Simple Indicators of Energy Malnutrition in Patients With Chronic Liver Diseases

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Abstract

Objective: Protein−energy malnutrition (PEM) is an important prognostic factor in patients with cirrhosis. Energy malnutrition (EM) is defined by the Japanese Society of Gastroenterology Guidelines for cirrhosis as a non-protein respiratory quotient <0.85, a % arm circumference (%AC) <95%, or a free fatty acid (FFA) value >660 µEq/L. The parameters associated with EM are difficult to measure in all patients. In this study, we evaluated simple indicators of EM.

Methods: This retrospective study included 295 patients with chronic liver diseases (CLDs) in whom serum FFA values or %AC were measured at the Department of Gastroenterology at the Municipal Hospital of Kofu. We examined the characteristics of the patients with EM.

Results: EM was observed in 36% of patients with CLDs without a late-evening snack (LES). The frequency of EM was high in patients with Child−Pugh grade B or C, γ-GTP level ≥100 U/ml, AST level ≥27 IU/l, and ALT level ≥27 IU/l in males, and Child−Pugh grade B or C, γ-GTP ≥84 U/ml, AST ≥24 IU/l, and ALT ≥28IU/l in females. Among the three indicators of Child−Pugh grade B or C, increased γ-GTP levels, and increased transaminase values, EM was observed in 16%, 35%, 59%, and 57% of patients who were positive for 0, 1, 2, or 3 of the indicators. The frequency of EM in patients with Child-Pugh grade A was high for increased γ-GTP, AST, and ALT levels. Among the two indicators of increased γ-GTP, and transaminase levels, 16%, 32%, and 67% of patients were positive for 0, 1, or 2 of the indicators.

Conclusion: Child-Pugh grade, transaminase values, and γ-GTP levels were useful indicators of EM in patients with CLDs. We should evaluate positively the presence of EM in cases with poor liver function, high transaminase concentrations, or high γ-GTP levels.

Background

Protein−energy malnutrition (PEM) is a prognostic factor in patients with cirrhosis. Protein malnutrition (PM) is defined by the Japanese Society of Gastroenterology Guidelines for cirrhosis as a serum albumin value ≤3.5g/dl, and energy malnutrition (EM) as a non-protein respiratory quotient (npRQ) <0.85, a % arm circumference (%AC) <95%, or a free fatty acid (FFA) value >660 µEq/L, for which therapeutic interventions are recommended[1]. Shiraki et al. used the npRQ from 294 cases with cirrhosis, including 154 Child−Pugh A cases, and reported that 43% of them had EM, 61% had PM, and 27% had PEM [2, 3]. Tajika et al. used the npRQ to report that 62% of patients with cirrhosis had EM, 70% had PM, and 50% had PEM [4]. Carvalho et al. examined %AC, % arm muscle circumference, and serum albumin values, using the formula reported by Medenhall et al. for the diagnosis of malnutrition, and found that 21%, 52% and 58% of Child−Pugh A, B, and C patients with cirrhosis had PEM, respectively [5, 6].

However, the parameters that are normally used to diagnose EM, including npRQ, %AC, and FFA, are difficult to measure in all patients in clinical practice. In this study, we examined the usual indicators of EM and analyzed the characteristics of patients with chronic liver disease in an effort to find simple indicators of EM.

Methods

Patients

From April 2019 to February 2020, we studied 295 patients with chronic liver diseases (CLDs) in whom serum FFA values or %AC were measured and analyzed retrospectively at the Department of Gastroenterology at the Municipal Hospital of Kofu. All patients participating in this study provided informed consent, and the study was conducted according to the

Helsinki Declaration and approved by the Ethics Committee for Clinical Studies of the Municipal Hospital of Kofu (Rinshoukenkyu-Rrinrishinsa-linkai (in Japanese), approval number 31-8).

Evaluation of serum FFA

Serum FFA values were measured in venous blood collected between 7 and 10 AM after fasting overnight from 8 PM the previous night for 10–14 h. After collection, blood was refrigerated at 4°C and prompt testing was conducted within 24 h using an enzymatic assay [7]. EM was defined as a serum FFA value >660 μEq/L in this study [1-4]

Evaluation of %AC

We measured the arm of the non-paralyzed side and non-dominant arm using the insert-tape and adipometer from the Japanese anthropometry reference data (JARD) 2001. AC was measured at the midpoint of the height between the acromion process and the olecranon process. Three measurements were taken and the mean value was used. JARD2001 provided data on body measurements of 5,492 healthy subjects adjusted for gender and age; moreover, for percent notation, the median was calculated as 100% [8, 9]. EM was defined as a %AC <95% in this study [1-4].

Statistical analysis

Values are shown as the median and range. Fisher's test was used for categorical variables. The Kolmogorov–Smirnov test was used to evaluate normality. Student's t-test was used for continuous variables. The best cut-off values in the receiver operating characteristic (ROC) analysis were determined by the Youden index. Significance was at P <0.05. All statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria); more specifically, it is a modified version of the R commander designed to include statistical functions that are frequently used in biostatistics[10].

Results

Baseline characteristics of the study subjects

The characteristics of the study subjects (n = 295) are shown in Table 1 and Figure 1. The median age of the patients was 72 (range, 20–94) years, with 172 males (58%). One hundred patients (34%) had chronic hepatitis, while 195 patients (66%) had liver cirrhosis. One hundred and one patients (34%) reported a history of therapy for hepatocellular carcinoma. Patients with EM had a significantly shorter survival than did patients without EM (P <0.001) (Figure 2). Nineteen cases have used a late-evening snack (LES). LES has been reported to decrease FFA, and only 276 cases without LES were included in the follow study [11].

Baseline characteristics of patients without a LES

The median age of patients without a LES (n = 276) was 72(20-94) years, and the cohort included 158 males (57%). We found 100 cases (36%) of chronic hepatitis and 176 cases (64%) of liver cirrhosis, whereas the number of cases of hepatitis B virus, hepatitis C virus, alcohol, nonalcoholic steatohepatitis, and other conditions was 37, 130, 35, 53, and 21, respectively. Two hundred and eighteen, 49, and 9 patients were Child–Pugh A, B, and C grade. Regarding comorbid diseases, we identified 76 cases of diabetes, 33 of chronic heart disease, 19 of chronic lung disease, 26 of cerebrovascular disease, and 26 of chronic renal failure. EM was observed in 98 cases (36%).

Risk factors for EM in patients with CLDs without a LES

Table 2 shows the characteristics of patients without a LES who were grouped as having or not having EM. The frequency of EM was significantly higher in patients with Child−Pugh grade B or C (OR 2.8, $P < 0.001$), low body mass index (BMI) (OR 1.1, $P = 0.001$), increased gamma glutamyltransferase (γ-GTP) levels (OR 1.01, $P < 0.001$), increased aspartate aminotransferase (AST) levels (OR 1.02, $P < 0.001$), and increased alanine aminotransferase (ALT) levels (OR 1.02, $P < 0.001$) (Table 3). Using the cut-off values calculated from the ROC curves, in males (n = 158), Child−Pugh grade B or C (OR 2.9, $P < 0.001$), BMI<22 (OR 2.1, $P = 0.031$), γ-GTP ≥100 U/ml (OR 6.5, $P < 0.001$), AST ≥27 IU/l (OR 3.3, $P < 0.001$), ALT ≥27 IU/l (OR 2.4, $P = 0.016$); and in females (n = 118), Child−Pugh grade B or C (odds ratio 2.8, $P = 0.031$), γ-GTP ≥84 U/ml (OR 3.4, $P = 0.020$), AST ≥24 IU/l (OR 3.2, $P = 0.013$), ALT ≥28IU/l (OR 3.4, $P = 0.0028$) values were risk factors for EM (Table 4). Among the three common items of Child−Pugh grade B or C, increased γ-GTP levels, and increased transaminase levels, EM was observed in 16%, 35%, 59%, and 57% of patients who were positive for 0, 1, 2, or 3 of the items, respectively (Figure 3).

Risk factors for EM in patients without LES classified as Child−Pugh grade A

In Child−Pugh grade A patients without a LES (n = 218), the frequency of EM was high among patients with increased γ-GTP (males ≥100, females ≥84 U/ml) (OR 6.7, $P < 0.001$), increased AST (males ≥27, females ≥24 IU/l) (OR 3.4, $P < 0.001$), and increased ALT (males ≥27, females ≥28 IU/l) (OR 2.7, $P < 0.001$) levels. High γ-GTP and high transaminase values were independent factors for predicting the presence of EM in patients with Child-Pugh grade A (Table 5).Among the two items of increased γ-GTP and increased AST or ALT levels, 16%, 32%, and 67% of cases were positive for 0, 1, or 2 of the items, respectively (Figure 4).

Discussion

PEM is a poor prognosis factor in chronic liver disease [1, 2, 11, 12] and has been associated with abdominal fluid retention, hepatic encephalopathy, rupture of esophageal gastric varicose veins, hepato-renal syndrome, sarcopenia, and decreased quality of life (QOL) [2, 13, 14]. In Japan, according to the treatment guidelines for liver cirrhosis of the Japanese Gastroenterological Society, EM is defined as a npRQ <0.85, %AC <95%, or FFA >660 µEq/L [1]. However, compared with PM, which is diagnosable based on albumin values alone, it is difficult to measure the parameters that are used to diagnose EM in all patients. Therefore, EM is often underdiagnosed, particularly in early-stage CLDs such as chronic hepatitis and Child−Pugh A cirrhosis. In this study, we focused on EM and examined the simple items that are easy to use in daily clinical care as indicators of EM.

Measurement of the npRQ using indirect calorimetry is an established method for the diagnosis of EM[15]. In patients with cirrhosis, EM is associated with a decrease in glycogen storage caused by increased energy consumption at rest and liver atrophy. The sugar ratio, which is an energy source during early morning fasting, decreases and the lipid ratio increases. As a result, EM occurs [16]. Increased insulin resistance and increased blood concentrations of glucagon, catecholamines, and cortisol are also involved in reducing the utilization efficiency of carbohydrates as an energy substrate. A previous study using the npRQ revealed that age >64 years, AST >40 IU/L, branched-chain amino acid to tyrosine ratio ≤5.2, and increased serum hyaluronic acid levels were associated with PEM[3, 17]. However, npRQ measurement is costly and can only be carried out in a limited number of facilities. Therefore, a simple substitute marker for the diagnosis of EM is required, and %AC and FFA have been reported to be useful correlates of npRQ measurement[18, 19]. In this study, we used %AC or FFA to diagnose EM, as we were not able to measure npRQ at our facility.

%AC is a method that is used for evaluating muscle mass based of body measurements and is employed as a parameter of nutritional assessment. %AC is correlated with the skeletal muscle mass measurements of the whole body in the elderly, as obtained from dual-energy X-ray absorptiometry [9]. A decrease in AC is a poor prognosis factor for healthy

elderly people, and a decrease in AC over time is associated with a deterioration of the activities of daily living in the elderly Japanese people [20]. The survival of patients whose AC was in the 10th or lower percentile was significantly shorter [18, 21]. Although the measurement error is minimized by the standardization of the methods of measurement, the measurer must be an expert who is familiar with the procedure. The measurement error is large in cases involving thick subcutaneous fat [9]; moreover, we should consider the measurement errors resulting from fluid retention in patients with decompensated cirrhosis [22, 23].

FFA accounts for approximately 5% of total lipids, and its blood concentrations are regulated by uptake into the liver through the action of the hormone-sensitive lipase and lipoprotein lipase (LPL) enzymes [24]. Plasma levels of FFA were correlated with npRQ (r = −0.39, P < 0.001), and the FFA value that predicted a npRQ of 0.85 was 660 µEq/L. In patients with cirrhosis, decreased liver processing of FFA and increased LPL activity result in increased FFA levels [25, 26]. FFA is associated with hepatic encephalopathy and the onset of dementia in patients with cirrhosis [19, 24, 27-30]. FFA decreases with dietary intake, exercise, and use of hypoglycemic agents, but it increases with fasting, smoking, aging, growth hormone, and catecholamines [31]. Therefore, it is necessary to consider the patient's background when diagnosing EM based on FFA.

In this study, we report for the first time that Child−Pugh grade and increased levels of γ-GTP, AST, and ALT may suggest EM in patients with CLDs. Our facility cannot measure npRQ and FFA using the in-house testing system, and we believe this report is useful for the simple enclosurement of patients with EM. In patients with CLDs, Child−Pugh grade B or C, and high levels of γ-GTP, AST, or ALT were risk factors for EM, and patients who were positive for 0, 1, 2, or 3 of the items developed EM in 16%, 35%, 59%, and 57% of cases, respectively. In patients with Child−Pugh grade A in whom the levels of γ-ATP, AST, or ALT were measured, those positive for 0, 1, or 2 of the items developed EM in 16%, 32%, and 67% of cases, respectively.

The blood concentration of cytokines is reported to be significantly higher in patients with cirrhosis than in non-cirrhosis patients because of abnormal intestinal flora, bacterial translocation resulting from portal hypertension, and a decrease in reticuloendothelial function [32, 33]. The secretion of cytokines is mainly due to the infiltration of lymphocytes into the liver as a result of inflammation and liver damage. In particular, the tumor necrosis factor-α (TNF-α), interleukin (IL)-1, or IL-6, inhibits glucose oxidation, thus affecting fat combustion, and is associated with EM in patients with cirrhosis [32, 34-39]. In cases of inflammation and liver damage showing high values of γ-GTP and transaminases, blood cytokine levels are expected to increase, and the frequency of EM expected to increase.

For the treatment of malnutrition in patients with cirrhosis, guidelines such as ESPEN and ASPEN have been proposed [1, 11, 40]. Patients with EM showed increased AC and reduced FFA after 1 month of diet management [41]. After the administration a LES to patients with EM, a decrease in FFA and an improvement in QOL were observed [14, 41-43]. In this study, FFA values were significantly higher in cases without a LES compared with those with a LES (453 ± 307 vs. 278 ± 359 µEq/L, P = 0.031) (Figure 5). Further research is needed regarding the relationship between changes in FFA, %AC, treatment intervention, and prognosis.

This study had some limitations. It was conducted at a single facility and included a small number of cases, with few cases of Child−Pugh grade B or C. Furthermore, the relationship between ethiology, physical activity, and EM could not be investigated. Among the 43 cases in which both FFA and %AC were measured, there were 19 cases in which the results regarding the judgement of EM based on FFA and %AC differed. Three cases had %AC ≥95% and FFA >660µEq/L, and all of whom were female and were diagnosed with myopenia based on CT imaging. Conversely, the remaining 16 cases had %AC<95% and FFA ≤660, 13 of whom were male. The diagnosis of EM based on %AC alone in women or FFA alone in men can be difficult, and measurements of both %AC and FFA should be performed whenever possible. In addition, EM cases tended to have radiological attenuation of iliopsoas muscle, low subcutaneous fat mass index (SFMI), and low visceral fat mass index (VFMI) in this study. The radiological attenuation of iliopsoas muscle, SFMI, and VFMI are

findings suggesting low BMI, muscle atrophy, and fat infiltration. Detailed studies by sex including imaging should be conducted in the future.

In clinical practice, it is difficult to measure npRQ, %AC, and FFA in all cases of CLDs. This is the first report to predict EM using low-cost, and simple standardized test items, such as γ-GTP, AST, and ALT levels. Nevertheless, it will be necessary to accumulate additional case data for further analysis.

Conclusion

The predictive factors of EM in patients with CLDs were Child-Pugh grade, transaminase values, and γ-GTP values. This information may help select cases to be actively evaluated for the presence of EM using accurate diagnostic methods, such as npRQ, %AC, and FFA.

Declarations

Authors' information

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Tables

Table1. Baseline characteristics of patients with chronic liver diseases.

		All (n=295)	LES- (n=276)	LES+ (n=19)	P value
Age: years		72(63-80)	72(63-79)	71(65-81)	0.99
Men: n (%)		172 (58%)	158 (58%)	14 (74%)	0.23
LC: n (%)		195 (66%)	176 (64%)	19 (100%)	0.001
Child-Pugh grade: n (%)	A/B/C	224/57/14(76/19/5%)	218/49/9(79/18/3%)	6/8/5(32/42/26%)	<0.001
Comorbidities: n (%)	Diabetes	79(27%)	76 (28%)	3 (16%)	0.42
	Heart disease	35(12%)	33 (12%)	2 (11%)	1.0
	Chronic lung disease	19(6.4%)	19 (7%)	0(0%)	0.62
	Cerebrovascular disease	26(8.8%)	26 (10%)	0(0%)	0.43
	Chronic renal disease	30(10%)	26 (10%)	4 (21%)	0.12
BMI: kg/m^2		23(21-25)	23(20-25)	23(21-25)	0.64
%AC: %		92(80-99)	92(80-99)	84(80-97)	0.67
L4 SFMI:cm^2/m^2		38(24-57)	38(25-58)	28(17-52)	0.12
L4 VFMI:cm^2/m^2		39(24-56)	39(25-58)	32(22-48)	0.17
Albumin: g/dl		4.0(3.5-4.3)	4(3.6-4.3)	2.9(2.6-3.6)	<0.001
Total bilirubin: g/dl		0.8(0.6-1.2)	0.8(0.6-1.2)	1.2(0.65-1.9)	0.037
γ-GTP: U/l		34(21-90)	33(20-87)	87(32-106)	0.044
AST:IU/l		28(20-42)	27(20-42)	36(25-51)	0.12
ALT:IU/l		22(15-35)	22(15-35)	24(13-34)	0.91
Platelet: ×10^3/μl		152(111-196)	154(116-198)	96(80-132)	<0.001
Prothrombin time: %		85(71-95)	85(72-95)	64(60-83)	0.003
Free fatty acid: μEq/l		400(179-616)	415(198-616)	100(62-399)	0.003

Continuous values are expressed as median and range. LES; late evening snack, BMI; body mass index, AC; Arm circumference, SFMI; subcutaneous fat mass index, VFMI; visceral fat mass index, γ-GTP; gamma-glutamyl transpeptidase, AST; asparate aminotransferase, ALT; alanine aminotransferase.

Table2. Characteristics of patients without a LES; patients with EM versus patients without EM.

		Without EM (n=178)	With EM (n=98)	P value
Age: years		71(61-79)	63(66-81)	0.12
Men: n (%)		105 (59%)	53 (54%)	0.45
Child-Pugh grade: n (%)	A/B/C	152/21/5(85/12/3%)	66/28/4(67/29/4%)	0.001
Comorbidities: n (%)	Diabetes	46(26%)	30(31%)	0.48
	Heart disease	22(12%)	11(11%)	0.85
	Chronic lung disease	14(8%)	5(5.1%)	0.46
	Cerebrovascular disease	21(11%)	6(6.1%)	0.60
	Chronic renal disease	18(10%)	8(8.2%)	0.67
BMI: kg/m^2		23(21-25)	21(19-24)	0.001
%AC: %		99(97-104)	84(75-90)	<0.001
L4 SFMI: cm^2/m^2		47±27	40±32	0.063
L4 VFMI: cm^2/m^2		45±25	39±25	0.069
Radiological attenuation of iliopsoas muscle: HU		49±12	46±13	0.051
γ-GTP: U/l		32(19-61)	47(23-162)	0.001
AST:IU/l		26(19-37)	32(25-52)	<0.001
ALT:IU/l		20(15-30)	28(17-43)	0.003
Platelet: ×10^3/μl		160(122-194)	153(97-205)	0.33
Free fatty acid: μEq/l		323(168-482)	753(544-940)	<0.001

Continuous values are expressed as median and range. LES; late evening snack, EM; energy malnutrition, BMI; body mass index, AC; Arm circumference, SFMI; subcutaneous fat mass index, VFMI; visceral fat mass index, HU; Hounsfield Units, γ-GTP; gamma-glutamyl transpeptidase, AST; asparate aminotransferase, ALT; alanine aminotransferase.

Table3. Univariate analysis of factors linked to EM in patients with chronic liver disease without a LES.

	Odds ratio	95% CI	P value
Age: years	1.02	1.0-1.04	0.073
Males	0.81	0.49-1.3	0.40
Child-Pugh grade B or C	2.8	1.6-5.1	<0.001
BMI:kg/m^2	0.91	0.85-0.98	0.010
γ-GTP: U/l	1.01	1.0-1.01	<0.001
AST: IU/L	1.02	1.01-1.03	<0.001
ALT: IU/L	1.02	1.01-1.03	<0.001

LES; late evening snack, EM; energy malnutrition, BMI; body mass index,γ-GTP; gamma-glutamyl transpeptidase, AST; asparate aminotransferase, ALT; alanine aminotransferase.

Table4. Univariate analysis of factors linked to EM in patients with chronic liver disease without a LES.

	Males			Females		
	Odds ratio	95% CI	P value	Odds ratio	95% CI	P value
Child-Pugh grade B or C	2.9	1.4-6.2	<0.001	2.8	1.1-7.4	0.031
BMI: kg/m^2	0.89	0/80-0.99	0.025	0.93	0.85-1.0	0.18
High γ-GTP: U/l	6.5	3.0-14	<0.001	3.4	1.2-9.4	0.020
High AST: IU/L	3.3	1.4-7.7	<0.001	3.2	1.3-8.0	0.013
High ALT: IU/L	2.4	1.2-4.9	0.016	3.4	1.5-7.5	0.0027

LES; late evening snack, EM; energy malnutrition,γ-GTP; gamma-glutamyl transpeptidase, AST; asparate aminotransferase, ALT; alanine aminotransferase.

Table5. Univariate and Multivariate analyses of factors linked to EM in patients with Child-Pugh A without LES.

	Univariate			Multivariate		
	Odds ratio	95% CI	P value	Odds ratio	95% CI	P value
High γ-GTP: U/l	6.7	3.0-15	<0.001	5.1	2.2-12	<0.001
High transaminases: IU/L	3.7	1.8-7.6	<0.001	2.7	1.3-5.6	<0.001

LES; late evening snack, EM; energy malnutrition, γ-GTP; gamma-glutamyl transpeptidase, AST; asparate aminotransferase, ALT; alanine aminotransferase.

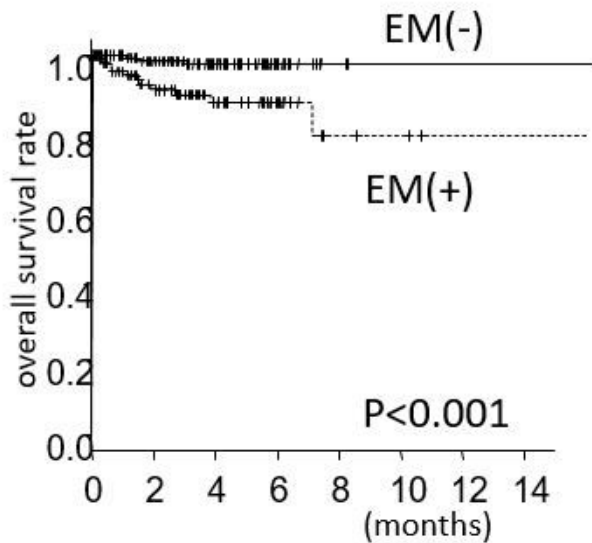# Figures
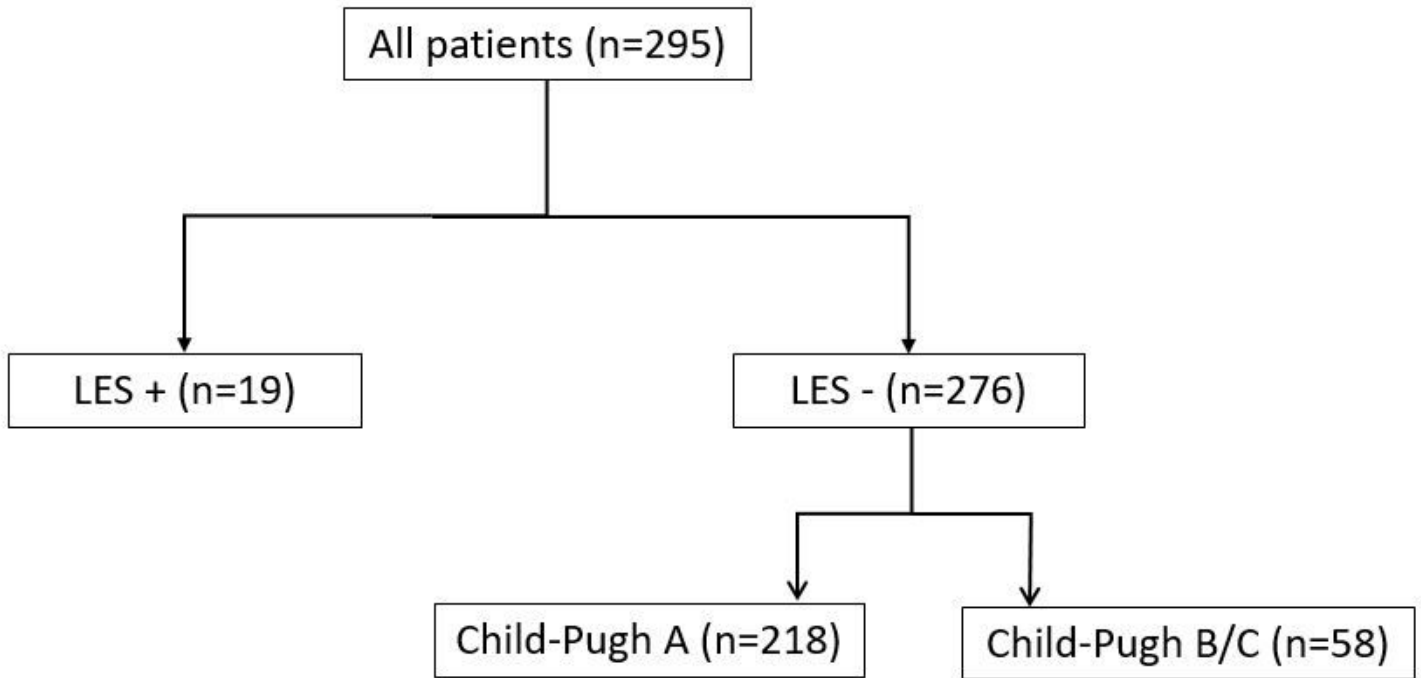
Figure 1

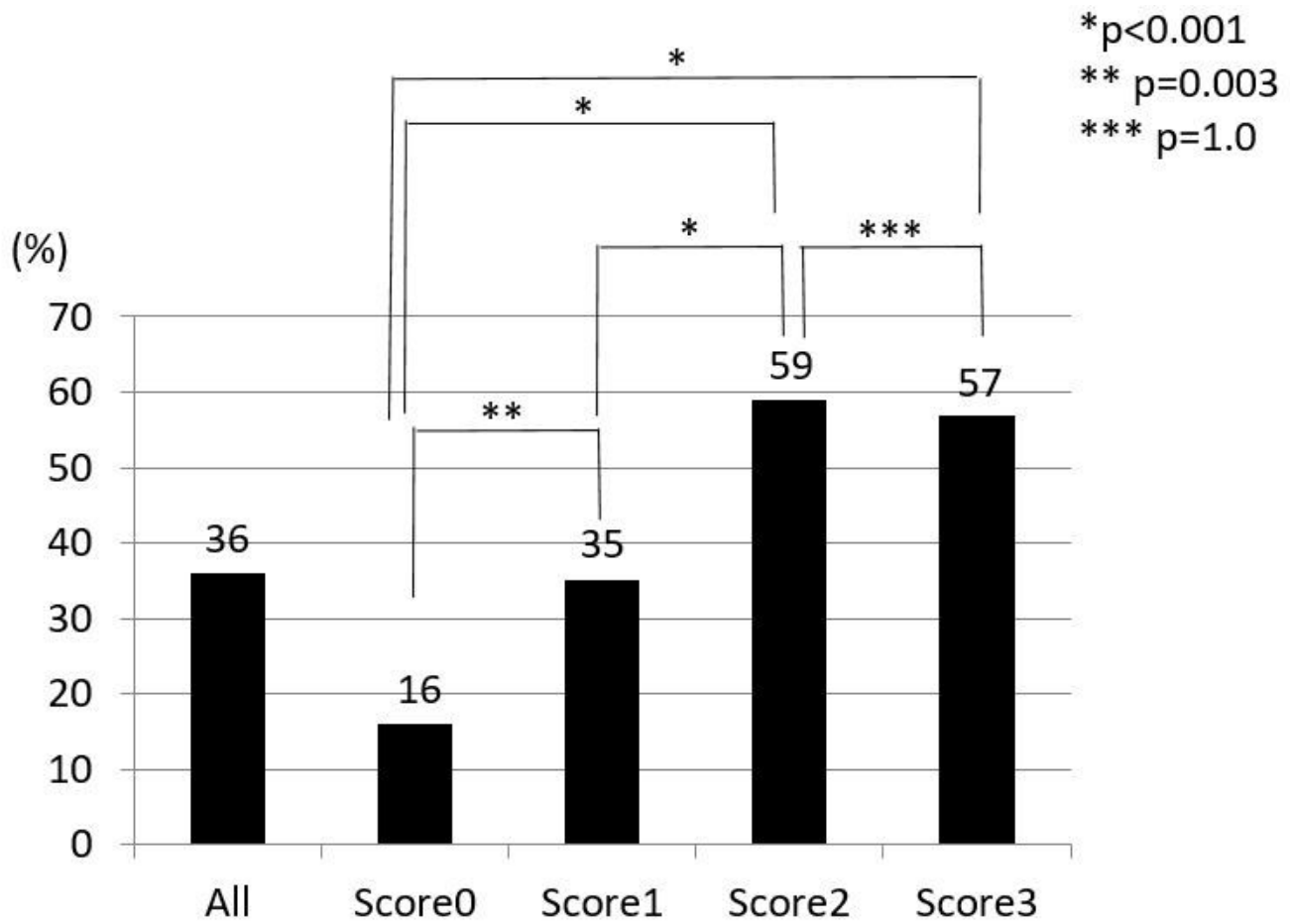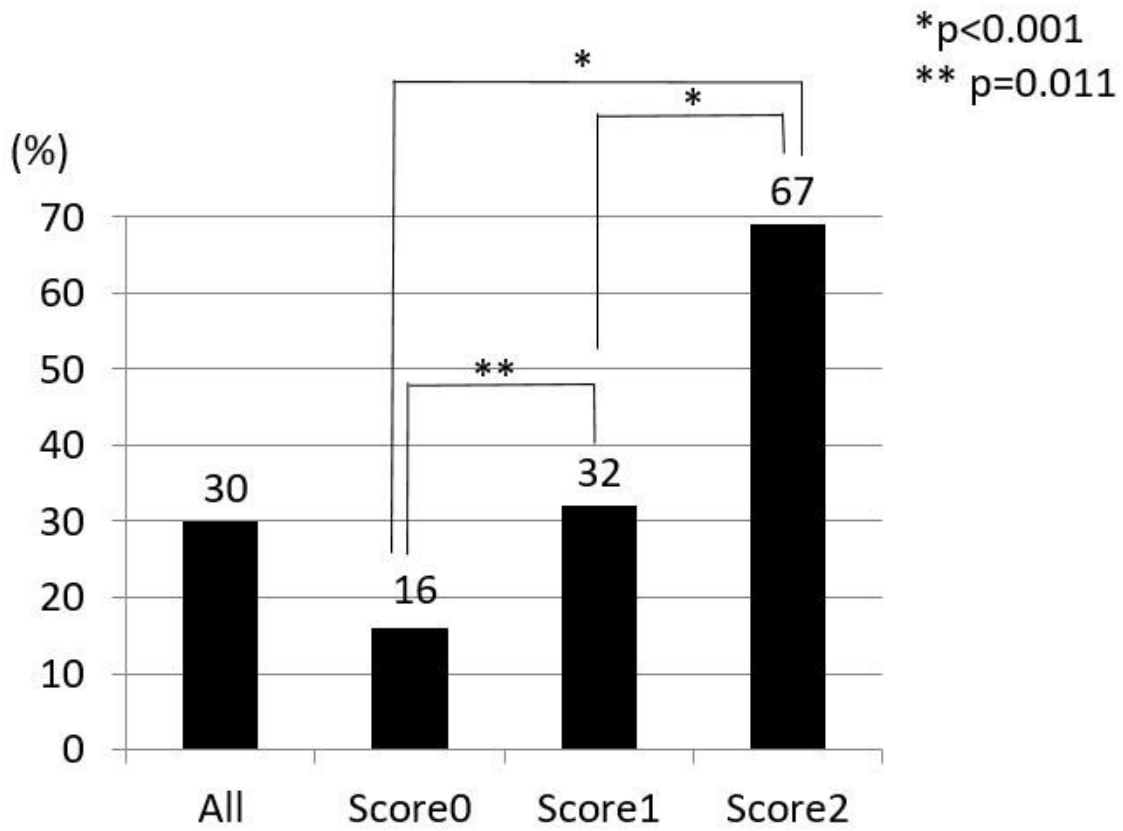Patient flow in this study.

Figure 2

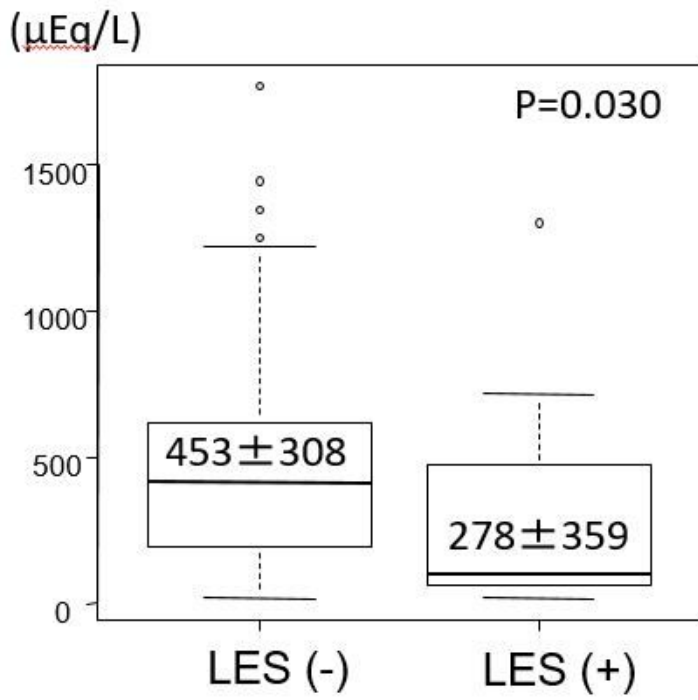Overall survival; patients with EM versus patients without a EM.

Figure 3

Frequency of EM in patients with chronic liver diseases stratified by three risk scores (Child–Pugh grade B or C, increased γ-GTP, and increased AST or ALT).

Figure 4

Frequency of EM in patients with Child-Pugh grade A stratified by two risk scores (increased γ-GTP, and increased AST or ALT).

Figure 5

FFA levels between the patients with a LES and those without a LES.