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Liver function and energy metabolism in hepatocellular carcinoma developed in patients with hepatitis B-related cirrhosis

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Abstract

Energy metabolism in patients with Hepatocellular carcinoma (HCC) accompanying by hepatitis B cirrhosis is unknown.

To compare the differences in liver functions and energy metabolism between patients with hepatitis B-related cirrhosis and patients with HCC.

This was a retrospective study of patients with hepatitis B-related cirrhosis (LC group, n = 75) and patients with HCC accompanying by hepatitis B cirrhosis (HCC group, n = 80) treated in Beijing You'an Hospital between January 2013 and June 2017. The resting energy expenditure (REE), respiratory quotient (RQ), carbohydrate oxidation rate (CHO%), fat oxidation rate (FAT%), and protein oxidation rate (PRO%) were measured using a metabolic cart. Liver function, renal function, blood coagulation, etc. were collected.

Compared to the LC group, patients with HCC had normal metabolism, but RQ (0.83 ± 0.07 vs 0.85 ± 0.08, $P = .073$) and CHO% (35.5% vs 49%, $P = .013$) were lower and FAT% was higher (41% vs 33%, $P = .030$). Compared with patients with LC group, albumin (ALB), γ-glutamyltranspeptadase (GGT), alkaline phosphatase (AKP), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), and prothrombin time activity (PTA) were elevated in the HCC group, while total bilirubin (TB), total bile acid (TBA), and international normalized ratio (INR) were reduced ($P < .05$). Cholinesterase (CHE) was positively correlated with RQ, CHO, and CHO% ($P < .05$), while negatively correlated with FAT and FAT% ($P < .05$). AKP was negatively correlated with RQ, CHO, and CHO% ($P < .05$), while positively correlated with FAT and FAT% ($P < .05$). TBA was negatively correlated with RQ and CHO ($P < .05$), while positively correlated with FAT ($P < .05$).

HCC leads to increased liver synthetic function and improve the liver functions of patients with LC, at least to some extent, but the nutritional metabolism was poor.

Abbreviations: AFP = alpha-fetoprotein, AKP = alkaline phosphatase, ALB = albumin, ALT = alanine aminotransferase, APASL = Asian Pacific Association for the Study of the Liver, Apo A1 = Apollpoprotein A-1, Apo B = Apollpoprotein B, AST = aspartate aminotransferase, BCLC = Barcelona Clinic Liver Cancer, BMI = body mass index, CHE = cholinesterase, CHO = carbohydrate oxidation, CHO% = carbohydrate oxidation rate, CREA = creatinine, DB = direct bilirubin, FAT = fat oxidation, FAT% = fat oxidation rate, GGT = γ-glutamyltranspeptadase, GLOB = globulin, HCC = Hepatocellular carcinoma, HDL-C = high-density lipoprotein cholesterol, LDL-C = low-density lipoprotein cholesterol, MREE = measured REE, PREE = predicted rest energy consumption, PRO = protein oxidation, PRO% = protein oxidation rate, PTA = prothrombin time activity, REE = resting energy expenditure, RQ = respiratory quotient, TB = total bilirubin, TBA = total bile acid, TC = total cholesterol, TG = triglyceride.

Keywords: carbohydrate oxidation, cirrhosis, energy metabolism, fatty acid oxidation, hepatitis B, hepatocellular carcinoma, protein oxidation

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Meixin Ren and Juan Li contributed equally to this work.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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1. Introduction

The liver is the central metabolic organ in the human body. Patients with liver cirrhosis have liver damage and varying degrees of abnormalities in energy metabolism.[1] Previous studies have shown that patients with cirrhosis are in a low metabolic state characterized by low glucose oxidation rate (CHO%) and with the main energy supply being proteins.[1–4] With the aggravation of cirrhosis, CHO% decreases significantly, resting energy expenditure (REE) and respiratory quotient (RQ) tend to decrease, while protein oxidation rate (RPO%) increases.[1–4] The Child-Pugh classification is negatively correlated with REE, RQ, and CHO%.[4]

Hepatocellular carcinoma (HCC) occurs all over the world, mainly in the Asia-Pacific coast and southeastern Africa, while Australia, Europe, North America and other regions are low incidence areas.[5] Hepatocellular carcinoma (HCC) accounts for more than 90% of malignant liver tumors, it is the fifth cancer in term of incidence rate worldwide, and the third leading cause of mortality. In China, HCC ranks fourth among the malignant tumors and is the third cause of cancer-related death, representing a serious public health issue.[6,7] HCC is closely associated with cirrhosis. The prevalence of cirrhosis in patients with HCC is 84.6% and the incidence of HCC after liver cirrhosis is 49.9%.[8]

Although the pathogenesis of malignant tumors has not yet been elucidated, there is increasing evidence that malignant tumors are a metabolic-related disease.[9] Patients with malignant tumors are generally in a state of high metabolism, with increased mobilization of endogenous fat, decreased glucose utilization, consumption of fat and fat-free masses, and loss of somatic cell population. An early study by Dagnelie et al[10] showed that gluconeogenesis in the liver increases in tumor patients with distant metastasis. Leiffers et al[11] showed that patients with colorectal cancer have high liver and tumor metabolism, causing cachexia in the last few months of their lives. Guglielmi et al[12] showed that well-nourished cirrhosis and HCC display normal oxidative patterns. Recent metabolomics studies have identified some abnormal metabolites and pathways in patients with cirrhosis and HCC.[12–15] Nevertheless, there are few studies on the comparison of poor metabolic indicators between patients with HCC and patients with liver cirrhosis.

It is well known that end-stage liver diseases are accompanied by severe loss of liver functions. With advancing degree of cirrhosis, the treatment opportunities of HCC are gradually lost and prognosis worsens. Liver tissue would be more damaged if HCC occurs on the basis of liver cirrhosis, which is undoubtedly a "disaster" for the patients. On the other hand, it can be observed that liver functions are still good for some patients with large HCC, while liver functions worsens for some patients with HCC of Child-Pugh grade A after HCC resection, with a high risk of liver failure. Improvement of liver functions in patients with liver cirrhosis and HCC could lead to the hypothesis of "compensation for liver functions" for HCC and cirrhosis. Whether palliative therapy should be considered for these patients to avoid decompensation of liver functions and even liver failure after surgical resection of large HCC could be explored.

Therefore, this study aimed to examine the differences of liver functions and energy metabolism between patients with hepatitis B-related cirrhosis and patients with HCC, as well as to investigate the relationship between liver functions and energy metabolism. The results could provide a basis for better nutritional support of HCC patients and for the selection of clinical treatment regimens for these patients.

2. Methods

2.1. Study design and patients

This was a retrospective study. The subjects were patients with hepatitis B virus-associated cirrhosis (LC group) and patients with HCC (HCC group) treated at the Beijing You'an Hospital from January 2013 to June 2017. This study was approved by the Ethics Committee of Beijing You'an Hospital. This study was reviewed and approved by the medical research ethics committee of Beijing You'an Hospital, Capital Medical University.

Inclusion criteria: Patients with hepatitis-B cirrhosis and hepatitis B-related HCC of 18 to 65 years of age. The diagnostic criteria of hepatitis-B cirrhosis referred to the guideline of the Asian Pacific Association for the Study of the Liver (APASL) in 2012.[16] The diagnostic criteria for HCC referred to the clinical practice guide of the Asia Pacific Hepatocellular Carcinoma Association (2017 edition).[17]

Exclusion criteria:

1. Patients combined with or overlapped with other viral infections: positive result for any one of anti-HAV-IgM, anti-HCV, anti-HDV, anti-HEV, CMV, EBV, or anti-HIV.
2. Patients combined with diseases such as thyroid disease, kidney disease, active tuberculosis, mental illness, and other malignant tumors.
3. Patients who used adrenal cortex hormones or bronchodilators such as β-agonists and theophylline within 12 hours, as well as patients who drank caffeinated drinks such as tea and coffee.
4. Patients combined with other liver diseases such as alcoholic liver disease, fatty liver disease, drug liver disease, and autoimmune hepatitis.
5. Patients combined with severe hydrothorax and ascites, as well as severe infections, etc.

2.2. Grouping

1. According to the Child-Pugh classification,[18] grade A was 5–6 points, grade B was 7–9 points and grade C was ≥10 points. The LC and HCC groups were divided into 3 subgroups, respectively: the LC-A, HCC-A, LC-B, HCC-B, LC-C, and HCC-C groups.
2. Tumor staging: Based on Barcelona Clinic Liver Cancer Staging System (BCLC),[19] the patients in the HCC group were divided into the 4 groups (HCC-1, HCC-2, HCC-3, and HCC-4) groups according to the A, B, C, and D stages.

2.3. Data collection

All data were obtained from the HSP 2008 system of the Beijing You'an Hospital. Liver functions were tested using an AU5400 automatic biochemical analyzer (Olympus, Tokyo, Japan). Results of routine liver functions were obtained from biochemical examination, including alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (TB), alkaline phosphatase (AKP), γ-glutamyltranspeptidase (GGT), albumin (ALB), cholinesterase (CHE), and total bile acid (TBA). Blood coagulation was tested using a CA-7000 automatic blood coagulation instrument (Sysmex, Kobe, Japan). All clinical

biochemical measurements were performed using an AU5400 automatic biochemical analyzer (Olympus, Tokyo, Japan), including prothrombin time activity (PTA). All instruments were operated using the manufacturers' reagents and instructions.

2.4. Metabolic measurements

Indirect measurement of energy metabolism was determined using a CCM/D nutritional metabolism test system (referred to as metabolism cart) (MGC Diagnostics Corp., Saint Paul, MN). The patients were required to be fasting for 8 to 10 hours. The patients were in the supine position. The test was performed 30 minutes after avoiding muscle activity with an ambient temperature of 24 to 26°C, humidity of 45% to 60% and atmospheric pressure of 101 to 102.4 kPa. The exhaled gas was collected using hood ventilation, which was recorded once every 2 to 5 seconds. The average O_2 consumption and CO_2 production per minute were calculated automatically. Each test was performed for 15 to 20 minutes. The subjects were required to remain awake during the entire test and be as quiet as possible.

The actual measurement of resting energy expenditure (REE) was performed based on oxygen consumption (VO_2, ml/min) and carbon dioxide production (VCO_2, ml/min). The value calculated by the metabolic cart was regarded as the measured REE (MREE). The simplified Weir formula was used in the calculation:[13] REE (kcal/d) = $(3.941 \times VO_2 + 1.106 \times VCO_2) \times 1.44$. The predicted rest energy consumption (PREE) was automatically calculated by the metabolic cart using the Harris-Benedict (H-B) formula:[14] PREE (male, kcal/d) = 66.4730 × 13.7721 × body weight (kg) + 5.033 × height (cm) − 6.7550 × age (years); or PREE (female, kcal/d) = 655.0955 + 9.5634 × body weight (kg) + 1.8496 × height (cm) × 4.6756 × age (year). REE% = MREE/PREE < 90% was considered as low metabolism, 90% to 110% was considered as normal metabolism, and >110% was considered as high metabolism.[20]

The respiratory quotient (RQ) was the ratio of VCO_2 to VO_2 per unit of time: $RQ = VCO_2/VO_2$, representing the ratio of the 3 major nutrients. RQ was different if oxidizing substrates were different. RQ of 100% carbohydrate was 1.0. RQ of 100% fat was 0.7, RQ of 100% protein was 0.8, and RQ of mixed nutrients was 0.85 to 0.90.

Urine at 24 hours was collected, and quantitative measurement of urea nitrogen was tested using an AU5400 automatic biochemical analyzer (Olympus, Tokyo, Japan). The oxidation rate of the 3 major nutrients was automatically obtained after inputting the total urea nitrogen at 24 hours: carbohydrate oxidation rate (CHO%), fat oxidation rate (FAT%), and protein oxidation rate (PRO%). PRO% was normally about 10% to 15%, CHO% was normally about 50% to 55% normal, and FAT% was normally about 30% to 35%.

2.5. Statistical analysis

Normal distribution was tested using the Kolmogorov-Smirnov test for continuous data. Continuous data meeting the normal distribution were presented as means ± standard deviation (SD) and analyzed using the independent sample *t* test. Data not meeting the normal distribution were presented as median (range) and analyzed using the Mann-Whitney *U* test. Categorical data were expressed as frequency (percentage) and analyzed using the chi-square test or Fisher exact test. Correlation analyses were performed using the Pearson correlation coefficient. Statistical analysis was performed using SPSS 23.0 (IBM, Armonk, NY). Two-sided *P* values < .05 were considered statistically significant.

3. Results

3.1. Baseline characteristics

Table 1 shows the baseline characteristics of the 2 groups of patients. There were 80 patients in the HCC group and 75 in the LC group. There were no significant differences in age, gender, and BMI (body mass index) between the 2 groups (age, 52.02 ± 8.41 vs 49.40 ± 10.17, *P* = .081; gender (male), 73 (91.3%) vs 63 (84%), *P* = .169; BMI, 22.63 ± 3.83 vs 23.63 ± 3.55, *P* = .096). According to the Child-Pugh classification, the HCC and LC groups were divided into 3 subgroups, respectively, including 33 patients in the HCC-A group, 33 in the HCC-B group, 14 in the HCC-C group, 23 in the LC-A group, 30 in the LC-B group, and 22 in the LC-C group. There was no significant difference in the distribution of the Child-Pugh grades between the 2 groups (grade A 41.3% vs 30.7%; grade B 41.3% vs 40%; grade C 17.5% vs 29.3%, *P* = .170). According to the Barcelona Clinic Liver Cancer Staging, HCC patients were divided into 4 groups, including 33 patients (41.3%) in stage A (HCC-1 group), 13 (16.2%) in stage B (HCC-2 group), 21 (26.3%) in stage C (HCC-3 group), and 13 (16.3%) in stage D (HCC-4 group).

3.2. Indicators of liver functions

Table 2 presents the indictors of liver functions of the 2 groups. Comparison between the HCC and LC groups showed that TB (mmol/L) was lower (24.4 (18.3–37.9) mmol/L vs 30.1 (18.9–60.1) mmol/L, *P* = .039), TBA (mmol/L) was lower (20.8 (11.5–57.1) mmol/L vs 35.2 (19.0–83.5) mmol/L, *P* = .016), ALB (g/L) was higher significantly (35.5 ± 5.6 g/L vs 31.9 ± 6.6 g/L, *P* < .001), GGT (U/L) was higher (134.2 (53.9–257.1) U/L vs 53.7 (31.9–98.7) U/L, *P* < .001), AKP (U/L) was higher (126.5 (79.3–220.7) U/L vs 95.0 (69.3–133.8) U/L, *P* = .004), TC (mmol/L) was higher (3.805 (3.245–4.5) mmol/L vs 3.51 (2.65–4.08) mmol/L, *P* = .016), LDL-C (mmol/L) was higher (2.14 (1.73–2.8) mmol/L vs 1.89 (1.34–2.36) mmol/L, *P* = .006), and CHE (U/L) was higher (3260.5 (2257.5–5218.5) U/L vs 2882 (2083–4583) U/L, *P* = .368). Comparison between the HCC and LC groups showed that ALT and AST were slightly higher, but without

Table 1

Characteristics of the patients.

	LC	HCC	
	n = 75	n = 80	*P*
Gender (male)	63 (84.0%)	73 (91.3%)	.169
Age (yr)	49.4 ± 10.2	52.0 ± 8.4	.081
BMI	23.63 ± 3.55	22.63 ± 3.83	.096
Child-Pugh			.170
A	23 (30.7)	33 (41.3%)	
B	30 (40.0)	33 (41.3%)	
C	22 (29.3)	14 (17.5%)	
BCLC		Stage A 33 (41.3%)	
		Stage B 13 (16.2%)	
		Stage C 21 (26.3%)	
		Stage D 13 (16.3)	
Tumor diameter (cm)		5.1 (2.6–11.6)	

Child classes: A, 5–6 points; B, 7–9 points; C, 10–15 points.
BCLC = Barcelona Clinic Liver Cancer, BMI = body mass index.

Table 2

Comparison of liver function between the 2 groups.

	LC	HCC	
	n = 75	n = 80	*P*
ALT (U/L)	36.2 (27.1–63.7)	36.4 (28.0–62.0)	.596
AST (U/L)	45.3 (33.3–78.1)	58.9 (33.1–123.2)	.220
TB (umol/L)	30.1 (18.9–60.1)	24.4 (18.3–37.9)	.039
DB (umol/L)	13.6 (6.6–25.7)	9.10 (5.45–15.60)	.085
ALB (g/L)	31.9 ± 6.6	35.5 ± 5.6	<.001
GLOB (g/L)	29.9 ± 7.2	29.2 ± 5.1	.517
GGT (U/L)	53.7 (31.9–98.7)	134.2 (53.9–257.1)	<.001
AKP (U/L)	95.0 (69.3–133.8)	126.5 (79.3–220.7)	.004
CHE (U/L)	2882 (2083–4583)	3260.5 (2257.5–5218.5)	.368
TBA (umol/L)	35.2 (19.0–83.5)	20.8 (11.5–57.1)	.016
CREA (μmol/L)	64.0 ± 15.5	60.6 ± 14.5	.161
Urea (mmol/L)	5.16 ± 1.62	4.93 ± 1.59	.384
GLU (mmol/L)	5.79 ± 2.60	5.31 ± 1.82	.180
PTA (%)	67.2 ± 21.5	80.3 ± 16.1	<.001
INR	1.33 ± 0.26	1.17 ± 0.17	<.001
AFP (ng/mL)	6.22 (3.03–59.70)	50.63 (5.93–2077)	.001
TG (mmol/L)	0.79 (0.54–1.19)	0.87 (0.67–1.13)	.193
TC (mmol/L)	3.51 (2.65–4.08)	3.805 (3.245–4.5)	.016
HDL-C (mmol/L)	0.92 (0.68–1.17)	1.015 (0.8–1.25)	.149
LDL-C (mmol/L)	1.89 (1.34–2.36)	2.14 (1.73–2.8)	.006
Apo A1 (g/L)	0.90 (0.60–1.16)	0.96 (0.74–1.18)	.494
Apo B (g/L)	0.64 (0.49–0.87)	0.74 (0.66–0.895)	.020

AFP = alpha-fetoprotein, AKP = alkaline phosphatase, ALB = albumin, ALT = alanine transaminase, Apo A1 = Apollpoprotein A-1, Apo B = Apollpoprotein B, AST = aspartate transaminase, CHE = cholinesterase, CREA = creatinine, DB = direct bilirubin, GGT = γ-glutamyltranspeptadase, GLOB = globulin, GLU = glucose, HDL-C = high-density lipoprotein cholesterol, INR = international normalized ratio, LDL-C = low-density lipoprotein cholesterol, PTA = prothrombin time activity, TB = total bilirubin, TBA = total bile acids, TC = total cholesterol, TG = total triglycerides.

statistical significance. There were no significant differences in renal functions between the 2 groups. PTA (%) was higher in the HCC group compared to the LC group (80.3 ± 16.1 vs 67.2 ± 21.5, $P < .001$), while INR was lower (1.17 ± 0.17 vs 1.33 ± 0.26, $P < .001$), suggesting that indicators of liver synthesis and metabolism of patients with HCC were better than those with LC. AFP (ng/ml) in the HCC group was significantly higher compared to the LC group (50.63 (5.93–2077) ng/ml vs 6.22 (3.03–59.70) ng/ml, $P = .001$). In this study, the level of AFP in HCC group was lower than the diagnostic criteria (AFP > 500 ng/ml), suggesting that the possibility of hepatocellular carcinoma with normal or low levels of AFP.

Table 3 shows the indicators of liver functions between the 2 groups with the same Child-Pugh classification. Compared to the LC-A group, INR (1.07 ± 0.09 vs 1.14 ± 0.13, $P = .019$) and TBA (mmol/L) (13.1 (5.3–20.8) mmol/L vs 19.7 (11.9–28.8) mmol/L, $P = .018$) were lower in the HCC-A group, while there were no significant differences in the other indicators. Compared to the LC-B group, AST (U/L) (71.1 (44.3–128.6) U/L vs 42.85 (34.4–57.8) U/L, $P = .002$) was higher, ALB (g/L) was higher (33.30 ± 4.52 g/L vs 30.66 ± 4.78 g/L, $P = .028$), GGT (U/L) was higher (164.5 (70.2–258.05) U/L vs 46.05 (32.5–83.1) U/L, $P < .001$), and AKP (U/L) was higher (140.35 (99.9–231.35) U/L vs 84.15 (70.1–114.2) U/L, $P < .001$) in the HCC-B group, while the other indicators were not significantly different. Compared with the LC-C group, in the HCC-C group, AST (U/L) was higher (142.55 (67.7–236.2) U/L vs 75.9 (50.9–113.5) U/L, $P = .036$), ALB (g/L) was higher (32.09 ± 5.16 g/L vs 27.47 ± 5.30 g/L), $P = .015$), GGT (U/L) was higher (293.65 (153.2–505) U/L vs 68.4 (35.9–114.2) U/L, $P < .001$), AKP (U/L) was higher (214.6 (155.1–355.1) U/L vs 132.95 (88.3–170.9) U/L, $P = .004$), PTA (%)was higher (74.12 ± 14.12% vs 47.5 ± 8.58%, $P < .001$), TC (mmol/L) was higher (3.705 (3.01–4.86) mmol/L vs 2.58 (2.33–3.57) mmol/L, $P = .048$), and LDL-C (mmol/L) was higher (2.44 (1.89–3.36) mmol/L vs 1.26 (0.92–1.9) mmol/L, $P = .003$), while the other indicators were not significantly different. The results suggest that with the aggravation of liver damage, improvement of liver synthesis and metabolic indicators were more significant in the HCC group compared to the LC group.

Table 4 shows the liver function indicators for HCC patients with different BCLC stages. The results suggested that with worsening tumor stage, liver damage of patient aggravated, ALT

Table 3

Comparison of liver function indexes between the 2 groups under the same Child–Pugh classification.

	Stage A			Stage B			Stage C		
Item	LC-A (n = 23)	HCC-A (n = 33)	*P*	LC-B (n = 30)	HCC-B (n = 33)	*P*	LC-C (n = 22)	HCC-C (n = 14)	*P*
ALT (U/L)	32.8 (27.4–44.3)	34.9 (26–57.8)	.764	32.65 (20.6–63.7)	36.5 (31.4–75.1)	.162	52.95 (28.1–69.2)	46.65 (32.9–71.8)	.897
AST (U/L)	34.6 (27.8–49.8)	33.5 (26.3–43.8)	.334	42.85 (34.4–57.8)	71.1 (44.3–128.6)	.002	75.9 (50.9–113.5)	142.55 (67.7–236.2)	.036
TB (umol/L)	19.8 (13.7–25.5)	19.9 (14–24.2)	.960	29.35 (18.2–55.6)	28.6 (20–41.9)	.773	73.85 (59.7–113.3)	38.6 (27.1–145.2)	.194
DB (umol/L)	4.8 (3.4–8.4)	5.7 (4.1–10.6)	.777	11.85 (7.6–19.6)	13.1 (6.9–23.3)	.853	34.85 (24.1–66.1)	22.6 (13.4–75)	.446
ALB (g/L)	37.75 ± 5.51	39.04 ± 4.75	.354	30.66 ± 4.78	33.3 ± 4.52	.028	27.47 ± 5.3	32.09 ± 5.16	.015
GLOB (g/L)	27.73 ± 6.37	26.7 ± 4.13	.465	28.47 ± 6.13	31.11 ± 5.42	.075	34.05 ± 8.02	30.76 ± 4.19	.168
GGT (U/L)	50.2 (28.9–98.7)	55.9 (36.6–154)	.583	46.05 (32.5–83.1)	164.5 (70.2–258.05)	<.001	68.4 (35.9–114.2)	293.65 (153.2–505)	<.001
AKP (U/L)	92.8 (51.3–122.9)	76.7 (63.9–132.6)	.459	84.15 (70.1–114.2)	140.35 (99.9–231.35)	<.001	132.95 (88.3–170.9)	214.6 (155.1–355.1)	.004
CHE (U/L)	4614 (3175–6374)	5237 (4105–6811)	.364	2783.5 (2297–3882)	2588 (2157–3318)	.315	2148.5 (1485–2880)	1974 (1495–2679)	.783
TBA (umol/L)	19.7 (11.9–28.8)	13.1 (5.3–20.8)	.018	36.4 (24.6–78)	27.35 (14.35–44.45)	.251	85.05 (37.8–98.9)	102.3 (57.1–167.1)	.206
CREA (umol/L)	63.72 ± 12.99	63.75 ± 13.7	.994	64.41 ± 15.58	60.15 ± 12.4	.371	63.82 ± 18.19	54.41 ± 19.4	.149
Urea (mmol/L)	4.69 ± 1.07	4.46 ± 1.41	.530	5.25 ± 1.54	5.03 ± 1.57	.575	5.54 ± 2.09	5.83 ± 1.72	.666
GLU (mmol/L)	6.02 ± 2.84	5.36 ± 1.07	.225	5.86 ± 2.6	5.44 ± 2.54	.524	5.47 ± 2.42	4.89 ± 1.07	.406
PTA (%)	80.76 ± 22.62	89.94 ± 13.57	.063	71.37 ± 16.81	73.29 ± 14.65	.630	47.5 ± 8.58	74.12 ± 14.12	<.001
INR	1.14 ± 0.13	1.07 ± 0.09	.019	1.28 ± 0.21	1.24 ± 0.18	.528	1.6 ± 0.19	1.24 ± 0.15	.437
AFP (ng/mL)	4.49 (2.1–14.92)	7.64 (2.69–210.9)	.206	8.19 (2.87–80.8)	67.96 (12.53–3921)	.003	13.945 (3.7–50.51)	1117.1 (134.4–17941)	<.001
TG (mmol/L)	0.88 (0.58–1.32)	0.9 (0.75–1.13)	.726	0.8 (0.59–1)	0.745 (0.6–1.04)	.734	0.66 (0.39–1.24)	0.935 (0.66–1.23)	.183
TC (mmol/L)	3.63 (3.3–4.31)	4.19 (3.45–4.58)	.234	3.64 (3.18–3.97)	3.64 (3.16–4.31)	.700	2.58 (2.33–3.57)	3.705 (3.01–4.86)	.048
HDL-C (mmol/L)	0.98 (0.89–1.24)	1.09 (0.9–1.39)	.205	1.04 (0.75–1.31)	1.04 (0.83–1.22)	1	0.69 (0.36–0.91)	0.6 (0.37–0.97)	1
LDL-C (mmol/L)	2.08 (1.8–2.79)	2.2 (2.03–2.81)	.263	1.96 (1.47–2.39)	1.8 (1.43–2.775)	.823	1.255 (0.92–1.9)	2.44 (1.89–3.36)	.003
Apo A1 (g/L)	1.09 (0.88–1.32)	1.13 (0.95–1.31)	.807	0.965 (0.75–1.245)	0.945 (0.82–1.1)	.711	0.515 (0.46–0.77)	0.665 (0.42–0.73)	.746
Apo B (g/L)	0.66 (0.52–0.91)	0.74 (0.66–0.9)	.462	0.675 (0.485–0.885)	0.73 (0.68–0.86)	.343	0.5499995 (0.37–0.73)	0.775 (0.62–0.95)	.041

AFP = alpha-fetoprotein, AKP = alkaline phosphatase, ALB = albumin, ALT = alanine transaminase, Apo A1 = Apollpoprotein A-1, Apo B = Apollpoprotein B, AST = aspartate transaminase, CHE = cholinesterase, CREA = creatinine, DB = direct bilirubin, GGT = γ-glutamyltranspeptadase, GLOB = globulin, GLU = glucose, HDL-C = high-density lipoprotein cholesterol, INR = international normalized ratio, LDL-C = low-density lipoprotein cholesterol, PTA = prothrombin time activity, TB = total bilirubin, TBA = total bile acids, TC = total cholesterol, TG = total triglycerides.

Table 4

Comparison of the difference of liver function in patients with hepatocellular carcinoma according to Barcelona staging.

	Stage A	Stage B	Stage C	Stage D	
	HCC-1 (n = 33)	HCC-2 (n = 13)	HCC-3 (n = 21)	HCC-4 (n = 13)	*P*
ALT (U/L)	35.1 (26.6–59.5)	29.7 (23.2–36.1)	38.1 (30.5–87.5)	48.3 (36.5–71.8)†	.120
AST (U/L)	40.6 (31.1–82.5)	44.2 (32.7–66)	64.6 (36.1–128.6)	161.9 (69.5–236.2)*,†,‡	.001
TB (μmol/L)	21.7 (15.7–36.2)	21.7 (18.8–34.8)	24.7 (19.9–30.7)	38.9 (27.1–145.2)*,†,‡	.035
DB (μmol/L)	7 (5.1–13.5)	7.2 (5.7–14)	8.4 (4.4–13.3)	24.4 (14.2–75)*,†,‡	.008
ALB (g/L)	35.9 ± 5.08	34.28 ± 4.08	37.6 ± 6.38	32.03 ± 5.37*,‡	.065
GLOB (g/L)	29.24 ± 5.5	28.45 ± 5.59	28.56 ± 4.79	31.07 ± 4.2	.299
GGT (U/L)	69.85 (39–183)	81.5 (53.9–156.5)	178.5 (63.6–259)	401.8 (163.8–505)*,†,‡	.005
AKP (U/L)	115.35 (75.75–140.35)	79.3 (65.4–185.1)	138.1 (91.3–252.9)	230.1 (162.1–355.1)*,†,‡	.002
CHE (U/L)	3648 (2456–5224)	2973 (2157–4272)	4786 (3227–6811)	1951 (1495–2656)*,†,‡	.001
TBA (μmol/L)	16.4 (7.7–39.1)	19.7 (13.4–37.4)	13.9 (7.2–31.8)	103.3 (57.1–167.1)*,†,‡	<.001
GLU (mmol/L)	5.21 ± 1.36	5.61 ± 1.19	5.53 ± 2.87	4.9 ± 1.11	.284
PTA (%)	79.82 ± 19.6	79.31 ± 14.3	84.9 ± 11.38	75.08 ± 14.22‡	.310
INR	1.19 ± 0.19	1.16 ± 0.16	1.1 ± 0.12	1.24 ± 0.16‡	.142
AFP (ng/mL)	27.87 (5.62–483.6)	16.75 (7.64–9240)	67.96 (2.69–8836)	926.2 (134.4–9418)*	.080
TG (mmol/L)	0.825 (0.67–1.1)	0.81 (0.595–1.13)	0.915 (0.625–1.14)	0.97 (0.68–1.23)	.772
TC (mmol/L)	3.77 (3.22–4.31)	4.02 (3.43–4.19)	4.41 (3.42–4.79)	3.68 (3.01–4.86)	.455
HDL-C (mmol/L)	1.09 (0.83–1.34)	1.01 (0.74–1.26)	1.09 (0.92–1.35)	0.6 (0.37–0.97)	.010
LDL-C (mmol/L)	2.045 (1.375–2.775)	2.14 (1.905–2.465)	2.435 (2.02–3.35)	2.41 (1.89–3.36)	.177
Apo A1 (g/L)	1.085 (0.875–1.26)	0.865 (0.685–1.155)	1.02 (0.855–1.165)	0.64 (0.42–0.73)	<.001
Apo B (g/L)	0.71 (0.635–0.895)	0.72 (0.58–0.76)	0.75 (0.68–1.01)	0.78 (0.66–0.95)	.477

AFP = alpha-fetoprotein, AKP = alkaline phosphatase, ALB = albumin, ALT = alanine transaminase, Apo A1 = Apollpoprotein A-1, Apo B = Apollpoprotein B, AST = aspartate transaminase, CHE = cholinesterase, CREA = creatinine, DB = direct bilirubin, GGT = γ-glutamyltranspeptadase, GLOB = globulin, GLU = glucose, HDL-C = high-density lipoprotein cholesterol, INR = international normalized ratio, LDL-C = low-density lipoprotein cholesterol, PTA = prothrombin time activity, TB = total bilirubin, TBA = total bile acids, TC = total cholesterol, TG = total triglycerides.

* compared to HCC-1, $P < .05$.

† compared to HCC-2, $P < .05$.

‡ compared to HCC-3, $P < .05$.

($P = .120$) and AST ($P = .001$) elevated, TB ($P = .035$) and DBil ($P = .008$) increased, ALB ($P = .065$) and CHE ($P = .001$) decreased, PTA ($P = .310$) reduced, while TC and LDL-C increased. Meanwhile, the indicators of liver synthetic functions improved in the HCC-3 group, which meant that ALB, CHE, and PTA increased, while INR decreased. Nevertheless, the above indicators were worse in the HCC-4 group. GGT and AKP increased significantly in the HCC-3 and HCC-4 groups compared to the HCC-1 and HCC-2 groups ($P < .05$).

3.3. Indicators of energy metabolism

Table 5 shows the indicators for energy metabolism between the 2 groups. Compared to the LC group, in the HCC group, both REE (kcal/d) and REE% were lower, but without significant difference (1396.93 ± 332.62 kcal/d vs 1468.4 ± 355.31 kcal/d, $P = .199$; 95.58 ± 19.65% vs 96.12 ± 18.99%, $P = .863$), RQ was lower (0.83 ± 0.07 vs 0.85 ± 0.08, $P = .073$), CHO% was lower (35.5 (27–51)% vs 49 (31–62)%, $P = .013$), FAT% was higher (41 (29–58)% vs 33 (18–52)%, $P = .030$), and RPO% was slightly higher (18.5 (13–24)% vs 18 (14–24)%, $P = .946$). The results suggest that patients in the HCC and LC groups had normal energy metabolism, but the proportions of the 3 major nutrients in the HCC group were unbalanced, and fat oxidation was the main energy supply.

Table 6 shows the differences in indicators of energy metabolism for patients in the HCC group with different Child-Pugh grades. The results showed that with the deterioration of liver functions, although MREE showed a progressive increasing trend (1380.82 ± 333.21 vs 1401.15 ± 336.91 vs

Table 5

Comparison of energy metabolism indexes between the 2 groups.

	LC (n = 75)	HCC (n = 80)	*P*
MREE (kcal/d)	1468.4 ± 355.31	1396.93 ± 332.62	.199
PREE (kcal/d)	1530.41 ± 220.97	1471.2 ± 234.32	.108
REE%	96.12 ± 18.99	95.58 ± 19.65	.863
RQ	0.85 ± 0.08	0.83 ± 0.07	.073
CHO (%)	49 (31–62)	35.5 (27–51)	.013
CHO (kcal/d)	609 (389.3–811.72)	471.245 (340.48–695.83)	.028
FAT (%)	33 (18–52)	41 (29–58)	.030
FAT (kcal/d)	449 (272.8–695.75)	568.875 (372.47–820.215)	.100
PRO (%)	18 (14–24)	18.5 (13–24)	.946
PRO (kcal/d)	246.7 4 (189.28–297.7)	254.13 (169.585–328.82)	.957

CHO% = carbohydrate oxidation rate, CHO = carbohydrate oxidation, FAT% = fat oxidation rate, FAT = fat oxidation, MREE = resting energy consumption, PREE = predict rest energy expenditure, PRO% = protein oxidation rate, PRO = protein oxidation, RQ = respiratory quotient.

Table 6

Comparison of energy metabolism among different Child-Pugh grades in patients with carcinoma.

	HCC-A (n = 33)	HCC-B (n = 33)	HCC-C (n = 14)	*P*
MREE (kcal/d)	1380.82 ± 333.21	1401.15 ± 336.91	1424.93 ± 343.62	.991
PREE (kcal/d)	1486.73 ± 207.8	1471.48 ± 273.85	1433.93 ± 201.66	.566
REE%	93.28 ± 19.98	96.57 ± 21.28	98.67 ± 14.97	.582
RQ	0.85 ± 0.06	0.82 ± 0.07	0.8 ± 0.08	.085
CHO (%)	39 (33–58)	34 (26.5–48)	28 (21–49)	.097
CHO (kcal/d)	510.68 (435.93–856.66)	455.7 (329.42–637)	354.4 (290.6–573.6)	.102
FAT (%)	40 (24–52)	41 (29–59)	55.5 (34–70)	.150
FAT (kcal/d)	499.32 (280.63–742.8)	579.15 (462.56–816)	738.44 (452.4–1017.1)	.173
PRO (%)	19 (13–26)	16 (13–24)	19.5 (14–24)	.984
PRO (kcal/d)	253.5 (171.73–339.71)	239.52 (172.05–308.64)	290.2 (167.44–331.44)	.850

CHO% = carbohydrate oxidation rate, CHO = carbohydrate oxidation, FAT% = fat oxidation rate, FAT = fat oxidation, MREE = resting energy consumption, PREE = predict rest energy expenditure, PRO% = protein oxidation rate, PRO = protein oxidation, RQ = respiratory quotient.

1424.93 ± 343.62). RQ gradually decreased (0.85 ± 0.06 vs 0.82 ± 0.07 vs 0.80 ± 0.08, *P* = .085). CHO% gradually decreased (39 (33–58)% vs 34 (26.5–48)% vs 28 (21–49)%, *P* = .097), while FAT% gradually increased (40 (24–52)% vs 41 (29–59)% vs 55.5 (34–70)%, *P* = .150). Although there was no significant difference, the trend was significant, suggesting that with the aggravation of liver damage, metabolism disorder of the 3 major nutrients was further aggravated, glucose oxidation decreased, while energy supply by fat oxidation increased, and nutritional status of the patients worsened.

Table 7 shows the differences in the indicators of energy metabolism based on BCLC staging. With the worsening of tumor stages, REE% decreased, which increased in HCC-4 group (96.6 ± 18.92% vs 93.62 ± 15.32% vs 92.16 ± 25.77% vs 100.46 ± 13.93%, *P* = .708). RQ decreased (0.84 ± 0.05 vs 0.79 ± 0.08 vs 0.84 ± 0.06 vs 0.81 ± 0.08). CHO% decreased (36 (32–51)% vs 28.5 (20–41)% vs 36 (28–54)% vs 29 (24–50)%). FAT% increased (38 (29–53)% vs 53 (43–67)% vs 40 (28–53)% vs 55 (34–60)%). Compared to the HCC-1 group, RQ, CHO%, and FAT% in the HCC-2 group were significantly different (*P* < .05). Meanwhile, we also found that the above indicators in the HCC-3 group were on the opposite, which meant that RQ and CHO% increased, while FAT% decreased, suggesting that HCC patients in grade D showed a high metabolic state. With the worsening of tumor stages, energy supply by fat oxidation became more and more important. Nevertheless, energy metabolism of HCC patients at grade C improved and energy supply by glucose oxidation increased, which were considered to be associated with the improvement of liver functions of patients at this stage.

3.4. Relationship of liver functions with energy metabolism in HCC patients

Table 8 shows the correlation between liver functions and energy metabolism in HCC patients. AST was negatively correlated with CHO% (r = −0.17067, *P* = .0362) and CHO (r = −0.16372, *P* = .0418). GGT was negatively correlated with CHO (r = −0.20043, *P* = .0127). AKP was negatively correlated with RQ (r = −0.26110, *P* = .0011), CHO% (r = −0.26461, *P* = .0011), and CHO (r = −0.23134, *P* = .0039), while positively correlated with FAT% (r = 0.21629, *P* = .0071) and FAT (r = 0.19526, *P* = .0152). CHE was positively correlated with RQ (r = 0.21393, *P* = .0075), CHO% (r = 0.16206, *P* = .0468), while negatively correlated with FAT% (r = −0.20454, *P* = .0107) and FAT (r = −0.18409, *P* = .0219). TBA was negatively correlated with RQ (r = −0.17568, *P* = .0293) and CHO (r = −0.16841, *P* = .0368), while positively correlated with FAT (r = 0.15987, *P* = .0476). TC was positively correlated with PRO% (r = 0.41659, *P* = < .0001) and PRO (r = 0.30928, *P* = < .0001).

Table 7

Comparison of energy metabolism in different stages of liver cancer according to Barcelona staging.

	Stage A	Stage B	Stage C	Stage D	
	HCC-1	HCC-2	HCC-3	HCC-4	*P*
MREE (kcal/d)	1482.64 ± 311.17	1334.92 ± 230.61	1267.86 ± 381*	1449.85 ± 344.24	.060
PREE (kcal/d)	1552.33 ± 261.16	1436.15 ± 178.34	1389.76 ± 206.51*	1431.85 ± 209.73	.100
REE%	96.6 ± 18.92	93.62 ± 15.32	92.16 ± 25.77	100.46 ± 13.93	.708
RQ	0.84 ± 0.05	0.79 ± 0.08*,†	0.84 ± 0.06	0.81 ± 0.08	.082
CHO (%)	36 (32–51)	28.5 (20–41)*	36 (28–54)	29 (24–50)	.170
CHO (kcal/d)	545.24 (462.4–738.09)	344 (221.34–477.28)	435.93 (329.42–777.6)	358.8 (305.37–573.6)	.026
FAT (%)	38 (29–53)	53 (43–67)	40 (28–53)	55 (34–60)	.094
FAT (kcal/d)	525.54 (380.4–801.15)	684.64 (552.98–910.53)*	460.65 (217.93–713.34)	669.76 (452.4–1017.1)	.183
PRO (%)	17 (12–27)	15 (13–22)	19 (15–23)	20 (14–24)	.802
PRO (kcal/d)	254.76 (166.18–344.6)	192.64 (161.85–282.26)	238.51 (172.05–290.7)	305.4 (195.14–331.44)	.460

CHO% = carbohydrate oxidation rate, CHO = carbohydrate oxidation, FAT% = fat oxidation rate, FAT = fat oxidation, MREE = resting energy consumption, PREE = predict rest energy expenditure, PRO% = protein oxidation rate, PRO = protein oxidation, RQ = respiratory quotient.

* represents compared to HCC-1 group, *P* < .05.

† represents compared to HCC-3, *P* < .05.

Table 8

Correlations between energy metabolism and liver function in patients with carcinoma.

	RQ	CHO (%)	CHO	FAT (%)	FAT	PRO (%)	PRO
ALT							
r	−0.06356	−0.08202	−0.09778	0.07357	0.03845	−0.00919	−0.01359
P	0.4320	0.3167	0.2261	0.3629	0.6348	0.9102	0.8668
AST							
r	−0.14293	−0.17067	−0.16372	0.11096	0.12109	0.11249	0.13054
P	0.0760	0.0362	0.0418	0.1693	0.1334	0.1662	0.1054
ALB							
r	0.14363	0.11030	0.08330	−0.13313	−0.13829	−0.00216	−0.05576
P	0.0746	0.1776	0.3028	0.0987	0.0862	0.9789	0.4908
GLOB							
r	0.07104	0.05229	0.12367	−0.08687	−0.03154	0.10165	0.17807
P	0.3797	0.5237	0.1252	0.2825	0.6968	0.2112	0.0266
GGT							
r	−0.15020	−0.15154	−0.20043	0.12442	0.11720	0.08072	0.08314
P	0.0630	0.0641	0.0127	0.1242	0.1478	0.3229	0.3053
AKP							
r	−0.26110	−0.26461	−0.23134	0.21629	0.19526	0.11235	0.14515
P	0.0011	0.0011	0.0039	0.0071	0.0152	0.1682	0.0725
CHE							
r	0.21393	0.16206	0.14596	−0.20454	−0.18409	0.02090	0.00690
P	0.0075	0.0468	0.0700	0.0107	0.0219	0.7976	0.9321
TBA							
r	−0.17568	−0.09234	−0.16841	0.14617	0.15987	−0.01644	−0.01324
P	0.0293	0.2611	0.0368	0.0705	0.0476	0.8407	0.8706
PTA							
r	0.10386	0.04883	−0.01120	−0.10463	−0.12246	0.07015	0.00032
P	0.1984	0.5516	0.8900	0.1951	0.1290	0.3889	0.9969
INR							
r	−0.07199	0.02226	0.03174	0.07201	0.10442	−0.10367	−0.05262
P	0.3734	0.7862	0.6951	0.3733	0.1960	0.2022	0.5155
AFP							
r	−0.01863	−0.03226	−0.00717	0.04846	0.02832	−0.08781	−0.05880
P	0.8180	0.6941	0.9295	0.5493	0.7265	0.2804	0.4674
TG							
r	−0.03914	−0.09047	−0.10444	0.06044	0.12924	0.04029	0.01410
P	0.6333	0.2758	0.2019	0.4610	0.1137	0.6256	0.8636
TC							
r	0.06979	−0.00918	−0.06647	−0.11413	−0.09971	0.41659	0.30928
P	0.3882	0.9109	0.4112	0.1573	0.2171	<.0001	<.0001
HDL-C							
r	−0.00207	0.02623	−0.03511	−0.01530	−0.01398	−0.00065	−0.00156
P	0.9800	0.7550	0.6718	0.8535	0.8661	0.9937	0.9850
LDL-C							
r	0.07227	−0.01630	−0.09915	−0.07801	−0.09223	0.12751	0.04402
P	0.3778	0.8447	0.2258	0.3410	0.2600	0.1212	0.5915
Apo A1							
r	0.14133	0.07534	0.06799	−0.16871	−0.15623	0.12911	0.18817
P	0.0845	0.3661	0.4084	0.0390	0.0562	0.1178	0.0211
Apo B							
r	0.04175	−0.02707	−0.06050	−0.05147	0.01136	0.13856	0.13050
P	0.6132	0.7465	0.4636	0.5330	0.8906	0.0942	0.1127

AFP = alpha-fetoprotein, AKP = alkaline phosphatase, ALB = albumin, ALT = alanine transaminase, Apo A1 = Apollpoprotein A-1, Apo B = Apollpoprotein B, AST = aspartate transaminase, CHE = cholinesterase, CHO% = carbohydrate oxidation rate, CHO = carbohydrate oxidation, CREA = creatinine, DB = direct bilirubin, FAT% = fat oxidation rate, FAT = fat oxidation, GGT = γ-glutamyltranspeptadase, GLOB = globulin, GLU = glucose, HDL-C = high-density lipoprotein cholesterol, INR = international normalized ratio, LDL-C = low-density lipoprotein cholesterol, PRO% = protein oxidation rate, PRO = protein oxidation, PTA = prothrombin time activity, RQ = respiratory quotient, TB = total bilirubin, TBA = total bile acids, TC = total cholesterol, TG = total triglycerides.

4. Discussion

In this study, the Child-Pugh scores were not statistically different between the HCC and LC groups, but ALB, CHE, TC, PTA, and INR in the HCC group were higher compared to the LC group, suggesting that the liver synthetic function was better in the HCC group. With the aggravation of liver damage, liver functions of the HCC group were still better than in the corresponding LC groups. An early study by Guglielmi et al[12] also revealed that ALB levels in the HCC group were high. It is well known that ALB levels are associated with prognosis,[21] which explains why it can be observed that the prognosis of some patients with HCC is better than for patients with cirrhosis.

About 75% of TC is synthesized by the liver. LDL-C is the lipoprotein with the highest cholesterol content. LDL-C is mainly synthesized by liver cells and its structural protein is apolipoprotein B. The levels of cholesterol and lipoprotein reflect the function of hepatocyte synthesis.[22] Previous studies have shown that secretion of liver cholesterol and lipoprotein decrease with the progression of cirrhosis.[23] In this study, TC, LDL-C, and ApoB in the HCC group were higher than in the LC group, suggesting that the synthetic function of liver was better in the HCC group.

In the present study, GGT and AKP in the HCC group were higher than in the LC group, suggesting that GGT and AKP can be used as predictors of hepatocellular carcinoma.[24,25] Serum GGT is mainly derived from the hepatobiliary system. Therefore, serum GGT increases when bile acid synthesis increases or bile excretion is blocked. In this study, GGT was higher in the HCC group, while TB and TBA were lower, which were considered to be caused by secretion of HCC instead of non-tumor invasion of biliary tract or disorder of biliary excretion. Previous studies have shown that HCC cells can secrete GGT.[26,27] Since the reverse differentiation of cancer cells is like the embryonic stage (the GGT content in the embryonic liver cells is about 30 times that of adulthood), the production of GGT increases. Meanwhile, the cancer tissue itself or surrounding inflammatory stimuli enhance the permeability of the liver cell membrane. Therefore, blood GGT is further elevated. Studies have shown that GGT levels are associated with the prognosis of HCC and cirrhosis.[28–30]

AKP is a marker of liver or bone diseases,[30] and is also associated with cancer.[31] Increased AKP is associated with worsening prognosis of HCC.[32] In this study, AKP in the HCC group was significantly higher than in the LC group, and with the progression of tumor stages, both AKP and GGT gradually increased, thus reflecting the occurrence and progression of HCC.

As what was found in our study, some indicators of liver synthetic function were better in the HCC group compared to the LC group, especially in patients with Child-Pugh grade C, suggesting that HCC cells may have the effect of compensating liver function deficits in patients with cirrhosis. For large hepatocellular carcinoma, if the tumor is removed, the compensation mechanism disappears and liver function deteriorates. Because of the compensation mechanism of HCC, the true liver functions before surgery are covered for this part of patients with cirrhosis, resulting in an illusion of good functions. Therefore, in clinical practice, we can observe that some patients with large HCC develop liver failure after surgery, and the condition deteriorates sharply. It has been confirmed that cancer cells can have certain properties of the source cells.[27] For example, keratin can still be synthesized in epithelial cancers and the HCC cells can express hepatocyte markers in the embryonic stage such as AFP, EP-CAM, and CK8. Cancer cells, especially those mature cells in the final stage of differentiation, can express metabolites of normal liver cells such as ALB and GGT. The metabolites they produce also play their corresponding role in the body, thereby compensating for the dysfunction of hepatocytes during cirrhosis. It has been reported that there are frequent cell communication between HCC cells and normal liver cells, and there is bi-directionality in their communication.[33] HCC cells have a mechanism that allows them to function as part of normal liver cells, compensating for the dysfunction caused by excessive cirrhosis and necrotic cells.

Energy metabolism refers to the energy production and utilization process of nutrients (mainly glucose, fat, and protein) in the body. Because measurement of REE is convenient and practical and can reflect the total energy consumption of the body every day, it is a common indicator for clinical study of human metabolic consumption. At present, there are few studies on energy metabolism of liver cirrhosis and related HCC using a metabolic cart. Previous studies have shown that patients with cirrhosis have low metabolism, characterized by low CHO% and with proteins as the main energy supply.[1–4] It is still controversial whether the reduction or increase of REE is correlated with cirrhosis,[34–36] but non-protein RQ is associated with the prognosis of liver cirrhosis[37] and HCC.[38,39] Previous studies by Wu et al[40] showed that patients with malignant tumors were not in a state of high metabolism, 24% of patients with malignant tumors were in low metabolic state, 46% of patients with malignant tumors were in normal metabolic state, and 30% of patients with malignant tumors were in high metabolic state. In this study, metabolic carts were used to analyze the energy metabolism of patients in the LC and HCC groups. The results showed that both HCC and LC patients had a normal metabolic state. REE and REE% in HCC patients were slightly lower compared to LC patients, but there was no significant difference for REE and REE%. REE% was significantly higher in patients with large HCC and there was high metabolism, suggesting that energy metabolism was related to liver functions and tumor size. Previous studies have shown that CHO% decreases with the aggravation of cirrhosis, while PRO% increases.[1–4,34] In this study, CHO% of both groups showed a decreasing trend, which decreased more significantly in the HCC group. Nevertheless, FAT% increased, suggesting that energy supply of the 3 major nutrients changed in the HCC group, which was mainly fat oxidation. Moreover, with the deterioration of liver functions, RQ and CHO% progressively decreased in the HCC group, while FAT% progressively increased, suggesting that with the destruction of tumor cells to liver tissue, the energy supply pattern by glucose oxidation of liver cells gradually changed to energy supply pattern by fat oxidation of tumor cells. The results of the BCLC staging showed that with the progression of tumor stages, RQ and CHO% decreased in patients with HCC, while FAT% increased, suggesting that tumor progression aggravated malnutrition. There was significant change in the HCC-2 group compared to the HCC-1 group, suggesting that increase in the number and size of tumors led to liver damage and poor energy metabolism. Indicators of energy metabolism were especially deteriorated in the HCC-4 group, which was consistent with the significant deterioration of liver functions in the HCC-4 group. Nevertheless, changes in the indicators for energy metabolism in the HCC-3 group showed the opposite, which was considered to be because patients suffered from vascular invasion and metastasis of tumor during the period, thus the tumor was strong, the number of tumor cells was higher, and functions also increased significantly. Therefore, performance of liver functions was improved. Improved liver functions resulted in the improvement of energy metabolism, but destruction of liver by tumor still aggravated. Thus, when tumor progressed to a certain degree, there would be deterioration of liver functions, as well as deterioration of energy metabolism, thus entering stage 4. Therefore, it suggested that the seemingly good indicators of liver functions do not represent truly good hepatocyte functions. The selection of clinical treatment options can not only refer to the indicators of liver functions, which should be evaluated comprehensively, and appropriate treatment plan should be adopted. Based on our findings, it could be recommended that

active nutritional intervention should be performed starting from patients at BCLC2 stage to improve liver functions, thus improving nutritional status and prognosis of the patients.

Although RQ in the LC and HCC groups was basically normal, the proportions of the 3 major nutrients were inconsistent with that of normal people, manifesting as significant increase in fat oxidation and significant decrease in carbohydrate oxidation, which was consistent with previous studies.[41,42] Changes of energy metabolism were similar to starvation condition, which may result in malnutrition. HCC was worse than cirrhosis, glucose oxidation was lower and fat oxidation was higher, thus aggravating fat decomposition and malnutrition. In patients with cancer, energy metabolism had its particularity due to the growth of tumors and metabolic changes in the body. A large number of studies in the 20th century demonstrated that resting energy metabolic rate of patients with malignant tumors was significantly higher than the predicted value and healthy control population. Nevertheless, some scholars in more recent years believe that resting energy expenditure of patients with malignant tumors does not increase significantly, but the body composition can be changed, manifesting as excessive fat consumption, emaciation, and even cachexia. The different cell proliferation cycles of tumor tissue can affect the metabolic process of various nutrients in the body, thus affecting the energy consumption of the body.

In this study, liver functions of patients with HCC improved compared to the LC group, but indicators of energy metabolism did not improve significantly. Moreover, with the progression of BCLC staging and aggravation of liver functions, energy metabolism deteriorated. Although HCC can improve the efficiency of glucose utilization through the glycolysis pathway, it cannot offset the reduction of RQ due to the consumption of lipids and proteins. In addition, HCC metabolic reprogramming may interfere with the pathways of glucose metabolism in other organs, which further reduces CHO%.[43,44] Although hepatocellular carcinoma cells have the function of hepatocyte synthesis, they still consume nutrients and cannot improve the nutritional metabolism of patients. With the progression of tumors, the limited anabolic function cannot offset the damage caused by the tumor, resulting in severe malnutrition and even dyscrasia, aggravating liver damage, and finally leading to death. This study demonstrated that indicators of liver functions (AST, CHE, GGT, AKP, TBA, and TC) in patients with HCC were correlated with indicators of energy metabolism. CHE was positively correlated with RQ and CHO%, while GGT and AKP were negatively correlated with CHO. Therefore, monitoring of the above indicators may have guiding significance for tumor progression and nutritional therapy in patients.

5. Conclusions

In summary, this study found that patients in the HCC group had improved function of hepatocyte synthesis (ALB, TC, LDL-C, GGT, PTA, INR) than those in the LC group, suggesting that hepatocellular carcinoma cells may have function of hepatocyte synthesis, and partly compensate liver function deficits in cirrhosis. Therefore, patients with cirrhosis accompanying by hepatocellular carcinoma needed to correctly evaluate the true liver functions after removal of the tumor. Liver functions should not be evaluated simply based on Child-Pugh classification. Blind resection of large tumors may lead to liver function deterioration postoperatively. In the absence of proper treatment, "coexistence with cancer" may be a better choice. In this study, it was found that fat oxidation was the main energy supply for HCC patients. With tumor progression, liver functions deteriorated and energy metabolism worsened. However, indicators of liver functions were correlated with indicators of energy metabolism. In particular, CHE was positively correlated with CHO% and negatively correlated with FAT%. Therefore, patients with hepatocellular carcinoma should be actively supplied with nutrients in order to improve liver functions and nutritional status, thus the patients can obtain treatment opportunity and survival time of patients can be prolonged.

This study still had certain limitations. Firstly, this study was a retrospective single-center study, which was limited to the available data in medical charts. In addition, there was no follow-up, thus the long-term results cannot be obtained, such as survival time. In addition, the theory of "liver function compensation" of hepatocellular carcinoma cells still needed to be further investigated by large samples and basic research.

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