Original Article

Effects of an individualized nutritional intervention on the prognosis of patients with liver failure

Xing Liu MD[1], Ming Kong PhD[2,3], Xin Hua MSc[4], Yinchuan Yang BSc[2], Manman Xu MSc[2], Yanzhen Bi MD[5], Lu Li MD[2], Zhongping Duan PhD[2,3], Yu Chen PhD[2,3]

[1]*Department of Infectious Disease, Linyi People's Hospital, Linyi, China*
[2]*Fourth Department of Liver Disease (Difficult & Complicated Liver Diseases and Artificial Liver Center), Beijing Youan Hospital, Capital Medical University, Beijing, China*
[3]*Beijing Municipal Key Laboratory of Liver Failure and Artificial Liver Treatment Research, Beijing, China*
[4]*Department of Clinical Nutrition, Beijing Youan Hospital, Capital Medical University, Beijing, China*
[5]*Department of Infectious Disease, Qingdao Municipal Hospital, Qingdao, China*

Background and Objectives: Patients with liver failure often have energy metabolism disorders and malnutrition, which lead to poor prognosis, rendering nutritional interventions essential. **Methods and Study Design:** Individualized nutritional interventions were offered according to the resting energy expenditure (REE) of patients with liver failure, and the patients were followed up for 180 days. **Results:** Sixty patients with liver failure were enrolled and grouped by their prognosis and energy intake. Model for end-stage liver disease (MELD) score and body fat mass of the nonsurvival group were significantly higher than those of the survival group ($p<0.05$), whereas the mean energy intake/REE (MEI/REE) and mean respiratory quotient (RQ) of the nonsurvival group were significantly lower than those of the survival group ($p<0.01$). Prediction REE (PredREE) was calculated using the Harris–Benedict formula. Most patients in the nonsurvival and survival groups had hypometabolic (REE/PredREE <0.9) and normal metabolic status (0.9<REE/PredREE<1.1; $p=0.014$), respectively. MEI/REE, MELD score, and REE/PredREE were independent predictors of survival in patients with liver failure. The optimal threshold for MEI/REE was 1.15 for predicting favorable prognosis, and the sensitivity and specificity of the threshold were 61.1% and 85.0%, respectively. The survival rates of patients in the <1.2-REE group and ≥1.2-REE group were 45.2% and 88.0%, respectively ($p=0.001$). **Conclusions:** Hypometabolism state and insufficient energy intake predict poor prognosis in patients with liver failure. Individualized nutritional interventions with energy intake ≥1.2 REE may improve the RQ and prognosis of such patients.

Key Words: liver failure, individualized nutritional intervention, respiratory quotient, resting energy expenditure, prognosis

INTRODUCTION

Characterized by jaundice, coagulopathy, ascites, and hepatic encephalopathy, liver failure is a commonly observed severe liver disease with an extremely high mortality rate.[1] Liver failure can have many causes, including infections and other factors such as alcohol consumption and drug damage. The main cause of liver failure in China is the hepatitis virus, especially the hepatitis B virus (HBV), followed by various drugs and hepatotoxic substances. Liver failure progresses rapidly, has a poor prognosis, and no effective medical treatment for liver failure exists, except for liver transplant.[2,3] However, the high cost and the scarcity of liver donors limits the applicability of liver transplant, rendering the treatment of liver failure challenging.

The liver has crucial functions in synthesis, metabolism, excretion, and biotransformation. When liver failure occurs, liver function is severely impaired, leading to energy metabolism disorders and malnutrition in patients. The substrate metabolism of patients with end-stage liver disease (ESLD) is similar to that of healthy individuals who are subjected to 3 days of starvation.[4-6] Because patients with ESLD have increased fat oxidation and reduced carbohydrate oxidation, they often have a low respiratory quotient (RQ).[4,6,7] The RQ is closely related to the severity of liver disease, and energy metabolism disorder occurs with deteriorating liver fuction.[7] Liver failure often results in a systemic inflammatory response, which is closely related to increased resting energy expenditure (REE).[8,9] Consequently, some patients with ESLD have hypermetabolic status, which is a cause of malnutrition. Metabolic abnormalities, poor dietary in-

Corresponding Author: Dr Yu Chen, Fourth Department of Liver Disease (Difficult & Complicated Liver Diseases and Artificial Liver Center), Beijing Youan Hospital, Capital Medical University, No. 8 Xitoutiao, Fengtai District, Beijing 100069, China.
Tel: +86 010 839 97157; Fax: +86 010 632 95285
Email: chybeyond1071@ccmu.edu.cn
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take, and malabsorption contribute to the prevalence of malnutrition in patients with ESLD,[10-14] thereby increasing the morbidity and mortality of these patients.[15-17] Early nutritional intervention can improve the nutritional status and prognosis of these patients.

Through this study, we investigated how individualized nutritional interventions can be used to improve the prognosis of patients with liver failure, a hitherto unexplored topic in the literature. To enroll patients with nutritional risk caused by liver failure, we screened for nutritional risk in patients with liver failure by using the Nutritional Risk Screening 2002 (NRS-2002) system.[18] We formed a nutrition support team (NST) comprising physicians, nurses, dietitians, and pharmacists. On the basis of comprehensive internal medicine treatment, individualized nutritional interventions for the patients were implemented by the NST. Data were gathered during the intervention to determine its effect on the prognosis of patients with liver failure.

METHODS

Patients and research design

This cohort study was conducted from December 2016 to March 2019 at the Fourth Department of Liver Disease, Beijing Youan Hospital, Capital Medical University, Beijing, China. The nutritional risk of patients with liver failure was screened using the NRS-2002, and 60 hospitalized patients (aged 18–70 years) with nutritional risk caused by liver failure were enrolled in the study; 3 of them had acute liver failure, 1 had subacute liver failure, and 56 had acute-on-chronic liver failure (ACLF). Among the patients with ACLF, 47 patients had HBV infection, 7 had ACLF caused by alcohol consumption, and 2 had ACLF from unknown causes. On the basis of comprehensive internal medicine treatment, individualized nutritional intervention was provided by the NST until the patients withdrew from the study, died, underwent a liver transplant, or were discharged. Dietary guidance and follow-up were continued for 180 days. At baseline and at each week after an individualized nutritional intervention was offered, the energy metabolism indicators, laboratory data, anthropometric measurements, and body composition index of the participants were examined and collected, and the energy intake, disease severity, and nutritional status and risk of the participants were assessed. The severity of liver failure was assessed using the Child–Pugh score and model for ESLD (MELD) score. Indirect calorimetry was used to measure the REE of the patients at baseline and at each week after the intervention, and the energy needs of the patients were accurately determined using their REE. The patients were divided into survival and nonsurvival groups (including patients who underwent a liver transplant) for further analysis. The American Society for Parenteral and Enteral Nutrition (ASPEN) states that patients with ESLD have an energy requirement between 1.2 and 1.4 times their REE.[19] Thus, patients were divided into a group with energy intake not less than 1.2 times their REE (≥1.2-REE group) and energy intake less than 1.2 times their REE (<1.2-REE group) to explore the effect of individualized nutritional intervention on the prognosis of liver failure. Liver failure was diagnosed as per conventional guidelines for the diagnosis and treatment of liver failure.1 None of the patients enrolled in the study had a history of thyroid dysfunction, diabetes, neoplasia, or other diseases that may affect diet and energy metabolism. No patient experienced gastrointestinal bleeding during the study. None of the patients took drugs that might have affected energy metabolism or coagulopathy. We excluded patients who engaged in drug abuse, had coinfection with human immunodeficiency virus, had other serious underlying diseases, showed poor compliance to treatment, or were pregnant or lactating. Patients younger than 18 years and older than 70 years were also excluded (Figure 1). All subjects signed an informed consent form prior to participation. The study protocol accorded with the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the Institutional Review Board of Beijing Youan Hospital (Approval Number: 2016–18). The clinical trial registration number at http://www.chictr.org.cn is ChiCTR1900020900.

Nutrition intake

The energy intake of each patient was assessed using their 24-h dietary record. All patients were provided with a standard hospital diet and six meals a day, with snacks

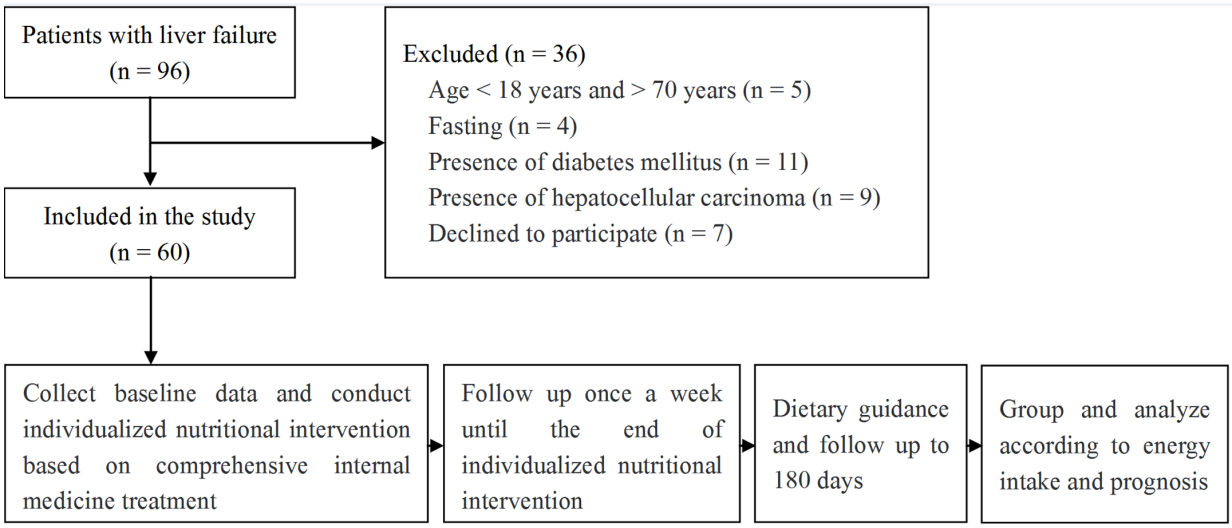

Figure 1. Flowchart of study patients.

between breakfast, lunch, and dinner and before bedtime. The energy needs of the patients were accurately determined using their REE. The patients' caloric intake of carbohydrates, fats, and proteins accounted for 74%, 16%, and 10% of their total caloric intake, respectively. Two dietitians recorded and analyzed the food intake of each patient at baseline and at each week after the nutritional intervention. Nutrient and energy intake values were calculated using the Chinese Food Composition Tables.20 All patients were encouraged to obtain nutrition through oral diet. Enteral or parenteral nutrition was provided if oral diet could not meet the nutritional needs of the patients.

Laboratory variables

Patient demographics, laboratory parameters, and clinical data were collected at baseline and at each week after the nutritional intervention. Serum biochemical parameters were measured using an Olympus Automatic Biochemical Analyzer AU5400 (Olympus, Tokyo, Japan). The severity of liver failure was evaluated using MELD and Child–Pugh scores. Child–Pugh score included hepatic encephalopathy, ascites, prothrombin time, albumin, and total bilirubin.[21] MELD score was calculated by total bilirubin, serum creatinine, and international normalized ratio (INR) of prothrombin time and then rounded to the nearest integer. The formula for calculating the MELD score was as follows: 9.6 × loge (creatinine mg/dL) + 3.8 × loge (bilirubin mg/dL) + 11.2 × loge (INR) + 6.4 × etiology (0 if cholestatic or alcoholic, 1 otherwise).[22]

Anthropometric measurements

A height–weight scale (RGZ120; Wuxi Weigher Factory, Wuxi, China) was used to measure the body weight and height of the patients. The precisions of the weight and height measurements were 0.1 kg and 0.1 cm, respectively. Body mass index (BMI) was calculated using the kg/m^2 formula. Patients with ascites or pedal edema needed to assess their dry weight and calculated their dry-weight BMI. The dry weight was assessed by the post-paracentesis body weight, or 5% of the patient's weight was subtracted in the case of mild ascites, 10% in the case of moderate ascites, and 15% in the case of severe ascites. If bilateral pedal edema was present, an additional 5% was subtracted.[23] Midarm circumference (MAC) and tricep skinfold thickness (TSF) were measured using a measuring tape and a skinfold caliper (Changshu Instrument Company, Changshu, China), respectively, at the midpoint between the acromion and olecranon of the left arm.[24] MAC and TSF were measured three times, and the average was recorded to minimize the influence of operational error on the results. Midarm muscle circumference (MAMC) was calculated using the following formula: MAMC (cm) = MAC (cm) − π × TSF (cm).

Body composition measurements

We used the following body composition indicators: extracellular water, intracellular water, total body protein, body fat mass (BFM), percent body fat (PBF), mineral, skeletal muscle mass, waist-to-hip ratio, and body cell mass. In this study, body composition was determined using the body composition analyzer InBody 720 (Biospace, Seoul, Korea; 1–1000 kHz). In general, body composition can be distinguished, on the basis of differences in the body's electrical conductivity, by the flow of an electrical current through different body tissues.[25] Our patients were tested on an empty stomach in the morning while wearing light clothing.

RQ and REE

The REE and RQ were measured using a cardiorespiratory diagnostics system for nutrition metabolism (Medical Graphics Corp., St Paul, MN, USA), and the gas and volume were calibrated before testing. The patients fasted for at least 8 h and rested in bed for at least 30 min in the morning before the test. The temperature of the room was maintained at 24°C–26°C with a humidity of 45%–60%. The actual REE was calculated using the Weir formula,[26] and the predicted REE (PredREE) was calculated using the Harris–Benedict formula.[27] REE/PredREE is the ratio of actual REE to predicted REE and facilitates comparisons between individuals. Energy metabolism state was then divided, on the basis of REE/PredREE, into the hypometabolic (REE/PredREE <0.9), normal metabolic (0.9<REE/PredREE<1.1), and hypermetabolic (1.1 <REE/PredREE) states.[28] VCO_2/VO_2 was used to calculate the RQ.

Statistical analysis

In our preliminary experiment, a 53.3% mortality was observed in the <1.2 REE group and 13.3% mortality was observed in the ≥1.2 REE group. To show the difference in mortality between the two groups, at least 24 patients needed to be assigned to each group (α=0.05, power=0.9) according to PASS version 15 (NCSS, LLC, Kaysville, UT, USA).

Continuous variables were described in terms of their median, interquartile range, and mean ± standard deviation, and categorical variables were described in terms of their frequency or percentage. In univariate analyses, categorical variables were analyzed using the $\chi 2$ test and continuity correction χ^2 test, and continuous variables were analyzed using the independent sample t test and Mann–Whitney U test. All variables with $p<0.10$ in the univariate analysis were analyzed in Cox proportional hazard regression model. In survival analysis, death and liver transplantation were terminal events. Survival data were analyzed using the Kaplan–Meier method. Differences between curves were evaluated using the log-rank test. Receiver operating characteristic (ROC) curve was used to evaluate the ability of mean energy intake/REE (MEI/REE) to predict the prognosis. Statistical analysis was performed using SPSS 19.0 statistical software (IBM Corp., Armonk, NY, USA), and $p<0.05$ indicated statistical significance.

RESULTS

Comparison of baseline data between survival and non-survival groups

Table 1 presents a baseline comparison of the demographic characteristics, disease etiology, energy metabolism, energy intake, disease severity, laboratory data, anthropometric measurements, and body composition index of the two groups. The MELD score and BFM in the non-

Table 1. Baseline comparison of survival and nonsurvival groups

Indicator	Non survival group	Survival group	*p* value
Number, n (%)	23 (38.3)	37 (61.7)	—
Women, n(%)	5 (21.7)	5 (13.5)	0.635
Age (y)	46.7±13.4†	43.0±12.8	0.292
Estimated dry-weight BMI (kg/m^2)	22.2, 20.1–26.2‡	21.7, 19.5–23.9	0.305
Classification, n (%)			0.271
ALF & SALF	0 (0.0)	4 (10.8)	
ACLF	23 (100)	33 (89.2)	
Etiology, n (%)			0.947
HBV	19 (82.6)	29 (78.4)	
Other	4 (17.4)	8 (21.6)	
Child–Pugh score	11, 10–12	11, 10–12	0.396
MELD score	26.0, 21.0–29.0	21.0, 19.0–24.0	0.001
Energy intake (kcal/d)/REE	0.89, 0.72–1.09	0.82, 0.56–1.08	0.549
RQ	0.78, 0.73–0.80	0.80, 0.77–0.85	0.057
REE (kcal/d)	1473, 1159–1637	1528, 1378–1641	0.194
REE/PredREE (%)	88.0±16.2	98.1±13.2	0.014
TSF (mm)	18.0, 9.5–28.3	14.0, 7.8–22.8	0.360
MAMC (cm)	21.7±3.1	22.3±2.6	0.466
ICW (L)	25.0±4.9	25.2±4.3	0.922
ECW (L)	16.1±3.2	15.9±3.0	0.765
TBP (kg)	10.8±2.1	10.9±1.8	0.845
BFM (kg)	16.4±8.2	11.5±5.5	0.015
SMM (kg)	30.7±6.3	30.8±5.6	0.930
PBF (%)	21.4±8.7	17.4±6.8	0.086
WHR	0.88, 0.81–0.92	0. 87, 0.82–0.90	0.489
BCM (kg)	35.8±6.9	36.0±6.2	0.918

ALF: acute liver failure; ACLF: acute-on-chronic liver failure; BMI: body mass index; BCM: body cell mass; BFM: body fat mass; ECW: extracellular water; HBV: hepatitis B virus; ICW: intracellular water; MELD: model for end-stage liver disease; MAMC: midarm muscle circumference; PredREE: predicted resting energy expenditure; PBF: percent body fat; RQ: respiratory quotient; REE: resting energy expenditure; SALF: subacute liver failure; SMM: skeletal muscle mass; TSF: triceps skinfold thickness; TBP: total body protein; WHR: waist-to-hip ratio.
†Mean±standard deviation (for all such indicated values).
‡Median, interquartile range (for all such indicated values)

survival group were significantly higher than those in the survival group, and REE/PredREE was significantly lower in the nonsurvival group than in the survival group, with statistical significance.

Comparison of energy intake/REE of the two groups and its effect on RQ

The two groups did not differ with respect to RQ or energy intake/REE at baseline (Table 1, Figure 2). After the individualized nutritional intervention, the MEI/REE and mean RQ of the survival group were significantly higher than those of the nonsurvival group (1.20, 1.04–1.52 vs. 0.98, 0.72–1.12, respectively, $p<0.001$; 0.82, 0.79–0.86 vs. 0.78, 0.77–0.82, respectively, $p = 0.007$; Figure 2).

Analysis of prognostic factors in patients with liver failure

In the univariate analysis, MELD score, MEI/REE, RQ, REE/PredREE, BFM, and PBF were considered potential prognostic factors for patients with liver failure ($p<0.10$). The variables with $p < 0.10$ were included in a subsequent Cox proportional hazard regression model, the results of which showed that MEI/REE, MELD score, and REE/PredREE were independent predictors of survival in patients with liver failure (Table 2).

ROC curve of MEI/REE in patients with liver failure

The area under the ROC curve of MEI/REE in patients with liver failure after the individualized nutritional intervention was 0.792 (95% CI: 0.671–0.913; $p<0.001$). The optimal threshold for predicting the survival prognosis of patients with liver failure by MEI/REE was 1.15, and the sensitivity and specificity were 61.1% and 85.0%, respectively (Figure 3).

Prognosis of patients with liver failure

The mortality rates of patients with liver failure and ACLF were 38.3% and 41.1%, respectively. Survival data were analyzed using the Kaplan–Meier method. Differences between curves were evaluated using the log-rank test. The survival rates at 180 days of the <1.2-REE and ≥1.2-REE groups were 45.2% and 88.0%, respectively ($p=0.001$; Figure 4).

Side effects

The individualized nutritional intervention had no obvi-

Table 2. Factors associated with survival in patients with liver failure

	B	HR (95%CI)	*p* value
MEI/REE	−3.34	0.04 (0.01–0.27)	0.001
MELD score	0.18	1.20 (1.03–1.40)	0.022
REE/PredREE	−0.07	0.94 (0.90–0.98)	0.002

CI: confidence interval; HR: hazard ratio; MEI: mean energy intake; MELD: model for end-stage liver disease; PredREE: predicted resting energy expenditure; REE: resting energy expenditure.

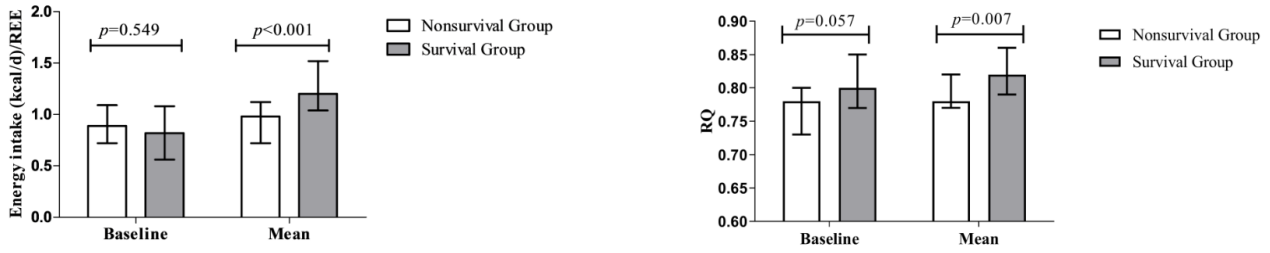

Figure 2. Comparison of energy intake/REE of the two groups and its effect on RQ. REE: resting energy expenditure; RQ: respiratory quotient.

ous side effects and was well tolerated by the patients with liver failure. Oral diet was easily accepted by the patients. Oral nutritional supplements could sometimes cause discomforts such as abdominal distension, diarrhea, and nausea in patients, but these symptoms could be alleviated by adjustment in the doses.

DISCUSSION

The liver plays a key role in regulating carbohydrate, fat, and protein metabolism. When liver failure occurs, the nutrient metabolism of the patient gets disrupted, dietary intake is reduced, and the digestion and absorption of nutrients are impaired, resulting in malnutrition. Malnutrition is a common complication in patients with ESLD[10-14] and is considered a predictor of morbidity and mortality in these patients.[29-31] Therefore, improving the malnutrition of patients with ESLD can improve their prognosis.

The RQ is a good indicator of substrate oxidation.[32,33] The nonprotein RQ is closely related to the severity of cirrhosis and is an independent risk factor for predicting the survival of patients with cirrhosis.[34] The RQ of patients with ACLF was significantly lower than that of patients with cirrhosis and chronic hepatitis B, and the RQ of the nonsurvival group of patients with ACLF was significantly lower than that of the survival group.[7] In the present study, the baseline RQ did not significantly differ between the nonsurvival and survival groups ($p = 0.057$), which is inconsistent with the results of another study.[7] To address this inconsistency, future studies should recruit a sample that is larger than the one in our study. After the individualized nutritional intervention, the MEI/REE and mean RQ (0.82, 0.79–0.86) of the survival group were significantly higher than those of the nonsurvival group. The median of the mean RQ in the survival group was 0.82, which was consistent with the optimal threshold (0.83) for the RQ when predicting the survival of patients with liver failure.[7] Compared with a single RQ value, using the mean RQ indicates that the results better reflect the evolution of the RQ from the baseline. Therefore, monitoring changes in the RQ of patients with liver failure is crucial for predicting their metabolic state and prognosis, and effective individualized nutritional intervention can improve the RQ of patients with liver failure.[35]

One-third of patients with liver cirrhosis have hypermetabolism and hypometabolism.[36] Patients with liver failure also tend to have hypermetabolism.[37-39] Hypermetabolism is a cause of malnutrition in patients with ESLD and results in their poor prognosis. REE is not related to the severity of liver disease.[7,34] In this study, the baseline REE did not significantly differ between the nonsurvival and survival groups. Given that REE cannot reflect the disease severity or prognosis of patients with liver failure, REE/PredREE was used in this study, which is defined as the ratio of the measured REE to the REE predicted using the Harris–Benedict formula. This ratio enables comparison of patients. Persistent hypermetabolism is an independent predictor of short-term mortality in patients with ACLF.[39] Patients with ESLD with hypermetabolism also have poor prognosis after a liver transplant.[40] The survival rate of patients with liver cirrhosis with a normal metabolic state is significantly higher than that of such patients with hypermetabolism or hypometabolism. Thus, energy

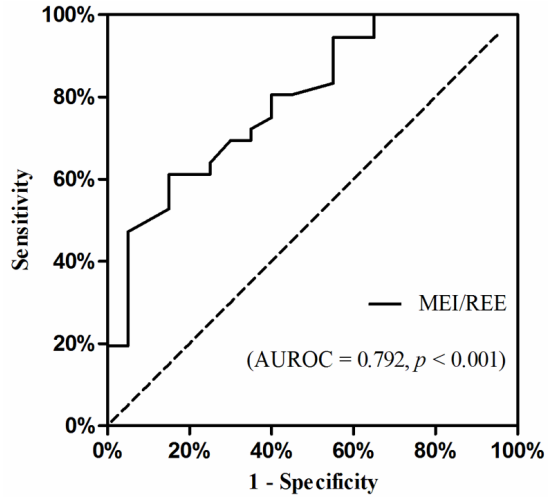

Figure 3. ROC curve of MEI/REE in patients with liver failure. AUROC: the area under the ROC curve; MEI: mean energy intake; ROC: receiver operating characteristic; REE: resting energy expenditure

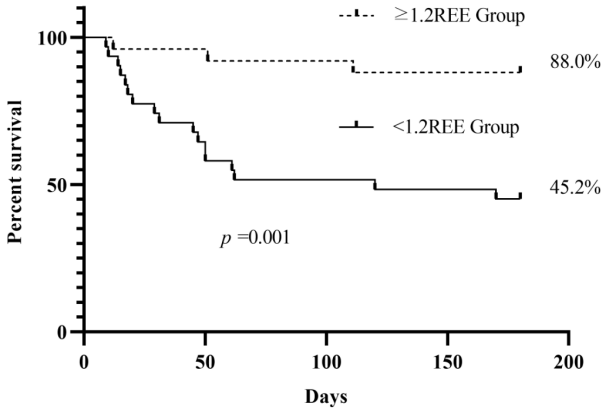

Figure 4. Kaplan–Meier estimates of survival in patients with liver failure. REE: resting energy expenditure.

metabolism can be used to predict survival in patients with liver cirrhosis.[34] In this study, most patients in the nonsurvival and survival groups had a hypometabolic state (REE/PredREE was 88.0%±16.2%) and normal metabolic state (REE/PredREE was 98.1%±13.2%), respectively, with a significant difference (p=0.014) between the groups. REE/PredREE is an independent predictor of survival in patients with liver failure. A hypometabolic state in patients with liver failure predicts poor prognosis. The evaluation of energy metabolism can also be used to predict the prognosis of patients with liver failure.

The patients in the two groups in our study did not significantly differ in terms of baseline energy intake/REE. After the individualized nutritional intervention, the MEI/REE (1.20, 1.04–1.52) of the survival group was significantly higher than that of the nonsurvival group. MEI/REE was an independent predictor of survival in patients with liver failure. The optimal threshold for predicting the survival of patients with liver failure by MEI/REE was 1.15, and the median MEI/REE in the survival group was 1.20; both these values are consistent with ASPEN's recommendation for the energy requirement of patients with ESLD to be 1.2–1.4 times their REE.[19] Therefore, insufficient energy intake in patients with liver failure predicts poor prognosis; to improve the nutritional status and prognosis of patients with liver failure, the patient's energy intake ought to be at least 1.2 times their REE.

In this study, the mortality rates of patients with liver failure and ACLF were 38.3% and 41.1%, respectively, which were lower than the almost 70% mortality rate in a previous report on ACLF.[41] The patients were divided into two groups depending on whether their energy intake was 1.2 times their REE.19 The survival rate of patients in the <1.2-REE group was significantly lower than that of patients in the ≥1.2-REE group. An individualized nutritional intervention providing an energy intake of ≥1.2 REE can improve the prognosis of patients with liver failure.

Conclusions

In conclusion, in patients with liver failure, hypometabolism state and insufficient energy intake predict poor prognosis. Individualized nutritional interventions with energy intake ≥1.2 REE may improve the RQ and prognosis of patients with nutritional risk caused by liver failure. Therefore, clinicians must evaluate malnutrition in patients with liver failure and use the evaluation results to implement individualized nutritional interventions and follow-up programs, which could improve the nutritional status and clinical outcomes of these patients. Owing to the small sample size of this study, further studies with larger sample sizes are warranted.

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AUTHOR DISCLOSURES

The authors have no conflicts of interest to declare.

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