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Factors Associated With Protein-energy Malnutrition in Chronic Liver Disease

Analysis Using Indirect Calorimetry

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Abstract: We aimed to elucidate the incidence of protein–energy malnutrition (PEM) in patients with chronic liver disease and to identify factors linked to the presence of PEM.

A total of 432 patients with chronic liver disease were analyzed in the current analysis. We defined patients with serum albumin level of ≤3.5 g/dL and nonprotein respiratory quotient (npRQ) value using indirect calorimetry less than 0.85 as those with PEM. We compared between patients with PEM and those witho ut PEM in baseline characteristics and examined factors linked to the presence of PEM using univariate and multivariate analyses.

There are 216 patients with chronic hepatitis, 123 with Child–Pugh A, 80 with Child–Pugh B, and 13 with Child–Pugh C. Six patients (2.8%) had PEM in patients with chronic hepatitis, 17 (13.8%) in patients with Child–Pugh A, 42 (52.5%) in patients with Child–Pugh B, and 10 (76.9%) in patients with Child–Pugh C ($P < 0.001$). Multivariate analysis revealed that Child–Pugh classification ($P < 0.001$), age ≥64 years ($P = 0.0428$), aspartate aminotransferase (AST) ≥40 IU/L ($P = 0.0023$), and branched-chain amino acid to tyrosine ratio (BTR) ≤5.2 ($P = 0.0328$) were independent predictors linked to the presence of PEM. On the basis of numbers of above risk factors (age, AST, and BTR), the proportions of patients with PEM were well stratified especially in patients with early chronic hepatitis or Child–Pugh A (n = 339, $P < 0.0001$), while the proportions of patients with PEM tended to be well stratified in patients with Child–Pugh B or C (n = 93, $P = 0.0673$).

Age, AST, and BTR can be useful markers for identifying PEM especially in patients with early stage of chronic liver disease.

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Abbreviations: %C = substrate oxidation of carbohydrate, %F = substrate oxidation rates of fat, %P = substrate oxidation of protein, ALT = alanine aminotransferase, AST = aspartate aminotransferase, BMI = body mass index, BTR = branched-chain amino acid (BCAA) to tyrosine ratio, HOMA-IR = homeostasis model assessment-insulin resistance, LC = liver cirrhosis, npRQ = non-protein respiratory quotient, PEM = protein-energy malnutrition, REE = rest energy expenditure, UN = urinary excretion of nitrogen, V_{CO2} = carbon dioxide production per minute, V_{O2} = oxygen consumption per minute.

INTRODUCTION

The liver plays a unique role in carbohydrate metabolism by maintaining glucose concentration levels in the normal range and it is also an essential organ for the metabolism of three major nutrients: protein, fat, and carbohydrate.[1–5] Liver cirrhosis (LC), which develops over a long period of time due to chronic inflammation, is often complicated with protein–energy malnutrition (PEM).[1,2,6] PEM is one of the most common complications in LC patients.[1,2,6] PEM is associated with an increased risk of complications, including ascites, variceal bleeding, hepatic encephalopathy, and hepatorenal syndrome, and thus, it is linked to high morbidity and mortality for LC patients.[1,2,4,6–9] Predicting the presence of PEM and appropriate nutritional support is therefore essential for improving prognosis in chronic liver disease patients with PEM.

Protein malnutrition can be assessed using serum albumin value.[10,11] It has been demonstrated that, in metabolic disorders of protein, the degradation and synthesis rates of albumin decreased and the half-life of serum albumin became longer.[12] In general, patients with serum albumin value of ≤3.5 g/dL are considered to have protein malnutrition and it is easily tested in clinical practice, although a previous study reported that conventional definition of hypoalbuminemia as a serum albumin level of ≤3.5 g/dL should be reconsidered.[10,11,13] On the contrary, measurement of nonprotein respiratory quotient (npRQ) using indirect calorimetry for assessing the degree of energy malnutrition is highly limited in daily clinical practice due to the high cost for indirect calorimetry. Thus, other alternative markers will be needed for predicting the presence of PEM.[14] Particularly, in early stages of chronic liver disease such as chronic hepatitis and Child–Pugh A, the presence of PEM tends to be overlooked, leading to the delay of initiation of nutritional support.[15] In addition, PEM is linked to sarcopenia, which is

characterized by the depletion of skeletal muscle mass and negatively effect on survival and quality of life in patients with LC and has thus recently attracted attention for clinicians.[6,16–18]

On the basis of these backgrounds, in the current study, we aimed to elucidate the incidence of PEM in patients with chronic liver disease and to identify factors linked to the presence of PEM.

PATIENTS AND METHODS

Patients

Between October 2005 and January 2012, nutritional evaluation was performed in a total of 600 patients with chronic liver disease at the Division of Hepatobiliary and Pancreatic disease, Department of Internal Medicine, Hyogo College of Medicine, Hyogo, Japan, using indirect calorimetry, anthropometry, and/or bio-electrical impedance analysis. Of these, indirect calorimetry was used for nutritional assessment in 494 patients. In the current analysis, we included the following variables into analysis: age, gender, cause of liver disease, body mass index (BMI), degree of liver fibrosis using liver biopsy sample, serum albumin, total bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), fasting blood sugar, total cholesterol, triglyceride, HbA1c, homeostasis model assessment-insulin resistance (HOMA-IR), branched-chain amino acid (BCAA) to tyrosine ratio (BTR). Only subjects with all these data available were included in our analysis. Thus, a total of 432 patients were analyzed in this study (Figure 1). Patients excluded from the current analysis had comparable baseline characteristics as compared with those analyzed in this study.

We defined patients with serum albumin level of $\leq$3.5 g/dL and npRQ less than 0.85 as those with PEM according to the previous reports.[19,20] We retrospectively investigated the energy metabolism and the proportion of patients with PEM in our cohort. In addition, we compared the baseline characteristics of patients with and without PEM and examined factors linked to the presence of PEM using univariate and multivariate analyses.

Liver biopsy samples were routinely obtained using percutaneous liver biopsy methods and well-trained pathologists in our hospital assessed the samples. Degree of fibrosis stages (F0–4) were assessed according to the METAVIR scoring system.[21,22] In performing liver biopsy, procedure-related death was not observed in all analyzed cases.

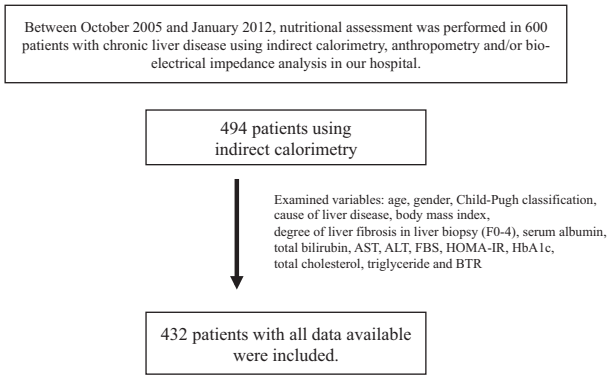

FIGURE 1. Study design. ALT, alanine aminotransferase, AST, aspartate aminotransferase, BTR, branched-chain amino acid (BCAA) to tyrosine ratio, FBS, fasting blood sugar, HOMA-IR, homeostasis model assessment-insulin resistance.

The ethics committee of Hyogo College of Medicine, Japan, approved the current study protocol and this study protocol complied with all of the provisions of the Declaration of Helsinki. Written informed consent was obtained from all subjects before assessing nutritional status using indirect calorimetry.

Indirect Calorimetry

Parameters measured by indirect calorimetry are carbon dioxide production per minute (V_{CO2}) and oxygen consumption per minute (V_{O2}). Total urinary excretion of nitrogen (UN) was measured as reported previously.[19,23] npRQ, rest energy expenditure (REE), substrate oxidation rates of fat (%F), carbohydrate (%C), and protein (%P) were calculated using following formulas: $npRQ = (1.44V_{CO2} - 4.890\ UN)/(1.44\,V_{O2} - 6.04\ UN)$; $REE\ (kcal/day) = 5.50\,V_{O2} + 1.76\,V_{CO2} - 1.99\ UN$; $F\ (g/24\,hour) = 2.432\,V_{O2} + 2.432\,V_{CO2} - 1.943\ UN$; $C\ (g/24\,hour) = 5.926\,V_{O2} + 4.189\,V_{CO2} - 2.539\ UN$; $P\ (g/24\,hour) = 6.250\ UN$; $\%F = 9.46F/REE \times 100$; $\%C = 4.18C/REE \times 100$; $\%P = 4.32P/REE \times 100$.[19,23–26] REE was determined for all subjects in the morning after an overnight fast (12 hours).

Statistical Analysis

In continuous variables, the statistical analysis among groups was performed using Student *t* test or Kruskal–Wallis test, as appropriate. Categorical variables were compared using Fisher exact tests or Pearson χ^2 test, as appropriate. Data were analyzed using univariate and multivariate analyses. Factors associated with the presence of PEM, defined as $P < 0.05$ in univariate analyses, were entered into multivariate logistic regression analysis. To analyze the significance of predictors of PEM in multivariate analysis, continuous variables were divided by the median values for all cases (n = 432) and treated as dichotomous covariates. Data are expressed as means ± standard deviation (SD) or median value (range). Values of $P < 0.05$ were considered to be statistically significant. Statistical analysis was performed with the JMP 9 (SAS Institute Inc., Cary, NC).

RESULTS

Baseline Characteristics

The baseline characteristics in the present study (n = 432) are summarized in Table 1. They included 224 males and 208 females. The mean (±SD) age was 61.4 ± 13.0 years. As for cause of background liver disease, there are 246 subjects in hepatitis C, 46 in hepatitis B, 6 in hepatitis B and C, 29 in alcoholic liver injury, and 106 in others. Others included autoimmune hepatitis, primary biliary cirrhosis, nonalcoholic steatohepatitis, nonalcoholic fatty liver disease, and cryptogenic chronic liver disease. In terms of degree of liver fibrosis, there are 7 subjects in F0, 94 in F1, 57 in F2, 58 in F3, and 216 in F4. In patients with F4, they included 123 patients with Child–Pugh A, 80 with Child–Pugh B, and 13 with Child–Pugh C.

npRQ Value According to the Degree of Liver Function

The median values (range) of npRQ in each group are as follows: 0.89 (0.63–1.37) in chronic hepatitis, 0.86 (0.66–1.23) in Child–Pugh A, 0.84 (0.71–1.30) in Child–Pugh B, and 0.82 (0.73–1.00) in Child–Pugh C ($P < 0.0001$) (Figure 2).

TABLE 1. Baseline Characteristics in the Present Analysis (n = 432)

Variables	N = 432
Age, y	61.4 ± 13.0
Gender, male/female	224/208
[0,1-2]Cause of liver diseases	
C/B/B and C/Alcoholic/Others	246/46/5/29/106
Body mass index, kg/m^2	22.7 ± 3.8
Grade of histological fibrosis, F0/1/2/3/4	7/94/57/58/216
AST, IU/L	53.4 ± 52.4
ALT, IU/L	56.0 ± 77.9
Total cholesterol, mg/dL	163.1 ± 40.1
Triglyceride, mg/dL	99.8 ± 56.0
Fasting blood glucose, mg/dL	104.4 ± 31.7
HbA1c, %	5.4 ± 1.0
HOMA-IR	3.7 ± 14.8
Serum albumin, g/dL	3.7 ± 0.5
Total bilirubin, mg/dL	1.1 ± 0.9
BTR	5.2 ± 1.9
REE, kcal/day	1311.2 ± 320.8
REE/body weight, kcal/day/kg	22.5 ± 4.3
npRQ	0.88 ± 0.10

Data are expressed as number or mean ± standard deviation. ALT = alanine aminotransferase, AST = aspartate aminotransferase, BTR = branched-chain amino acid to tyrosine ratio, HOMA-IR = homeostasis model assessment-insulin resistance, npRQ = nonprotein respiratory quotient, REE = rest energy expenditure.

Energy Metabolism Based on the Degree of Liver Function

Data for energy metabolism based on the degree of liver function are (all data are presented with mean value): 12.7% in the %C, 29.2% in the %F, and 58.1% in the %P in patients with chronic hepatitis; 12.4% in the %C, 40.3% in the %F, and 47.3% in the %P in patients with Child–Pugh A; 10.7% in the %C, 40.7% in the %F, and 48.6% in the %P in patients with Child–Pugh B; and 9.0% in the %C, 54.5% in the %F, and 36.5% in the %P in patients with Child–Pugh C. As the liver function deteriorates, the %C gradually decreased and the %F gradually increased (Figure 3).

Proportion of Patients With PEM According to the Degree of Liver Function

Six out of 216 patients (2.8%) had PEM in patients with chronic hepatitis (F0-F3), 17 out of 123 (13.8%) in patients with Child–Pugh A, 42 out of 80 (52.5%) in patients with Child–Pugh B, and 10 out of 13 (76.9%) in patients with Child–Pugh C ($P < 0.001$) (Figure 4A). Thus, in LC patients (n = 216), the proportion of patients with PEM was 31.9% (69/216). In patients with chronic hepatitis and PEM (n = 6), the degree of liver fibrosis is F1 in 2 patients, F2 in 3, and F3 in 1.

Univariate and Multivariate Analyses of Factors Associated With the Presence of PEM

Univariate analysis identified the following factors as significantly associated with the presence of PEM for all cases (n = 432): age ($P < 0.0001$); degree of liver function ($P < 0.0001$); AST ($P = 0.0016$); total bilirubin ($P = 0.0026$); total cholesterol ($P < 0.0001$); triglyceride ($P < 0.0001$); HbA1c ($P = 0.0016$); and BTR ($P < 0.0001$) (Table 2). The hazard ratios and 95% confidence intervals calculated using multivariate analysis for the eight factors with $P < 0.05$ in univariate analysis are detailed in Table 3. Age ≥64 years ($P = 0.0428$), Child–Pugh classification ($P < 0.0001$), AST ≥40 IU/L ($P = 0.0023$), and BTR ≤5.2 ($P = 0.0328$) were found to be significant prognostic factors linked to the presence of PEM.

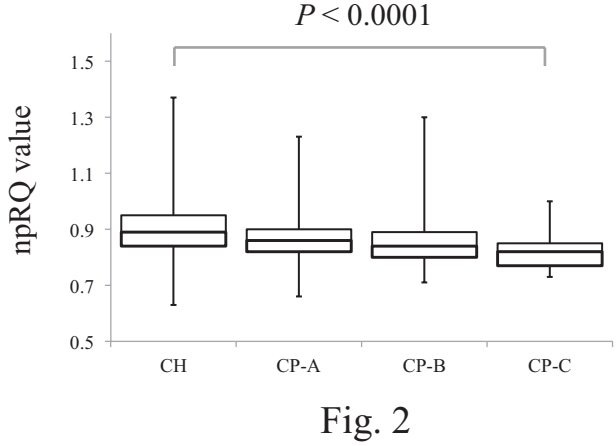

Fig. 2

FIGURE 2. npRQ value according to the degree of liver function, presented by box plots. The median values (range) of npRQ are 0.89 (0.63–1.37) in chronic hepatitis, 0.86 (0.66–1.23) in Child–Pugh A, 0.84 (0.71–1.30) in Child–Pugh B, and 0.82 (0.73–1.00) in Child–Pugh C. As the liver function deteriorates, npRQ values significantly decreased ($P < 0.0001$).

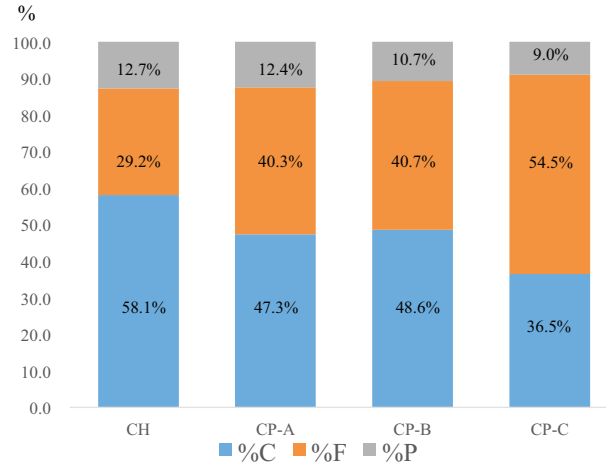

FIGURE 3. Energy metabolism according to the degree of liver function. %F, %C, and %P, substrate oxidation rates of fat, carbohydrate, and protein. The %C gradually decreased and the %F gradually increased as the liver functional reserve deteriorates.

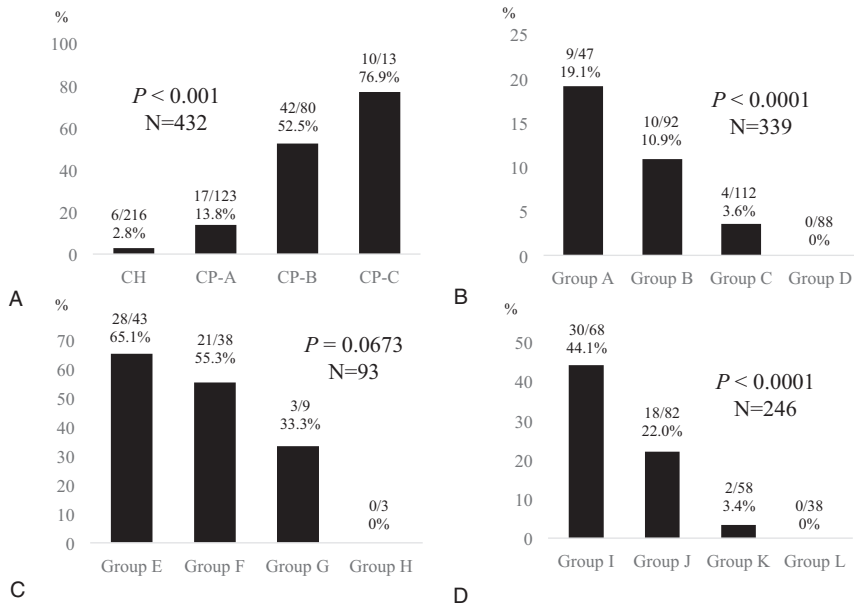

FIGURE 4. A, Proportion of patients with PEM according to the degree of liver function. The proportion of patients with PEM significantly increased as the liver function deteriorates ($P < 0.0001$). B, The proportion of patients with PEM based on numbers of significant factors in our multivariate analysis (age ≥64 years, AST ≥40 IU/L, and BTR ≤5.2) in patients with chronic hepatitis or Child–Pugh A (n = 339). Group A means patients with age ≥64 years, AST ≥40 IU/L, and BTR ≤5.2. Group B means patients who had any 2 factors out of the above 3 factors. Group C means patients who had any 1 factor out of 3 factors. Group D means patients who had none of 3 factors. The proportion of PEM among four groups were significantly stratified ($P < 0.0001$). C, The proportion of patients with PEM based on numbers of significant factors in our multivariate analysis (age ≥64 years, AST ≥40 IU/L, and BTR ≤5.2) in patients with Child–Pugh B or C (n = 93). Group E means patients with age ≥64 years, AST ≥40 IU/L, and BTR ≤5.2. Group F means patients who had any 2 factors out of the above 3 factors. Group G means patients who had any 1 factor out of 3 factors. Group H means patients who had none of 3 factors. The proportion of PEM among 4 groups tended to be significantly stratified ($P = 0.0673$). D, The proportion of patients with PEM based on numbers of significant factors in our multivariate analysis (age ≥64 years, AST ≥40 IU/L, and BTR ≤ 5.2) in patients with chronic hepatitis C related liver disease (n = 246). Group I means patients with age ≥64 years, AST ≥40 IU/L, and BTR ≤5.2. Group J means patients who had any 2 factors out of the above 3 factors. Group K means patients who had any 1 factor out of 3 factors. Group L means patients who had none of 3 factors. The proportion of PEM among 4 groups were significantly stratified ($P < 0.0001$).

TABLE 2. Comparison of Baseline Characteristics Between Patients With Protein–Energy Malnutrition (PEM) (n = 75) and Those Without PEM (n = 357)

Variables	PEM (n = 75)	Non-PEM (n = 357)	*P*
Age, y	67.2 ± 10.6	60.2 ± 13.1	<0.0001
Gender, male/female	40/35	184/173	0.801
BMI, kg/m^2	23.1 ± 4.0	22.6 ± 3.8	0.339
Degree of liver function			
CH/Child–Pugh, A/B/C	6/17/42/10	210/106/38 /3	<0.0001
Causes of liver disease			
C/B/B and C/Alcohol/Others	50/6/2/4/13	196/40/3/25/93	0.194
REE/body weight, kcal/day/kg	22.5 ± 3.4	22.5 ± 4.5	0.976
AST, IU/L	66.7 ± 53.0	50.6 ± 51.9	0.016
ALT, IU/L	54.6 ± 61.2	56.3 ± 81.0	0.845
Total bilirubin, mg/dL	1.58 ± 1.55	1.01 ± 0.65	0.0026
Total cholesterol, mg/dL	137.2 ± 33.4	168.5 ± 39.3	<0.0001
Triglyceride, mg/dL	78.3 ± 35.0	104.3 ± 58.6	<0.0001
Fasting blood glucose, mg/dL	104.4 ± 25.4	104.4 ± 32.9	0.991
HbA1c, %	5.0 ± 1.1	5.5 ± 0.9	0.0016
HOMA-IR	3.94 ± 7.5	3.63 ± 16.0	0.802
BTR	3.57 ± 1.58	5.58 ± 1.76	<0.0001

Data are expressed as number or mean ± standard deviation. ALT = alanine aminotransferase, AST = aspartate aminotransferase, BMI = body mass index, BTR = branched-chain amino acid to tyrosine ratio, CH = chronic hepatitis, HOMA-IR = homeostasis model assessment-insulin resistance, REE = rest energy expenditure.

TABLE 3. Multivariate Analysis of Factors Contributing to the Presence of Protein–Energy Malnutrition

		Multivariate Analysis	
Variables	**n**	**Hazard Ratio (95% CI)**	***P****
Age (y), ≥64 vs <64	214/218	1.958 (1.022–3.829)	0.0428
Degree of liver function			
Chronic hepatitis or C-P A vs C-P B or C	339/93	8.494 (4.109–18.374)	<0.001
Total bilirubin (mg/dL), ≥0.9 vs <0.9	239/193	1.255 (0.587–2.725)	0.5585
AST (IU/L), ≥40 vs <40	220/212	2.988 (1.471–6.318)	0.0023
Total cholesterol (mg/dL), ≤163 vs >163	220/212	1.681 (0.840–3.4328)	0.1429
Triglyceride (mg/dL), ≤88 vs >88	216/216	1.452 (0.740–2.873)	0.2780
HbA1c (%), ≥5.2 vs <5.2	228/204	1.310 (0.676–2.537)	0.4215
BTR, ≤5.2 vs >5.2	215/217	2.704 (1.082–7.428)	0.0328

AST = aspartate aminotransferase, BTR = branched-chain amino acid to tyrosine ratio, CI = confidence interval, C-P = Child–Pugh.
* Logistic regression analysis.

The Proportion of Patients With PEM Based on Numbers of Significant Factors in Multivariate Analysis (Age, AST Value, and BTR Value) in Patients With Chronic Hepatitis or Child–Pugh A (n = 339) and Those With Child–Pugh B or C (n = 93) and Those With HCV-positive Status (n = 246)

As in our multivariate analysis, age, AST value, and BTR value as well as Child–Pugh classification were found to be independent predictors linked to the presence of PEM, we performed subgroup analyses based on numbers of significant variables (age, AST, and BTR) in patients with chronic hepatitis or Child–Pugh A (n = 339) and those with Child–Pugh B or C (n = 93) and those with HCV-positive status (n = 246).

In patients with chronic hepatitis or Child–Pugh A (n = 339), the proportion of patients with PEM in those with age ≥64 years, AST ≥40 IU/L, and BTR ≤ 5.2 was 19.1% (9/47), while 10.9% (10/92) in those who had any 2 factors out of the above 3 significant factors, 3.6% (4/112) in those who had any 1 factor out of 3 factors, and 0% (0/88) in those who had none of 3 factors ($P < 0.0001$) (Figure 4B).

In patients with Child–Pugh B or C (n = 93), the proportion of patients with PEM in those with 3 significant factors was 65.1% (28/43), while 55.3% (21/38) in those who had any 2 factors out of 3 factors, 33.3% (3/9) in those who had any 1 factor out of 3 factors, and 0% (0/3) in those who had none of 3 factors ($P = 0.0673$) (Figure 4C).

In patients with HCV-related liver disease (n = 246), the proportion of patients with PEM in those with age ≥64 years, AST ≥40 IU/L, and BTR ≤5.2 was 44.1% (30/68), while 22.0% (18/82) in those who had any 2 factors out of the above 3 significant factors, 3.4% (2/58) in those who had any 1 factor out of 3 factors, and 0% (0/38) in those who had none of 3 factors ($P < 0.0001$) (Figure 4D).

DISCUSSION

To the best of our knowledge, this is the largest study for investigating nutritional status using indirect calorimetry in patients with chronic liver disease. As mentioned earlier, indirect calorimetry is expensive and clinicians are not usually familiar with this and PEM is closely associated with sarcopenia, which is reported to be an adverse predictive factor in patients with LC.[6,16–18] Thus, other alternative markers often used in daily clinical practice for predicting presence of PEM will be required for adequate nutritional support. Hence, we conducted the current analysis.

Our multivariate analysis revealed that Child–Pugh classification, age, AST value, and BTR value, which are available in clinical settings, were independent predictors linked to the presence of PEM and we demonstrated that using these variables, the risk groups of developing PEM were well stratified especially in patients with early stages of chronic liver disease. Despite its importance, PEM is often underdiagnosed in patients with chronic liver disease, particularly in the early stages of disease such as chronic hepatitis or Child–Pugh A.[15] Furthermore, in our results, it is of note that in patients who had none of 3 risk factors of age ≥64 years, AST ≥40 IU/L, and BTR ≤ 5.2, there was no patient with PEM in groups of chronic hepatitis or Child–Pugh A (n = 88) and Child–Pugh B or C (n = 3) and HCV-related liver disease (n = 38). This seems to provide useful information for clinicians in daily clinical practice. Our results shed some light on identifying patients with PEM and those without PEM in the field of chronic liver disease. Patients with our proposed multiple risk factors are potentially candidate for nutritional support, as they are expected to be complicated with PEM even if they are in the early stage of chronic liver disease.[10,11] On the other hand, contrary to our expectations, HOMA-IR was not a significant factor related to the presence of PEM and HbA1c value in the PEM group was significantly lower than that in the non-PEM group despite the fact that advanced liver fibrosis causes insulin resistance.[27,28] The reasons for these are unclear; however, liver function itself rather than insulin resistance may be associated with development of PEM.

Previous data have shown that LC patients often develop PEM at a rate of 25.1% to 65.5%,[7,22,29–32] although in our data, the proportion of PEM in LC patients was 31.9%. In 2002, Tajika et al[19] (Japanese investigators) reported that the proportion of PEM in LC patients was around 50%, which is significantly higher than our data. Due to the differences of baseline characteristics between our data and data of Tajika et al,[19] direct comparison in these 2 studies is difficult; however, the fact that eating habits in Japanese persons have changed and the advancement of therapy for LC patients in the last decade may explain these discrepancies.[3,20,33]

In our data of energy metabolism in indirect calorimetry, the %C gradually decreased and the %F gradually increased and npRQ value significantly decreased as the liver functional reserve deteriorates. As LC patients have poorer glycogen stores capacity and gluconeogenesis ability, they are prone to entering into a starvation state after an overnight fasting period.[1,14,16,34–36] In this situation, lipid metabolism is enhanced; energy metabolism shifts from a carbohydrate preference to lipid oxidation preference and it is well accepted that decreased glucose oxidation and increased fat oxidation are associated with reduction of npRQ value in LC patients.[1,14,16,34] Our results were consistent with previous reports.[19]

With the recent high prevalence of persons with obesity, the number of obese LC patients has been increasing.[16] In our results, BMI was not a significant factor linked to the presence of PEM. In our data, the proportions of patients with BMI $>25\,kg/m^2$, which is defined as obesity in our country, were 29.3% (22/75) in the PEM group and 21.8% (78/357) in the non-PEM group in our cohort.[37] Although BMI is a simple anthropometric index, BMI is limited anthropometrically, as it does not evaluate individual components of body weight such as muscle volume or regional fat distribution.[38] In that sense, BMI may not be useful for predicting PEM. Instead, sarcopenic obesity derived from excess adiposity (obesity) and low muscle mass (sarcopenia), which is an adverse predictor for LC patients, may be attributed to our results.[39,40] On the contrary, in patients with BMI $>25\,kg/m^2$ ($n = 100$), 65 (65.0%) had HOMA-IR ≥ 2.5. Furthermore, in limited patients with LC and BMI $>25\,kg/m^2$ ($n = 56$), 40 (71.4%) had HOMA-IR ≥ 2.5 in our study. Obesity and insulin resistance in LC patients are significant problem, as it can cause liver fibrosis progression and liver carcinogenesis, although this is beyond the scope of our current analysis.[16,27]

There are several limitations in this study. First, this study is a retrospective observational study. Second, in performing liver biopsy, sampling errors for evaluating the degree of liver fibrosis can occur. Third, npRQ value may be influenced by characteristics of diet or recent physical activity in each patient. Thus, we should interpret our current results with caution. However, in the current analysis, we demonstrated that age, AST value, and BTR value are significant predictors for the presence of PEM as well as Child–Pugh classification using large sample size. In conclusion, especially in early stage of chronic liver disease, such variables can be useful for identifying patients with PEM and those without PEM.

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