Observational Study

Medicine®

OPEN

Prognostic significance of nonprotein respiratory quotient in patients with liver cirrhosis

Hiroki Nishikawa, MD, PhD, Hirayuki Enomoto, MD, PhD*, Yoshinori Iwata, MD, PhD, Kyohei Kishino, MD, Yoshihiro Shimono, MD, Kunihiro Hasegawa, MD, Chikage Nakano, MD, Ryo Takata, MD, Akio Ishii, MD, PhD, Takashi Nishimura, MD, PhD, Kazunori Yoh, MD, PhD, Nobuhiro Aizawa, MD, PhD, Yoshiyuki Sakai, MD, PhD, Naoto Ikeda, MD, PhD, Tomoyuki Takashima, MD, PhD, Hiroko Iijima, MD, PhD, Shuhei Nishiguchi, MD, PhD

Abstract

The aim of this study was to examine the effect of nonprotein respiratory quotient (npRQ), as assessed using indirect calorimetry, on clinical outcomes in patients with liver cirrhosis (LC). A total of 244 LC patients were evaluated in this study. For the univariate analysis, for each continuous variable, the optimal cutoff value that maximized the sum of sensitivity and specificity was selected using receiver operating curve (ROC) analysis for survival. There were 137 men and 107 women with the median (range) age of 67 (25–90) years. Indirect calorimetry indicated that 54 patients (22.1%) had hepatocellular carcinoma (HCC) on radiological findings and 59 patients (24.2%) had protein energy malnutrition, as defined by npRQ <0.85 and serum albumin level <3.5 g/dL. In ROC analysis of npRQ for survival, the optimal cutoff point of npRQ was 0.849 for all cases (area under the ROC = 0.61272; sensitivity, 66.22%; and specificity, 57.06%). The median follow-up periods after indirect calorimetry were 4.35 years (range, 1.01–9.66 years) in patients with npRQ ≥0.85 (n = 122) and 3.71 years (range, 0.19–9.51 years) in patients with npRQ <0.85 (n = 122). The 1-, 3-, and 5-year cumulative OS rates in patients with npRQ ≥0.85 were 100%, 87.79%, and 77.24%, respectively, whereas those in patients with npRQ <0.85 were 94.26%, 73.65% and 57.78%, respectively ($P = 0.0004$). In the multivariate analysis, presence of HCC ($P = 0.0045$), body mass index ($P < 0.0001$), serum albumin ($P = 0.0441$), prothrombin time ($P = 0.0463$), npRQ ($P = 0.0024$), estimated glomerular filtration rate ($P = 0.0086$), and des-γ-carboxy prothrombin ($P = 0.0268$) were found to be significant predictors associated with OS. For all cases, risk stratification for survival was well performed using these significant variables. In conclusion, npRQ value, as assessed by indirect calorimetry, can be helpful for predicting clinical outcomes for LC patients.

Abbreviations: AFP = alpha-fetoprotein, AST = aspartate aminotransferase, AUROC = area under the receiver operating characteristic curve, BCAA = branched-chain amino acid, BMI = body mass index, BTR = branched-chain amino acid to tyrosine ratio, CI = confidence interval, DAA = direct acting antivirals, DCP = des-γ-carboxy prothrombin, eGFR = estimated glomerular filtration rate, HCC = hepatocellular carcinoma, HCV = hepatitis C virus, HR = hazard ratio, IFN = interferon, LC = liver cirrhosis, LES = late evening snack, npRQ = nonprotein respiratory quotient, OS = overall survival, PEM = protein-energy malnutrition, PT = prothrombin time, ROC = receiver operating characteristic curve, SVR = sustained virological response.

Keywords: clinical outcomes, liver cirrhosis, nonprotein respiratory quotient, validation

1. Introduction

The liver is an essential organ for the metabolism of 3 major classes of molecules: fat, protein, and carbohydrate.[1–4] Liver cirrhosis (LC) is known to be a terminal form of chronic liver disease and is accompanied by numerous nutritional disorders.[5] In addition, LC is often complicated with protein-energy malnutrition (PEM), which is associated with clinical outcomes in LC patients.[1–4,6,7] Energy malnutrition can be assessed by measuring the nonprotein respiratory quotient (npRQ) using indirect calorimetry.[8] RQs reflect which macronutrients are being metabolized: values that approach 0.7 indicate that lipids are being consumed and values that approach 1.00 indicate that carbohydrates are largely being burned.[9] A previous study reported that npRQ correlated significantly with arm circumference and arm muscle circumference but not with triceps skinfold thickness.[10] Another study demonstrated that the plasma level of free fatty acid was closely correlated with npRQ value.[11]

Conversely, various nutritional therapies for LC have been recently proposed and validated. These include branched-chain amino acid (BCAA) administration therapy, late evening snack (LES) with BCAA enriched snack, carnitine therapy, zinc replacement therapy, oral diet or exercise.[12–19] Particularly, BCAA therapy and LES have originated from Japan and many Japanese researchers have reported their usefulness in the clinic.[3,12,19–21] In addition, in hepatitis virus related LC patients, antiviral therapies have been recommended in recent years.[22–24]

Editor: Giovanni Tarantino.

The authors have no conflicts of interest to disclose.

Division of Hepatobiliary and Pancreatic Disease, Department of Internal Medicine, Hyogo College of Medicine, Hyogo, Japan.

* Correspondence: Hirayuki Enomoto, Division of Hepatobiliary and Pancreatic Disease, Department of Internal Medicine, Hyogo College of Medicine, 1-1, Mukogawacho, Nishinomiyashi, Hyogo 663-8501, Japan (e-mail: enomoto@hyo-med.ac.jp).

Medicine (2017) 96:3(e5800)

Received: 8 April 2016 / Received in final form: 10 December 2016 / Accepted: 12 December 2016

http://dx.doi.org/10.1097/MD.0000000000005800

In 2002, Tajika et al reported that the overall survival (OS) rate in patients with LC was significantly lower in subjects with npRQ <0.85 than in subjects with npRQ ≥0.85 ($P < 0.01$) and that npRQ was a useful predictor for LC patients.[8] However, as previously mentioned, over the period of more than 10 years, nutritional interventional therapies for LC have dramatically changed and thus nutritional status in LC patients has improved.[25] In the era of novel nutritional therapies for LC, whether npRQ can be a useful predictor for patients with LC remains unknown.[12–15]

The aim of this study was therefore to examine the impact of npRQ on clinical outcomes in patients with LC.

2. Patients and methods

2.1. Patients

Between August 2006 and January 2015, a total of 300 LC individuals with available data for indirect calorimetry were admitted at the Division of Hepatobiliary and Pancreatic disease, Department of Internal Medicine, Hyogo College of Medicine, Hyogo, Japan. Of these, 56 patients had been lost to follow up within 1 year after performing indirect calorimetry and were excluded from the analysis. Thus, a total of 244 LC patients were evaluated in this study. Follow-up observation after indirect calorimetry consisted of regular blood examinations and radiological evaluation by ultrasonography, computed tomography, or magnetic resonance imaging to detect hepatocellular carcinoma (HCC) every 3 to 6 months. LC was diagnosed radiologically and/or pathologically. In patients with serum albumin level <3.5 g/dL, BCAA granule therapy or LES with BCAA enriched snacks were considered.[26] In hepatitis virus related LC patients, antiviral therapies were considered.[26] We retrospectively examined baseline npRQ levels and other clinical variables on OS and examined variables associated with OS in the univariate and multivariate analyses. The npRQ level using indirect calorimetry was calculated, as reported previously.[27]

The present study comprised a retrospective analysis of patient clinical data. The ethics committee in our hospital approved the present study protocol and this study protocol strictly adhered to all provisions of the Declaration of Helsinki.

2.2. HCC diagnosis and HCC therapy

HCC was diagnosed radiologically or histologically based on the European Association for the Study of Liver guideline.[28] In some subjects who presented with atypical liver nodules, we conducted ultrasonography-guided tumor biopsy. As for HCC therapy, the most appropriate HCC therapy for each case, such as surgical resection, locoregional therapies, and systemic chemotherapy, including sorafenib, was chosen through a discussion with hepatologists, radiologists, and surgeons. In cases of HCC recurrence, the same strategy was chosen in each patient.

2.3. Statistical analyses

Categorical parameters were compared by Fisher exact test. Continuous parameters were compared by unpaired *t* test or Mann–Whitney *U* test as appropriate. In continuous variables, receiver operating characteristic curve (ROC) analysis for survival was performed by selecting the optimal cutoff point that maximized the sum of sensitivity and specificity. The cutoff points for each subject were used to divide the study population into 2 groups, which were then treated as dichotomous covariates in the univariate analysis. OS curves were generated using the Kaplan–Meier method and compared using the log-rank test. Parameters with a *P*-value <0.05 in the univariate analysis were entered into the multivariate analysis in the Cox proportional hazards model. OS was defined as the time interval from the date of performing indirect calorimetry until death from any cause or the last follow-up. Data are expressed as the median value (range). Values with $P < 0.05$ were regarded as those with statistical significance. Statistical analysis was performed with the JMP 11 (SAS Institute, Inc., Cary, NC).

3. Results

3.1. Baseline characteristics

The baseline characteristics of the evaluated subjects (n = 244) are presented in Table 1. There were 137 males and 107 females with a median (range) age of 67 (25–90) years. In terms of causes of LC, hepatitis B virus-related LC was found in 20 patients, hepatitis C virus-related LC in 143 patients, alcoholic liver disease-related LC in 29 patients and other causes in 52 patients. There were 152 patients with a Child–Pugh A score, 86 with a Child–Pugh B score and 6 with a Child–Pugh C score. The model for end-stage liver disease score ranged from −5.0 to 23.4 (median, 5.0). In this study, the npRQ ranged from 0.663 to 1.677 (median: 0.850). While performing indirect calorimetry, 54 patients (22.1%) were observed to have HCC on radiological findings. ROC analyses of npRQ for survival indicated that the optimal cutoff points of the npRQ score was 0.849 for both all cases (area under the ROC (AUROC) = 0.61272; sensitivity, 66.22%; and specificity, 57.06%) and for patients without HCC at indirect calorimetry (n = 190) (AUROC = 0.65678; sensitivity, 76.74%; and specificity, 57.14%) (Fig. 1). In the present study, 59 out of 244 patients (24.2%) had PEM as defined by npRQ <0.85 and serum albumin level <3.5 g/dL.[8]

Table 1

Baseline characteristics (n = 244).

Variables	Number or median value (range)
Age, y	67 (25–90)
Gender, male/female	137/107
Cause of liver disease, B/C/alcoholic/others	20/143/29/52
Child–Pugh classification, A/B/C	152/86/6
MELD score	5.5 (−5.0–23.4)
Presence of HCC, yes/no	54/190
AST, IU/L	43 (16–402)
ALT, IU/L	34 (9–497)
Serum albumin, g/dL	3.6 (2.0–4.7)
Total bilirubin, mg/dL	1.0 (0.3–12.3)
Prothrombin time, %	75.0 (22.5–115.6)
Platelet count, $\times 10^4/mm^3$	8.7 (2.5–42.8)
Total cholesterol, mg/dL	148 (70–292)
Triglyceride, mg/dL	76 (27–346)
BTR	4.19 (1.46–9.67)
eGFR, mL/min/1.73 m^2	76.7 (5.2–161.2)
BMI, kg/m^2	22.9 (13.1–35.9)
HOMA-IR	2.68 (0.07–36.41)
Nonprotein respiratory quotient	0.850 (0.663–1.677)
AFP, ng/mL	5.5 (0.8–1345)
DCP, mAU/mL	23 (5–2200)

AFP = alpha-fetoprotein, ALT = alanine aminotransferase, AST = aspartate aminotransferase, BMI = body mass index, BTR = branched-chain amino acid to tyrosine ratio, DCP = des-γ-carboxy prothrombin, eGFR = estimated glomerular filtration rate, HCC = hepatocellular carcinoma, HOMA-IR = homeostasis model assessment-insulin resistance, MELD = model for end-stage liver disease.

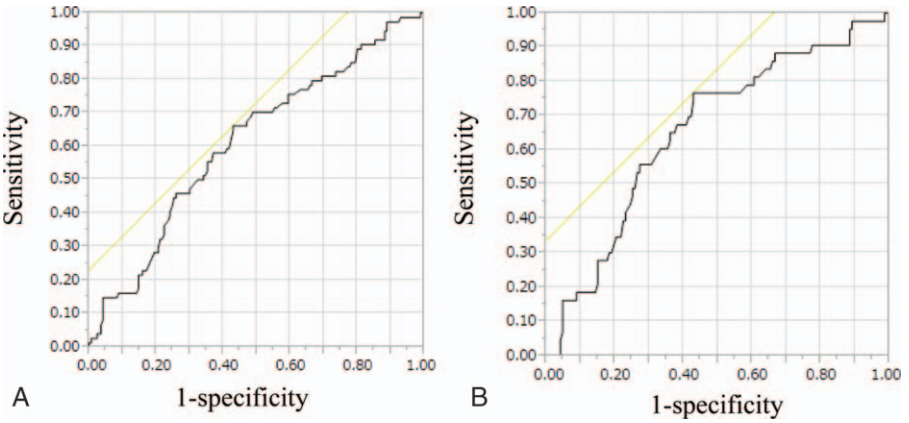


Figure 1. Receiver operating curve (ROC) analyses of npRQ for survival. (A) The optimal cutoff point of npRQ was 0.849 for all cases (area under the ROC (AUROC) = 0.61272; sensitivity, 66.22%; and specificity, 57.06%). (B) The optimal cutoff point of npRQ for patients without HCC, as indicated by indirect calorimetry (n = 190), was 0.849 (AUROC = 0.65678; sensitivity, 76.74%; and specificity, 57.14%).

3.2. Comparison of OS in patients with npRQ ≥0.85 and npRQ <0.85 for all cases (n = 244)

The median follow-up periods after indirect calorimetry were 4.35 years (range, 1.01–9.66 years) in patients with npRQ ≥0.85 (n = 122) and 3.71 years (range, 0.19–9.51 years) in patients with npRQ <0.85 (n = 122). The 1-, 3-, and 5-year cumulative OS rates in patients with npRQ ≥0.85 were 100%, 87.79%, and 77.24%, respectively, while those in patients with npRQ <0.85 were 94.26%, 73.65%, and 57.78%, respectively ($P = 0.0004$) (Fig. 2).

3.3. Comparison of OS in patients with npRQ ≥0.85 and npRQ <0.85 for patients without HCC, as indicated by indirect calorimetry (n = 190)

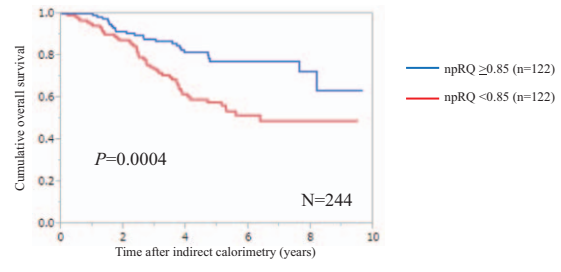
We also performed subanalyses in patients excluding patients that have HCC, as indicated by indirect calorimetry (n = 190). The median follow-up periods after indirect calorimetry were 4.47 years (range, 1.17–9.66 years) in patients with npRQ ≥0.85 (n = 94) and 3.75 years (range, 0.19–9.51 years) in patients with npRQ <0.85 (n = 96). The 1-, 3-, and 5-year cumulative OS rates in patients with npRQ ≥0.85 were 100%, 95.49%, and 87.98%, respectively, while those in patients with npRQ <0.85 were 93.75%, 80.84%, and 62.5%, respectively ($P < 0.0001$) (Fig. 3).

3.4. Causes of death

Seventy-four patients (30.3%) died during the follow-up period. The causes of death were liver failure in 29 patients, HCC progression in 37 patients and miscellaneous causes in 8 patients.

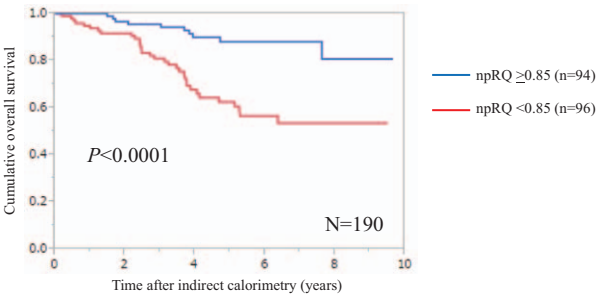
3.5. Univariate and multivariate analyses of factors contributing to OS for the entire cohort

Univariate analysis identified the following factors as significantly associated with OS for the entire cohort (n = 244): age ≥70 years ($P = 0.0008$); presence of HCC ($P < 0.0001$); Child–Pugh A ($P = 0.0091$); aspartate aminotransferase (AST) ≥56 IU/L ($P = 0.0359$); alanine aminotransferase ≥59 IU/L ($P = 0.0063$); serum albumin ≥3.7 g/dL ($P = 0.0046$); prothrombin time (PT) ≥77.3% ($P = 0.0036$); triglyceride ≥72 mg/dL ($P = 0.0028$); estimated glomerular filtration rate (eGFR) ≥78.35 mL/min/1.73 m^2 ($P = 0.0028$); body mass index (BMI) ≥22.2 kg/m^2 ($P = 0.0001$); npRQ ≥0.85 ($P = 0.0004$); alpha-fetoprotein (AFP) ≥5.7 ng/mL



Patients at risk	0-year	2-year	4-year	6-year	8-year
npRQ ≥0.85	122	104	75	29	9
npRQ <0.85	122	100	49	24	3

Figure 2. Cumulative overall survival for all cases based on npRQ value. The 1-, 3-, and 5-year cumulative overall survival rates in patients with npRQ ≥0.85 (n = 122) were 100%, 87.79%, and 77.24%, respectively, while those in patients with npRQ <0.85 (n = 122) were 94.26%, 73.65%, and 57.78%, respectively ($P = 0.0004$).



Patients at risk	0-year	2-year	4-year	6-year	8-year
npRQ ≥0.85	94	85	61	22	8
npRQ <0.85	96	81	40	22	3

Figure 3. Cumulative overall survival for patients without HCC, as indicated by indirect calorimetry, based on npRQ value. The 1-, 3-, and 5-year cumulative overall survival rates in patients with npRQ ≥0.85 (n = 94) were 100%, 95.49%, and 87.98%, respectively, while those in patients with npRQ <0.85 (n = 96) were 93.75%, 80.84%, and 62.5%, respectively ($P < 0.0001$).

Table 2

Univariate analyses of factors linked to overall survival for all cases (n = 244).

Variables	Number of each category	Univariate *P*
Age, y, ≥70, yes/no	96/148	0.0008
Gender, female/male	137/107	0.1108
Cause of liver diseases, B/C/alcoholic/others	20/143/29/52	0.0776
Child–Pugh classification, A/B or C	152/92	0.0091
Presence of HCC, yes/no	54/190	<0.0001
AST ≥56 IU/L, yes/no	78/166	0.0359
ALT ≥59 IU/L, yes/no	54/190	0.0063
Serum albumin ≥3.7 g/dL, yes/no	102/142	0.0046
Total bilirubin ≥0.9 mg/dL, yes/no	161/83	0.7934
Prothrombin time ≥77.3%, yes/no	105/139	0.0036
Platelet count $\geq 6.1 \times 10^4/mm^3$, yes/no	183/61	0.1616
Total cholesterol ≥157 mg/dL, yes/no	101/143	0.0702
Triglyceride ≥72 mg/dL, yes/no	142/102	0.0028
BTR ≥3.55, yes/no	168/76	0.0726
eGFR ≥78.35 mL/min/1.73 m^2, yes/no	115/129	0.0018
BMI ≥22.2 kg/m^2, yes/no	145/99	0.0001
HOMA-IR ≥2.35, yes/no	140/104	0.1123
Nonprotein respiratory quotient ≥0.85, yes/no	122/122	0.0004
AFP ≥5.7 ng/mL, yes/no	117/127	0.0002
DCP ≥40 mAU/mL, yes/no	58/186	<0.0001

AFP = alpha-fetoprotein, ALT = alanine aminotransferase, AST = aspartate aminotransferase, BMI = body mass index, BTR = branched-chain amino acid to tyrosine ratio, DCP = des-γ-carboxy prothrombin, eGFR = estimated glomerular filtration rate, HCC = hepatocellular carcinoma, HOMA-IR = homeostasis model assessment-insulin resistance.

($P = 0.0002$); and des-γ-carboxy prothrombin (DCP) ≥40 mAU/mL ($P < 0.0001$) (Table 2). The hazard ratios (HRs) and 95% confidence intervals (CIs) calculated by using multivariate analysis for the 13 significant variables ($P < 0.05$) in the univariate analysis are presented in Table 3. BMI ($P < 0.0001$), npRQ ($P = 0.0024$), presence of HCC ($P = 0.0045$), serum albumin ($P = 0.0441$), PT ($P = 0.0463$), eGFR ($P = 0.0086$), and DCP ($P = 0.0268$) were revealed to be significant predictors related to OS in multivariate analysis (Table 3).

Table 3

Multivariate analyses of factors linked to overall survival for all cases (n = 244).

Variables	Multivariate analysis		
	Odds ratio*	95% CI	*P*
Age, y	1.005	0.976–1.036	0.7525
Child–Pugh classification A	0.685	0.343–1.362	0.2802
Presence of HCC	2.352	1.314–4.113	0.0045
AST	0.999	0.981–1.017	0.9256
ALT	0.988	0.968–1.004	0.1651
Serum albumin	0.531	0.288–0.983	0.0441
Prothrombin time	0.970	0.941–0.999	0.0463
Triglyceride	1.0022	0.995–1.009	0.5499
eGFR	0.984	0.973–0.996	0.0086
BMI	0.869	0.811–0.931	<0.0001
Nonprotein respiratory quotient	0.0126	0.0005–0.233	0.0024
AFP	1.001	0.999–1.003	0.1824
DCP	1.0007	1.0001–1.0012	0.0268

AFP = alpha-fetoprotein, ALT = alanine aminotransferase, AST = aspartate aminotransferase, BMI = body mass index, CI = confidence interval, DCP = des-γ-carboxy prothrombin, eGFR = estimated glomerular filtration rate, HCC = hepatocellular carcinoma.

* When one unit changes in continuous variables.

3.6. Univariate and multivariate analyses of parameters contributing to OS in patients without HCC, as indicated by indirect calorimetry (n = 190)

Univariate analysis identified the following factors as significantly linked to OS for patients without HCC, as indicated by indirect calorimetry (n = 190): age ≥71 years ($P = 0.0001$); Child–Pugh A ($P = 0.0039$); AST ≥49 IU/L ($P = 0.0078$); serum albumin ≥3.7 g/dL ($P = 0.0162$); PT ≥77.3% ($P = 0.0033$); triglyceride ≥68 mg/dL ($P = 0.0035$); BCAA to tyrosine ratio (BTR) ≥3.55 ($P = 0.0257$); eGFR ≥85.67 mL/min/1.73 m^2 ($P = 0.0270$); BMI ≥22.3 kg/m^2 ($P = 0.0002$); npRQ ≥0.85 ($P < 0.0001$); and DCP ≥26 mAU/mL ($P = 0.0003$) (Table 4). The HRs and 95% CIs calculated by using the multivariate analysis for the eleven significant predictors ($P < 0.05$) in the univariate analysis are shown in Table 5. BMI ($P = 0.0004$), npRQ ($P = 0.0053$), serum albumin ($P = 0.0022$), and ALT ($P = 0.0018$) were found to be significant predictors associated with OS in the multivariate analysis (Table 5).

3.7. Comparison of baseline characteristics in patients with npRQ ≥0.85 and npRQ <0.85 for all cases

We also compared baseline characteristics in patients with npRQ ≥0.85 and npRQ <0.85 for all cases. The serum albumin level ($P = 0.0049$) and PT ($P = 0.0166$) in patients with npRQ ≥0.85 were significantly higher than those in patients with npRQ <0.85 (Table 6). In other variables, no significant differences were found between the 2 groups.

3.8. Construction of predictive model for all cases and for patients without HCC, as indicated by indirect calorimetry

Based on significant variables in multivariate analyses, we constructed a predictive model for all cases and for patients

Table 4

Univariate analyses of factors linked to overall survival in patients without hepatocellular carcinoma at indirect calorimetry (n = 190).

Variables	Number of each category	Univariate *P*
Age, y, ≥71, yes/no	59/131	0.0001
Gender, female/male	109/81	0.2452
Cause of liver diseases, B/C/alcoholic/others	18/97/27/48	0.5081
Child–Pugh classification, A/B or C	116/74	0.0039
AST ≥54 IU/L, yes/no	56/134	0.1154
ALT ≥49 IU/L, yes/no	53/137	0.0078
Serum albumin ≥3.7 g/dL, yes/no	85/105	0.0162
Total bilirubin ≥0.9 mg/dL, yes/no	128/62	0.7107
Prothrombin time ≥77.3%, yes/no	79/111	0.0033
Platelet count $\geq 11.4 \times 10^4/mm^3$, yes/no	57/133	0.4063
Total cholesterol ≥131 mg/dL, yes/no	134/56	0.0526
Triglyceride ≥68 mg/dL, yes/no	120/70	0.0035
BTR ≥3.55, yes/no	130/60	0.0257
eGFR ≥85.67 mL/min/1.73 m^2, yes/no	78/112	0.0270
BMI ≥22.3 kg/m^2, yes/no	108/82	0.0002
HOMA-IR ≥2.35, yes/no	107/83	0.1267
Nonprotein respiratory quotient ≥0.85, yes/no	94/96	<0.0001
AFP ≥5.2 ng/mL, yes/no	85/105	0.0969
DCP ≥26 mAU/mL, yes/no	73/117	0.0003

AFP = alpha-fetoprotein, ALT = alanine aminotransferase, AST = aspartate aminotransferase, BMI = body mass index, BTR = branched chain amino acid to tyrosine ratio, DCP = des-γ-carboxy prothrombin, eGFR = estimated glomerular filtration rate, HOMA-IR = homeostasis model assessment-insulin resistance.

Table 5

Univariate and multivariate analyses of factors linked to overall survival in patients without hepatocellular carcinoma at baseline (n = 190).

Variables	Multivariate analysis		
	Odds ratio*	95% CI	*P*
Age, y	1.030	0.991–1.072	0.1389
ALT	0.983	0.965–0.996	0.0018
Child–Pugh A	0.606	0.247–1.453	0.2624
Serum albumin	0.328	0.166–0.663	0.0022
Prothrombin time	0.974	0.941–1.007	0.1216
Triglyceride	1.003	0.993–1.013	0.4952
eGFR	0.990	0.975–1.006	0.2047
BMI	0.834	0.745–0.925	0.0004
Nonprotein respiratory quotient	0.0028	2.531×10^{-5} to 0.199	0.0053
BTR	1.070	0.811–1.386	0.6254
DCP	1.003	0.998–1.007	0.2235

ALT = alanine aminotransferase, BMI = body mass index, BTR = branched chain amino acid to tyrosine ration, CI = confidence interval, DCP = des-γ-carboxy prothrombin, eGFR = estimated glomerular filtration rate.
* When one unit changes in continuous variables.

Table 6

Comparison of baseline characteristics in patients with npRQ ≥0.85 and npRQ <0.85 for all cases (n = 244).

	npRQ ≥0.85 (n = 122)	npRQ <0.85 (n = 122)	*P*
Age, y	66 (41–83)	67 (25–90)	0.8677
Male/female	73/49	64/58	0.3020
Cause of liver disease, B/C/alcoholic/others	11/74/16/21	9/69/13/31	0.4517
Presence of HCC, yes/no	28/94	26/96	0.8776
AST, IU/L	41 (16–218)	44 (16–402)	0.6992
ALT, IU/L	34 (10–497)	34.5 (9–437)	0.8641
Serum albumin, g/dL	3.6 (2.2–4.7)	3.5 (2.0–4.7)	0.0049
Total bilirubin, mg/dL	1.0 (0.3–11.2)	1.1 (0.3–12.3)	0.6892
Prothrombin time, %	77.2 (39.0–115.6)	71.5 (22.5–101.8)	0.0116
Platelet count, $\times 10^4/mm^3$	8.5 (3.0–30.4)	8.9 (2.5–42.8)	0.3162
Total cholesterol, mg/dL	154 (84–231)	145 (70–292)	0.6083
Triglyceride, mg/dL	83 (27–346)	73.5 (30–187)	0.6495
BTR	4.36 (1.65–9.67)	4.00 (1.46–9.25)	0.1904
eGFR, mL/min/1.73 m^2	73.61 (5.23–139.38)	78.69 (6.17–161.24)	0.0917
BMI, kg/m^2	22.7 (15.3–33.3)	23.1 (13.1–35.9)	0.5486
HOMA-IR	2.76 (0.20–36.41)	2.55 (0.07–21.14)	0.4963
AFP, ng/mL	5.5 (0.8–728.8)	5.5 (1.0–1345.0)	0.4998
DCP, mAU/mL	23.0 (5.0–1980)	22.5 (8.0–2200)	0.5406

Data are expressed as median value (range).
AFP = alpha-fetoprotein, ALT = alanine aminotransferase, AST = aspartate aminotransferase, BMI = body mass index, BTR = branched-chain amino acid to tyrosine ratio, DCP = des-γ-carboxy prothrombin, eGFR = estimated glomerular filtration rate, HCC = hepatocellular carcinoma, HOMA-IR = homeostasis model assessment-insulin resistance, npRQ = nonprotein respiratory quotient.

without HCC, as indicated by indirect calorimetry. For all cases, patients without HCC, patients with npRQ ≥0.85, patients with eGFR ≥78.35 mL/min/1.73 m^2, patients with BMI ≥22.2 kg/m^2, patients with serum albumin ≥3.7 g/dL, patients with PT ≥77.3% or patients with DCP <40 mAU/mL were given by 1 point. Total points were calculated in each case. Total points ranged from 0 to 7. Subjects were divided into 3 groups based on total points (5 or more points: Group A (n = 91); 3 or 4 points: Group B (n = 109); and 2 or less point: Group C (n = 44)). Significant differences were found between each of the 2 groups in terms of OS (Group A vs B: $P < 0.0001$, Group B vs C: $P < 0.0001$ and Group A vs C: $P < 0.0001$) (Fig. 4A).

Similarly, for patients without HCC, as indicated by indirect calorimetry, patients with npRQ ≥0.85, patients with BMI ≥22.3 kg/m^2, patients with serum albumin ≥3.7 g/dL, and patients with ALT <49 IU/L were given by 1 point and total points were calculated in each case. Total points ranged from 0 to 4. They were divided into 3 groups based on total points (4 points: Group a (n = 19); 2 or 3 points: Group b (n = 130); and 0 or 1 point: Group c (n = 41)). Significant differences were observed between

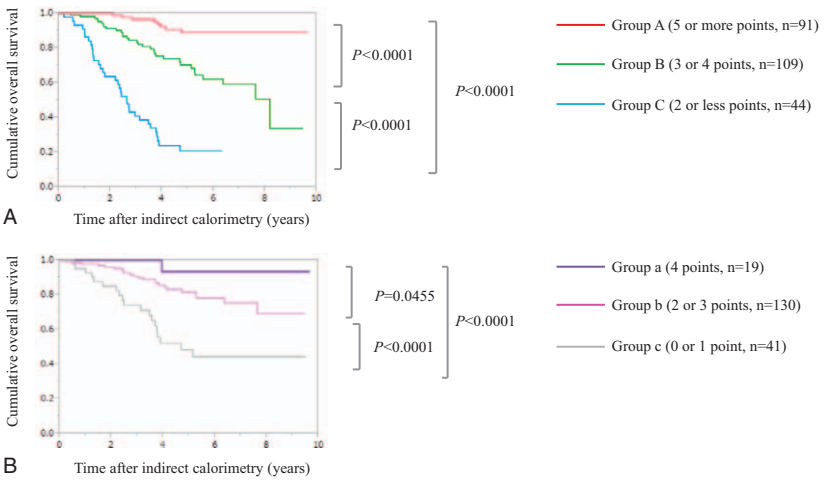


Figure 4. Our proposed predictive model for survival based on significant variables, as determined by multivariate analyses. (A) For all cases. Patients without HCC, patients with npRQ ≥0.85, patients with eGFR ≥78.35 mL/min/1.73 m^2, patients with BMI ≥22.2 kg/m^2, patients with serum albumin ≥3.7 g/dL, patients with PT ≥77.3% or patients with DCP <40 mAU/mL were given by one point. Total points were calculated in each case. Total points ranged from 0 to 7. Subjects were divided into three groups based on total points (5 or more points: Group A (n = 91); 3 or 4 points: Group B (n = 109); and 2 or less point: Group C (n = 44)). There were significant differences between each of the 2 groups in terms of OS (Group A vs B: $P < 0.0001$, Group B vs C: $P < 0.0001$ and Group A vs C: $P < 0.0001$). (B) For cases without HCC, as indicated by indirect calorimetry. Patients with npRQ ≥0.85, patients with BMI ≥22.3 kg/m^2, patients with serum albumin ≥3.7 g/dL and patients with ALT <49 IU/L were given by one point and total points were calculated in each case. Total points ranged from 0 to 4. They were divided into 3 groups based on total points (4 points: Group a (n = 19); 2 or 3 points: Group b (n = 130); and 0 or 1 point: Group c (n = 41)). Significant differences were observed between groups in terms of OS (Group a vs b: $P = 0.0455$, Group b vs c: $P < 0.0001$ and Group a vs c: $P < 0.0001$) (B).

groups in terms of OS (Group a vs b: $P=0.0455$, Group b vs c: $P<0.0001$ and Group a vs c: $P<0.0001$) (Fig. 4B).

3.9. Cumulative OS rates in hepatitis C virus (HCV)-related LC patients based on npRQ value

In 143 HCV-related LC patients, 123 patients (86.0%) had a high HCV viral load (≥5 log IU/mL) at baseline. During the follow-up period, 50 patients (35.0%) achieved sustained virological response (SVR). Of these, 31 patients were treated with interferon (IFN)-based therapies, while 19 patients were treated with IFN-free direct acting antiviral (DAA) therapies and only 3 patients died during the follow-up period. The 1-, 3-, and 5-year cumulative OS rates in HCV-related LC patients with SVR were 98.0%, 96.0%, and 93.6%. In terms of OS, the difference in patients who achieved SVR with npRQ ≥0.85 (n=27) and those with npRQ <0.85 (n=23) did not reach significance ($P=0.6398$).

4. Discussion

To the best of our knowledge, this is the first validation study for the report of Tajika et al.[8] As mentioned previously, in the era of novel nutritional therapies for LC, whether the npRQ can be a useful predictor for patients with LC is unclear.[12–15] Therefore, we conducted this observational study to address this urgent clinical question.

Previously, the proportion for PEM in LC patients was reported to be as high as 65% to 90%.[5,8,29] While in our present data, 59 out of 244 patients (24.2%) had PEM. These improvements in nutritional status in LC patients may be attributed to the progress for LC therapy over a period of more than 10 years.

In our study, higher npRQ value is significantly related to favorable OS for all cases and for cases without HCC, as indicated by indirect calorimetry, and optimal cutoff points of npRQ for survival in all cases and in patients without HCC, as indicated by indirect calorimetry, are both 0.849, which agree with data in the study by Tajika et al.[8] These results suggest that the npRQ value can be helpful for predicting survival in patients with LC and the data in Tajika et al study were validated by our data. Furthermore, our constructed predictive model can be promising for the development of a risk stratification method for predicting survival, although it should be validated in other independent cohorts.

A decrease in the npRQ value indicates a decrease in glycogen storage in the liver.[8] In LC patients, hepatocytes require the consumption of more adenosine-5′-triphosphate (ATP) to overcome the disease. When there is a shortage in ATP supply, liver function deteriorates. In patients with LC status, oxygen will be consumed more quickly to overcome disease, which will result in a shortage of oxygen for ATP synthesis in hepatocytes. Thus, hepatocytes activate the glycolysis pathway, which does not require oxygen to produce ATP.[30] These may well explain why LC patients with higher npRQ value have favorable clinical outcomes.

Higher eGFR value was a favorable independent predictor for all cases, as indicated by indirect calorimetry, in our multivariate analyses. Renal function in LC patients is of importance prognostically.[31,32] Indeed, the model for end-stage liver disease includes serum creatinine level.[33] Conversely, higher BMI was associated with better clinical outcome in our analysis. Furthermore, in this study, patients with BMI ≥25 kg/m^2, which defines obesity in Japan, had significantly better survival than those without this BMI level across all patients ($P=0.0023$) and for patients without HCC, as indicated by indirect calorimetry ($P=0.0106$).[25] Our data indicate that LC patients with obesity can produce favorable clinical outcomes, although sarcopenic obesity is growing to have a significant role as an adverse predictor due to the double metabolic burden derived from excess adiposity (obesity) and low muscle mass (sarcopenia).[25] LC patients can experience complications of sarcopenia.[34] Although examining the effect of sarcopenic obesity on survival is beyond the scope of our current analysis, this clinical entity will attract attention in the future.

In our results, the serum albumin level and PT in patients with npRQ ≥0.85 were significantly higher than those in patients with npRQ <0.85. One possible reason for these results is that more advanced LC status can be easily complicated with PEM.[1–4] Conversely, it is also of note that the prevalence of HCC in patients with npRQ ≥0.85 (23.0%, 28/122) was almost identical to that in patients with npRQ <0.85 (21.3%, 26/122). Therefore, the presence of HCC may not affect the npRQ value.

For the entire cohort, 74 patients (30.3%) died during the follow-up period, while in HCV-related LC patients with SVR (n=50), only 3 patients died. Achievement of SVR could have strong survival impact.[35] In these patients, the effect of the npRQ value may diminish.

We acknowledge several limitations to this study. First, evaluation for extrahepatic shunts and blood ammonia levels potentially affecting prognosis was not performed in our analysis.[36,37] Second, this is a retrospective observational study. Third, a considerable number of subjects were excluded from our analysis because of a loss of follow-up within a short period of time after performing indirect calorimetry, thereby resulting in bias. Fourth, measurement of the npRQ value using indirect calorimetry is not easy to perform in daily clinical practice due to its high cost. Thus, our results may be unable to be applied to patients in other institutions that do not have this equipment. However, our current results demonstrated that the npRQ value is associated with clinical outcomes in LC patients.

In conclusion, the npRQ value, as assessed by indirect calorimetry, can be helpful for predicting outcomes for LC patients even in the era of established nutritional interventional treatments for LC. In patients with lower npRQ value, adequate interventions may be required.

Acknowledgments

The authors would like to thank Nozomi Kanazawa (Hyogo College of Medicine), Yoko Matsushita (Hyogo College of Medicine), and Sayaka Fujii (Hyogo College of Medicine) for data collection.

References

[1] Moctezuma-Velázquez C, García-Juárez I, Soto-Solís R, et al. Nutritional assessment and treatment of patients with liver cirrhosis. Nutrition 2013;29:1279–85.
[2] Charlton MR. Branched-chain amino acid enriched supplements as therapy for liver disease. J Nutr 2006;136(1 suppl):295S–8S.
[3] Kawaguchi T, Izumi N, Charlton MR, et al. Branched-chain amino acids as pharmacological nutrients in chronic liver disease. Hepatology 2011;54:1063–70.
[4] Moriwaki H, Miwa Y, Tajika M, et al. Branched-chain amino acids as a protein- and energy-source in liver cirrhosis. Biochem Biophys Res Commun 2004;313:405–9.

[5] Alberino F, Gatta A, Amodio P, et al. Nutrition and survival in patients with liver cirrhosis. Nutrition 2001;17:445–50.
[6] Saito M, Seo Y, Yano Y, et al. Short-term reductions in non-protein respiratory quotient and prealbumin can be associated with the long-term deterioration of liver function after transcatheter arterial chemo-embolization in patients with hepatocellular carcinoma. J Gastroenterol 2012;47:704–14.
[7] Sam J, Nguyen GC. Protein-calorie malnutrition as a prognostic indicator of mortality among patients hospitalized with cirrhosis and portal hypertension. Liver Int 2009;29:1396–402.
[8] Tajika M, Kato M, Mohri H, et al. Prognostic value of energy metabolism in patients with viral liver cirrhosis. Nutrition 2002;18: 229–34.
[9] Peng S, Plank LD, McCall JL, et al. Body composition, muscle function, and energy expenditure in patients with liver cirrhosis: a comprehensive study. Am J Clin Nutr 2007;85:1257–66.
[10] Terakura Y, Shiraki M, Nishimura K, et al. Indirect calorimetry and anthropometry to estimate energy metabolism in patients with liver cirrhosis. J Nutr Sci Vitaminol (Tokyo) 2010;56:372–9.
[11] Hanai T, Shiraki M, Nishimura K, et al. Free fatty acid as a marker of energy malnutrition in liver cirrhosis. Hepatol Res 2014;44:218–28.
[12] Nishikawa H, Osaki Y. Clinical significance of therapy using branched-chain amino acid granules in patients with liver cirrhosis and hepatocellular carcinoma. Hepatol Res 2014;44:149–58.
[13] Hayashi F, Matsumoto Y, Momoki C, et al. Physical inactivity and insufficient dietary intake are associated with the frequency of sarcopenia in patients with compensated viral liver cirrhosis. Hepatol Res 2013;43: 1264–75.
[14] Aoyama K, Tsuchiya M, Mori K, et al. Effect of a late evening snack on outpatients with liver cirrhosis. Hepatol Res 2007;37:608–14.
[15] Yamanaka-Okumura H, Nakamura T, Takeuchi H, et al. Effect of late evening snack with rice ball on energy metabolism in liver cirrhosis. Eur J Clin Nutr 2006;60:1067–72.
[16] Katayama K, Saito M, Kawaguchi T, et al. Effect of zinc on liver cirrhosis with hyperammonemia: a preliminary randomized, placebo-controlled double-blind trial. Nutrition 2014;30:1409–14.
[17] Nakanishi H, Kurosaki M, Tsuchiya K, et al. L-carnitine reduces muscle cramps in patients with cirrhosis. Clin Gastroenterol Hepatol 2015;13: 1540–3.
[18] Manguso F, D'Ambra G, Menchise A, et al. Effects of an appropriate oral diet on the nutritional status of patients with HCV-related liver cirrhosis: a prospective study. Clin Nutr 2005;24:751–9.
[19] Muto Y, Sato S, Watanabe A, et al. Effects of oral branched-chain amino acid granules on event-free survival in patients with liver cirrhosis. Clin Gastroenterol Hepatol 2005;3:705–13.
[20] Kawaguchi T, Taniguchi E, Sata M. Effects of oral branched-chain amino acids on hepatic encephalopathy and outcome in patients with liver cirrhosis. Nutr Clin Pract 2013;28:580–8.
[21] Morihara D, Iwata K, Hanano T, et al. Late-evening snack with branched-chain amino acids improves liver function after radiofrequency ablation for hepatocellular carcinoma. Hepatol Res 2012;42:658–67.
[22] Tamori A, Enomoto M, Kawada N. Recent advances in antiviral therapy for chronic hepatitis C. Mediators Inflamm 2016;2016:6841628.
[23] Asahina Y, Izumi N, Hiromitsu K, et al. JSH Guidelines for the Management of Hepatitis C Virus Infection: a 2016 update for genotype 1 and 2. Hepatol Res 2016;46:129–65.
[24] Tawada A, Kanda T, Yokosuka O. Current and future directions for treating hepatitis B virus infection. World J Hepatol 2015;7:1541–52.
[25] Shiraki M, Nishiguchi S, Saito M, et al. Nutritional status and quality of life in current patients with liver cirrhosis as assessed in 2007–2011. Hepatol Res 2013;43:106–22.
[26] Kumada H, Okanoue T, Onji M, et al. Guidelines for the treatment of chronic hepatitis and cirrhosis due to hepatitis C virus infection for the fiscal year 2008 in Japan. Hepatol Res 2010;40:8–13.
[27] Nishikawa H, Yoh K, Enomoto H, et al. Factors associated with protein-energy malnutrition in chronic liver disease: analysis using indirect calorimetry. Medicine (Baltimore) 2016;95:e2442.
[28] European Association for the Study of the LiverEuropean Organisation For Research And Treatment Of Cancer: EASL-EORTC Clinical Practice guidelines: management of hepatocellular carcinoma. J Hepatol 2012;56:908–43.
[29] Mueller MU. Malnutrition in cirrhosis. J Hepatol 1995;23(suppl 1): 31–5.
[30] Nishikawa T, Bellance N, Damm A, et al. A switch in the source of ATP production and a loss in capacity to perform glycolysis are hallmarks of hepatocyte failure in advance liver disease. J Hepatol 2014;60:1203–11.
[31] Cholongitas E, Shusang V, Marelli L, et al. Review article: renal function assessment in cirrhosis—difficulties and alternative measurements. Aliment Pharmacol Ther 2007;26:969–78.
[32] Cholongitas E, Arsos G, Goulis J, et al. Glomerular filtration rate is an independent factor of mortality in patients with decompensated cirrhosis. Hepatol Res 2014;44:E145–55.
[33] Singal AK, Kamath PS. Model for end-stage liver disease. J Clin Exp Hepatol 2013;3:50–60.
[34] Sinclair M, Gow PJ, Grossmann M, et al. Review article: sarcopenia in cirrhosis—aetiology, implications and potential therapeutic interventions. Aliment Pharmacol Ther 2016;43:765–77.
[35] Mandorfer M, Kozbial K, Schwabl P, et al. Sustained virologic response to interferon-free therapies ameliorates HCV-induced portal hypertension. J Hepatol 2016;[Epub ahead of print].
[36] Tarantino G, Citro V, Conca P, et al. What are the implications of the spontaneous spleno-renal shunts in liver cirrhosis? BMC Gastroenterol 2009;9:89.
[37] Tarantino G, Citro V, Esposito P, et al. Blood ammonia levels in liver cirrhosis: a clue for the presence of portosystemic collateral veins. BMC Gastroenterol 2009;9:21.