absorbable antibiotics.

The mechanism responsible for improvement in hyperammonemia by levocarnitine are unclear, although it is hypothesized that levocarnitine enhances ammonia processing in the urea cycle by increasing N-acetylglutamate, and also improves energy metabolism by increasing acetyl coenzyme A (CoA) or subsequently optimizing the acetyl CoA to free CoA ratio [25,26].

The present study had several limitations. First, although carnitine is distributed most in skeletal muscle, we did not measure carnitine content in skeletal muscle in the baseline study. It was hard to obtain skeletal muscle biopsies due to the ethical reason in our patient cohort. Second, our intervention study for refractory hyperammonemia in cirrhosis patients was not randomized or controlled. Additional studies are required to raise the evidence level. The third limitation was the lack of dose response analysis for levocarnitine preparation, since past reports [15, 24] employed a levocarnitine preparation at higher doses. In addition, shorter time course studies are also required, since clinical effects of levocarnitine on serum carnitine and blood ammonia levels had reached plateau within 1 month after treatment.

In particular, the target population of study C was cirrhosis patients who repeated hepatic encephalopathy associated with hyperammonemia. These patients had been initially treated with a protein-restricted diet, oral disaccharides such as lactulose and lactitol, oral branched-chain amino acids (BCAAs), or non-absorbable antibiotics, and their hepatic encephalopathy, along with hyperammonemia, was improved. However, with repeated episodes, both their blood ammonia levels and hepatic encephalopathy got resistant to such therapies, gradually. Therefore, in these patients, the improvement of hyperammonemia is considered to be effective to resolve or prevent hepatic encephalopathy. Since we observed 20% reduction of blood ammonia on mean basis in these patients by levocarnitine, we intended ROC analysis to show the threshold value of baseline serum carnitine that allows expecting beneficial effect of levocarnitine solely on hyperammonemia. Clinical significance of this cut-off value in the management of chronic recurrent hepatic encephalopathy should be evaluated in a future large scale trial, because the usefulness of blood ammonia level as a diagnostic marker of occult hepatic encephalopathy is under discussion [27].

Conclusions

Serum carnitine concentrations were within standard ranges in the majority of liver cirrhosis patients. At the same time, supplementation with a levocarnitine preparation improved refractory hyperammonemia in cirrhotics. Such patients may need carnitine supplementation even when their serum levels are in the range of healthy individuals. Further investigations are required to elucidate the optimal dosage and supplementation durations of levocarnitine in cirrhotic patients with refractory hyperammonemia.

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Figure legends

Figure 1

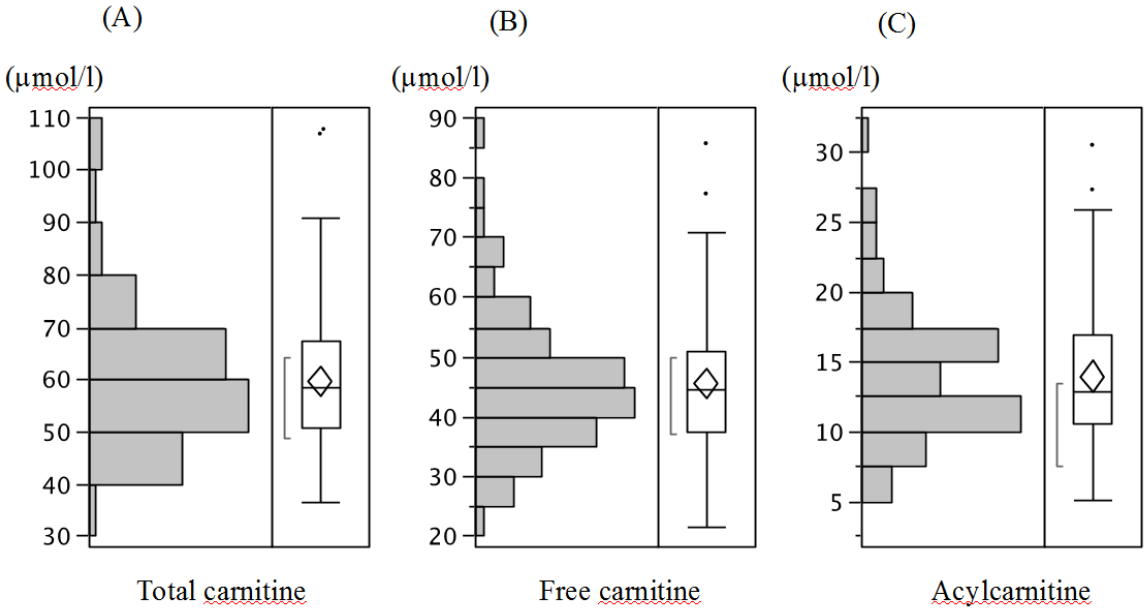

Figure 1. Serum carnitine concentrations in cirrhosis patients (N = 70). The serum total carnitine concentration was 68.4±4.7 μmol/L (A), the free carnitine concentration was 53.2±2.6 μmol/L (B), and the acylcarnitine concentration was 13.2±1.1 μmol/L (C). Reference values [18] are 45-91μmol/L, 36-74 μmol/L, and 6-23 μmol/L, respectively. Box plot showed median, lower quartile, and upper quartile in either panel. The whiskers showed the minimum and maximum values excluding the outliers in either panel. Figures of bracket expressesed the shortest range where half objects were within.

Figure 2

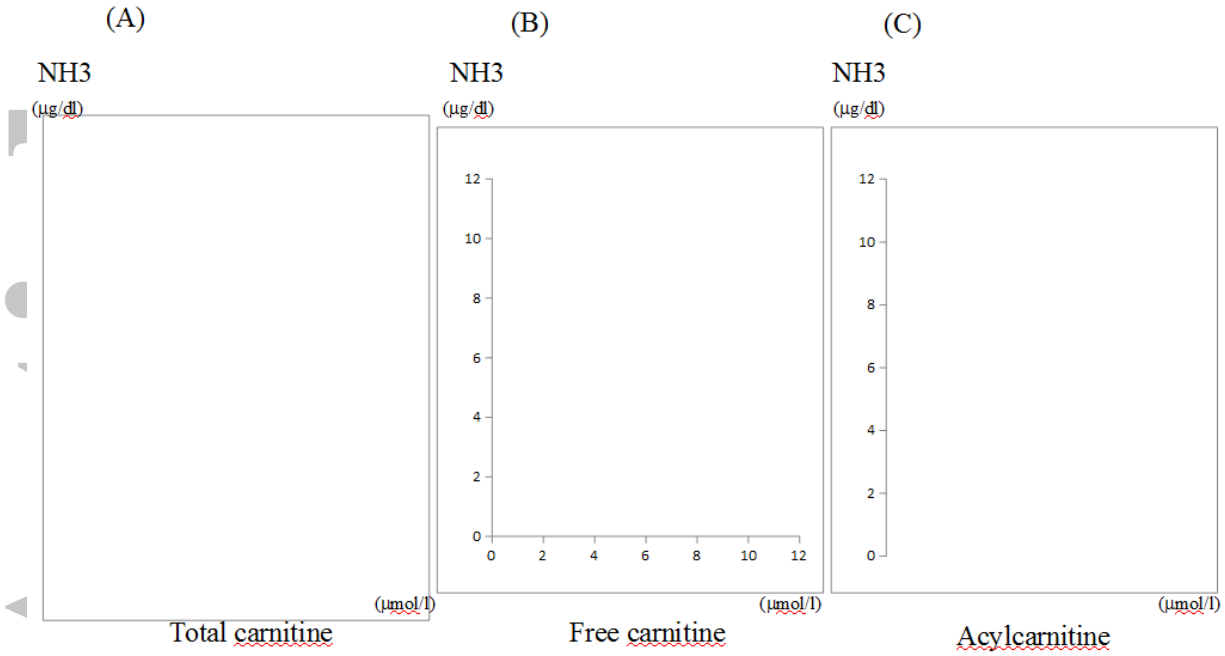

Figure 2. Correlation between serum total carnitine (A), free carnitine (B), or acylcarnitine (C) and blood ammonia concentrations in cirrhosis patients (N = 70). No significant correlation was found in either panel. (A; $r < 0.01$, $p = 0.977$, B; $r = 0.010$, $p = 0.945$, C; $r = 0.03$, $p = 0.807$,)

Figure 3

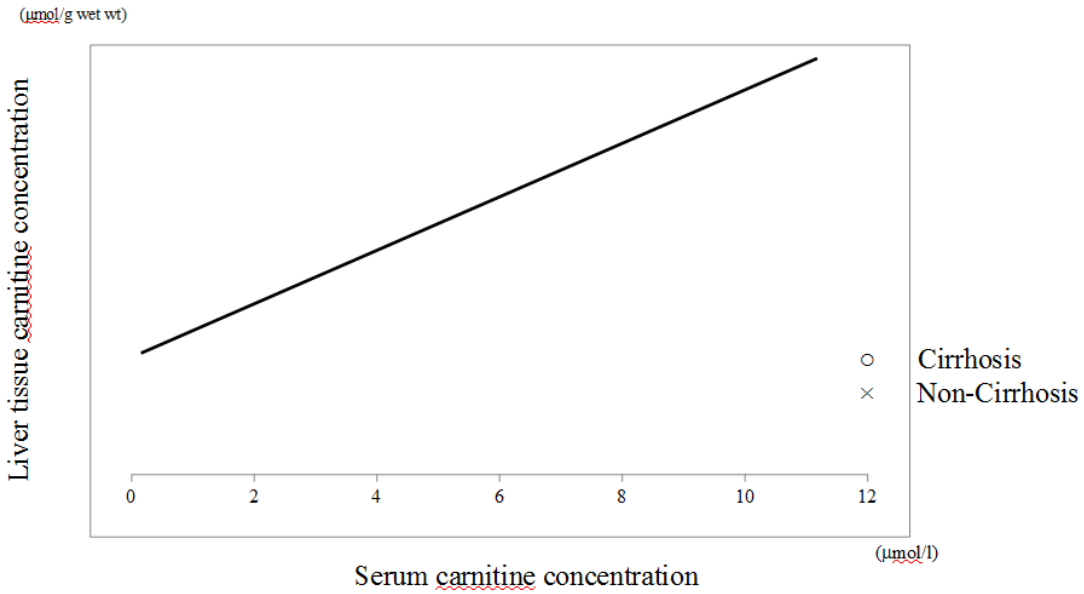

Figure 3. Correlation between serum and liver tissue total carnitine concentrations in cirrhotic patients (cross marks) and non-cirrhotic patients (open circles). N = 12, r = 0.69, $p < 0.05$.

Figure 4

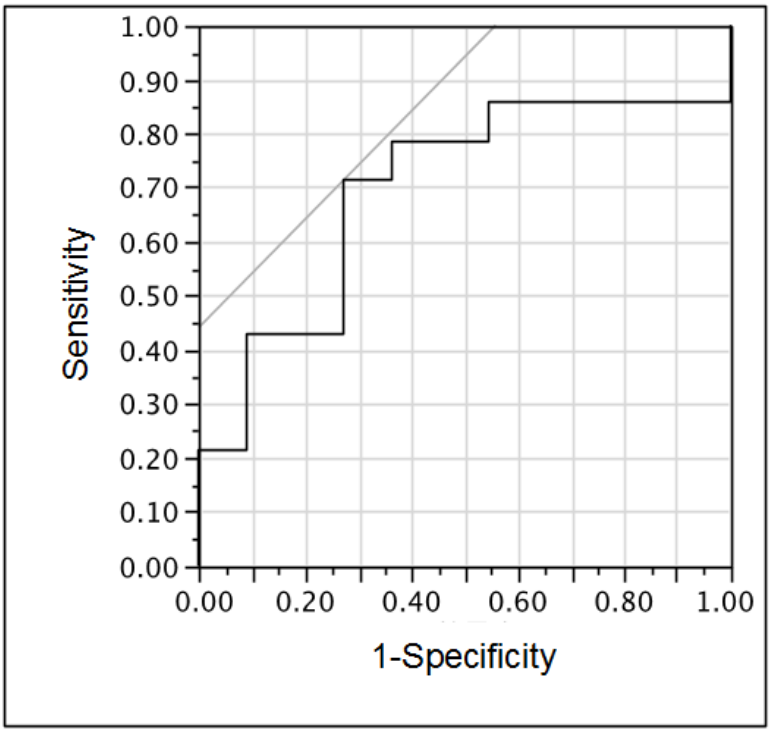

Figure 4. Receiver operating characteristic curve (ROC) analysis to identify the cut-off level of pre-supplementation total carnitine concentration for a 20% decrease in ammonia by L-carnitine. The cut-off level was 62.0 μmol/L with the area under the curve of 0.69 (sensitivity 0.71; specificity 0.73; positive predictive value 0.77; negative predictive value 0.67).

Table 1. Clinical and biochemical profiles of patients with liver cirrhosis

	N = 70
Age (years)	68.6 ± 9.3
Gender (Male / Female)	40 / 30
Child-Pugh grade (A / B / C)	26 / 18 /16
Etiology (HBV / HCV / Alcohol / Others)	8 / 37 / 14 / 11
Hepatocelluler carcinoma (+ / -)	34 / 36
Stage (I / II / III / IV)	9 / 5 / 10 / 10
Body mass index (kg/m^2)	22.9 ± 3.1
Total bilirubin (mg/dl)	1.1 ± 2.7
Albumin (g/dl)	3.2 ± 0.7
Alanine aminotransferase (IU/l)	39 ± 31.3
Prothrombin time (%)	72 ± 23.6
Ammonia (mg/dl)	73 ± 41.8
Creatinine (mg/dl)	0.81 ± 0.4
Platelet counts ($\times 10^4/\mu l$)	9.9 ± 9.1

Abbreviations: HBV, hepatitis B virus; HCV, hepatitis C virus

Data are presented as number of patients or mean ± S.D.

Table 2. Baseline clinical and biochemical profiles of patients with liver cirrhosis

	N = 27
Age (years)	66.0 ± 6.9
Gender (Male/Female)	9 / 18
Child-Pugh grade (A / B / C)	13 / 13 / 1
Etiology (HBV / HCV / Alcohol / Others)	4 / 13 / 5 / 5
Albumin (g/dl)	3.4 ± 0.3
Total bilirubin (mg/dl)	1.75 ± 0.63
Alanine aminotransferase (IU/l)	17 ± 9.3
Prothrombin time (%)	65 ± 16.1
Ammonia (μg/dl)	123 ± 29.2
Creatinine (mg/dl)	0.61 ± 0.20
Total carnitine (μmol/l)	61.8 ± 13.6
Free carnitine (μmol/l)	50.1 ± 11.8
Acylcarnitine (μmol/l)	11.6 ± 3.6

Abbreviations: HBV, hepatitis B virus; HCV, hepatitis C virus

Data are presented as number of patients or mean ± S.D.

Table 3. Changes in serum total carnitine, free carnitine, acylcarnitine, and ammonia concentrations after the levocarnitine preparation

	0 month	1 month	2 month	3 month
Total carnitine (mmol/l)	61.8 ± 13.6	97.3 ± 17.2*	101.1 ± 19.8*	122.9 ± 19.2*
Free carnitine (mmol/l)	50.1 ± 11.8	80.2 ± 14.3*	78.5 ± 15.5*	107.0 ± 14.4*
Acylcarnitine (mmol/l)	11.6 ± 3.6	16.7 ± 4.9*	21.4 ± 6.5*	22.5 ± 9.3*
Albumin (g/dl)	3.4 ± 0.3	3.3 ± 0.3	3.4 ± 0.3	3.4 ± 0.3
Total bilirubin (mg/dl)	1.75 ± 0.63	1.79 ± 0.64	1.85 ± 0.61	1.78 ± 0.73
Alanine aminotransferase (IU/l)	17 ± 9.3	18 ± 11.3	19 ± 7.2	19 ± 6.6
Prothrombin time (%)	65 ± 16.1	68 ± 14.0	66 ± 17.6	63 ± 18.1
Ammonia (mg/dl)	123 ± 29.2	101 ±34.4*	95 ± 31.5*	100 ± 36.5*

Each in comparison with 0 months *P value < 0.05