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# Nutritional Status in Liver Cirrhosis

Kazuyuki Suzuki, Ryujin Endo and Akinobu Kato

Additional information is available at the end of the chapter

## Abstract

The metabolism of many nutritional elements (carbohydrate, protein, fat, vitamins, and minerals) is gradually disturbed with progressive chronic liver diseases. In particular, protein-energy malnutrition (PEM) is known as the most characteristic manifestation of liver cirrhosis (LC) and is closely related to its prognosis. Recently, while sarcopenia (loss of muscle mass and strength or physical performance) has been discussed as an independent factor associated with prognosis in patients with LC, obesity and insulin resistance in patients with LC also contribute to carcinogenesis in LC. Deficiencies of zinc and carnitine are involved in the malnutrition in LC and are associated with hyperammonemia, which is related to the pathogenesis of hepatic encephalopathy. Because the nutritional and metabolic disturbances in LC are fundamentally influenced by many factors, such as the severity of liver damage, the existence of portal-systemic shunting, and inflammation, proper nutritional assessment is necessary for the nutritional management of patients with LC.

**Keywords:** liver cirrhosis, malnutrition, protein-energy malnutrition, sarcopenia, glucose intolerance

## 1. Introduction

The liver plays a central role in the metabolism of many nutritional elements (carbohydrate, protein, fat, vitamins, and minerals). The metabolism of these nutritional elements is gradually disturbed with progressive chronic liver disease. Protein-energy malnutrition (PEM) is the most characteristic manifestation and is closely related to the prognosis and the quality of life in liver cirrhosis (LC) [1–7]. PEM can lead to muscle atrophy and reduced strength [8–12],

which is defined as sarcopenia and has recently been considered an independent prognostic factor in LC with PEM [13–16], while overweight or obesity has been seen as one of the important factors related to carcinogenesis in LC [17]. The relationships among PEM, sarcopenia, and prognosis in LC are shown in **Figure 1**. Furthermore, glucose intolerance or diabetes mellitus (DM) is also an independent factor related to carcinogenesis in LC [18–23]. Serum zinc (Zn) and carnitine (CA) status are involved in the malnutrition in LC and are associated with hyperammonemia, which is related to the pathogenesis of hepatic encephalopathy (HE) [24–31].

Malnutrition in LC is affected by many factors, such as the severity of liver damage, the existence of portal-systemic shunting, and inflammation [10, 32]. Therefore, for the proper nutritional management of patients with LC, precise nutritional assessment is needed.
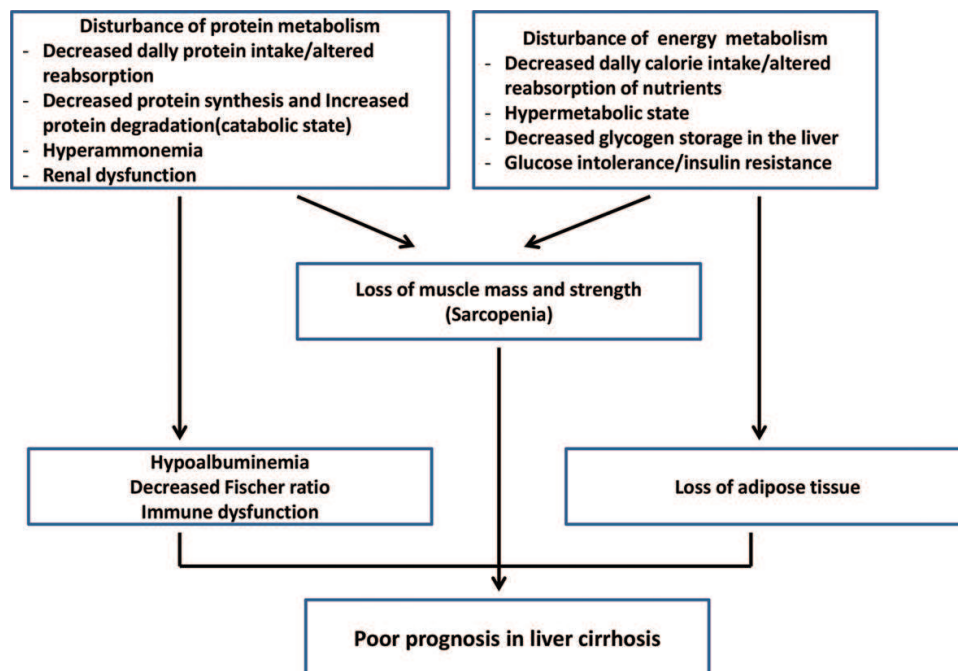


**Figure 1.** Relationships among protein-energy malnutrition, sarcopenia, and prognosis in liver cirrhosis patients.

This chapter focuses on the association between nutritional assessment and malnutrition in patients with LC.

## 2. Nutritional assessments

Recommended nutritional assessments in patients with LC are shown in **Table 1**. Static and dynamic status of nutrition should be necessary. Dietary assessment by a skilled dietitian is the first step in assessing nutritional status. Simple and easy applied methods, such as the subjective global assessment (SGA), mini nutritional assessment (MNA), and anthropometric parameters, are recommended in the assessment of nutritional status [32]. Biomarkers representing serum albumin (Alb) are important to assess nutritional status. However, because many biomarkers

1. **Static status of nutrition**

    a.  Daily food intake

    b.  Body composition analysis

        Height, body weight, body mass index, anthropometric parameters,

        bioelectrical impedance analysis (BIA)

    c.  Biomarkers

        Red blood cell count, hemoglobin, routine liver function tests, cholesterol, cholinesterase, albumin, rapid turnover proteins, adipocytokines (adiponectin, leptin, resistin, etc.), tumor necrosis factor-$\alpha$, ghrelin, vitamins, minerals, creatinine height index in urine

    d.  Immune reaction

        Total lymphocyte count, delated cutaneous hypersensitivity, purified protein derivate of tuberculin

    e.  Imaging

        Computer tomography (abdomen)

2. **Dynamic status of nutrition**

    a.  Energy metabolism using indirect calorimetry

    b.  Nitrogen balance

    c.  Biomarkers: plasma free amino acids pattern (Fischer ratio and BTR[*])

    d.  Urinary 3-methylhistidine excretion

[*]Fischer ratio, branched chain amino acids (BCAA)/phenylalanine + tyrosine; BTR, BCAA/tyrosine ratio.

Table 1. Recommended nutritional assessment in patients with liver cirrhosis.

are often affected by complications such as infection and renal dysfunction, the data must be carefully interpreted. Energy metabolism assessment (e.g., resting energy expenditure (REE), nonprotein respiratory quotient (npQR), and substrate oxidation rates for glucose, protein, and fat) using indirect calorimetry is the most useful method to assess whether patients with LC have PEM [32–35]. However, this method cannot be used routinely and easily to examine outpatients, because the indirect calorimeter has a high cost, and it takes time to perform the test.

## 2.1. Changes of body composition

Analysis of body composition includes height, body weight, body mass index (BMI), and anthropometric parameters. Anthropometric parameters include percent ideal body weight (IBM), triceps skin fold thickness (TSF), arm circumference (AC), and arm muscle circumference (AMC). Among these parameters, TSF and AMC are significantly correlated with muscle volume or the volume of total body fat mass [34, 35]. However, these parameters cannot be accurately estimated in patients with LC who have edema and/or ascites. Recently, new methods of body mass composition analysis using computer tomography and bioelectrical impedance analysis have been developed in daily clinical practice, but this method also cannot provide accurate results in patients with LC who have edema and/or ascites [12–14].

In various chronic liver diseases including LC, several previous reports have shown skeletal muscle loss using anthropometric parameters [1–4, 11]. This status has recently been defined

as sarcopenia, which shows loss of muscle mass and muscle strength or physical performance [8–12]. Although multiple factors, including differences in the etiology of LC, duration of disease, and the severity of liver damage, are related to the prevalence of sarcopenia in LC, sarcopenia is seen in approximately 30–70% of patients with LC [11–14, 35]. Additionally, a recent study showed that sarcopenia is a risk factor for recurrence in LC patients with hepatocellular carcinoma who undergo curative treatment [14].

Muscle mass is the result of a dynamic balance between protein synthesis and degradation [36–39]. This balance is regulated by two major branches of AKT (also known as protein kinase B) signaling pathways: the AKT/mammalian target of rapamycin (mTOR) pathway that controls protein synthesis and the AKT/forkhead box O (FOXO) pathway that controls protein degradation. Recent reports have shown that myostatin, a member of the transforming growth factor-β superfamily, has emerged as a key regulator of skeletal muscle mass [39]. Myostatin is also a key mediator between energy metabolism and endurance capacity of skeletal muscle [37–39].

On the other hand, the prevalence of LC patients with obesity has increased in the last decade [17]. The definition of obesity is different between Japan and European countries (body mass index (BMI) ≥ 25 kg/m$^2$ in Japan and ≥30 kg/m$^2$ in European countries). Obesity in patients with LC is associated with insulin resistance, which has been discussed as an important factor in carcinogenesis in LC [17–22].

### 2.2. Changes of biomarkers

Serum Alb is a main secretion protein synthesized by the liver and has multiple functions, such as the maintenance of colloid osmotic pressure, ligand binding and transport, and enzymatic and antioxidative activities [40, 41]. The synthesis and degradation rates of Alb in patients with LC are decreased compared with those in healthy individuals whose liver function is normal. In particular, the half-life of serum Alb is extended in patients with LC [42]. The serum Alb concentration is affected by the volume of daily food intake, digestion and absorption from the intestine, the degree of severity of liver damage, the imbalances of various hormone dynamics, and nutritional and catabolic status, such as that conferred by infections and burns [43]. However, serum Alb concentration is still frequently used as a biomarker of malnutrition and as an item of both the Child-Pugh classification score and the modified end-stage liver disease (MELD) score [44, 45]. Serum Alb is microheterogeneous with oxidized and reduced forms. Serum Alb concentration decreases, while the ratio of oxidized Alb increases, with LC progression [46, 47]. A recent report has shown that this ratio improved in patients with LC after supplemental treatment with a branched-chain amino acid (BCAA; valine, leucine, and isoleucine)-enriched formula [48]. These findings suggest that the oxidative status of serum Alb could provide a better assessment of malnutrition, though the measurement of serum levels of oxidized and reduced forms of Alb is time-consuming and inconvenient in the clinical setting.

Rapid turnover proteins such as transthyretin (prealbumin), retinol-binding protein, and transferrin are useful biomarkers of short-term nutritional status in patients with LC. The half-life time is 2 days for transthyretin, 0.4–0.7 days for retinol-binding protein, and 7–10 days for transferrin [49, 50]. These proteins are also influenced by baseline conditions such as surgery, infection, and

anemia [50]. Recent reports have suggested that serum retinol-binding protein 4 (RBP-4) is a biomarker for assessing malnutrition in patients with LC. Serum RBP-4 levels are decreased in patients with LC and directly related to the severity of liver damage according to the Child-Pugh classification, while these levels are not correlated with insulin resistance [51, 52].

The profiles of plasma amino acids show characteristic changes in patients with LC. In particular, the plasma concentration of BCAAs is decreased, while that of aromatic amino acids (AAA; phenylalanine (Phe) and tyrosine (Tyr)) is increased, resulting in a decreased BCAA/ AAA molar ratio (namely, the Fischer ratio) or the BCAA/Tyr ratio (BTR) [53–55]. BCAA is mainly metabolized and used to detoxify ammonia and for energy production in the skeletal muscle. AAA is metabolized in the liver and is a representative precursor of a neurotransmitter (dopamine) and a pseudo-neurotransmitter (octopamine), which are closely associated with the pathogenesis of HE [53]. The plasma Fischer ratio and serum BTR are significantly correlated with the serum Alb concentration and the severity of liver damage according to the Child-Pugh classification (**Figure 2**), but not with the degree of HE [32, 55]. Furthermore, serum BTR can help predict a decrease in serum Alb concentration associated with chronic liver diseases [56].

Adipocytokines are also biomarkers of nutritional status in patients with LC. Leptin, adipo-nectin, and resistin are representative peptide hormones that are produced by adipose tissue, and they are closely associated with insulin resistance and arteriosclerosis [32]. Serum leptin levels are higher in females than males among healthy individuals and patients with LC. These levels are correlated with AMC and TSF, but they are not correlated with the severity of liver
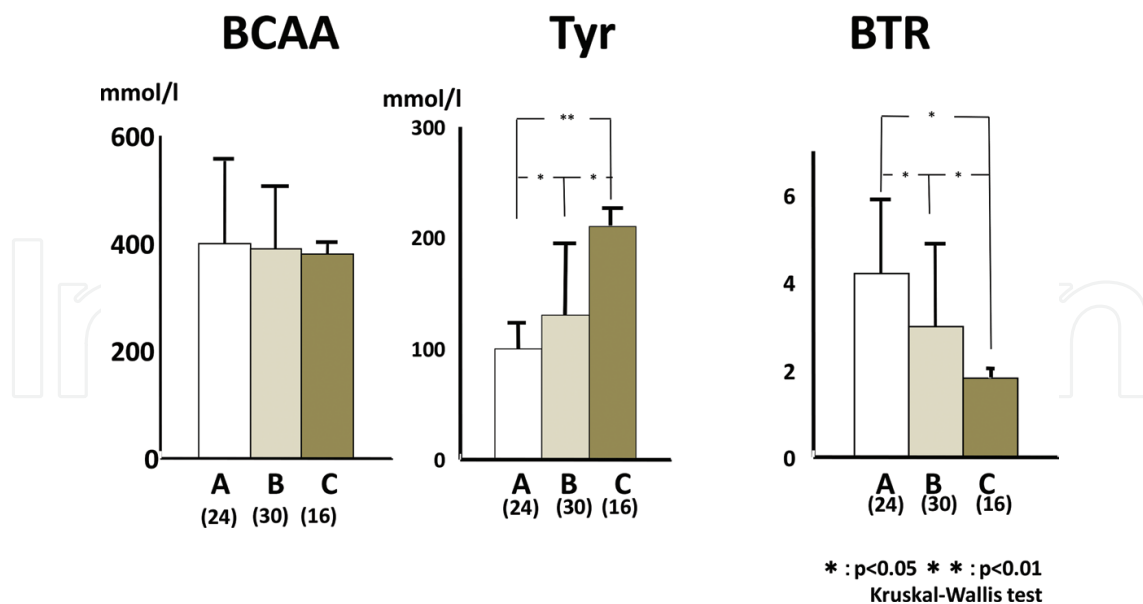


**Figure 2.** Plasma branched-chain amino acids, tyrosine, and the branched-chain amino acid to tyrosine ratio in patients with liver cirrhosis. Seventy cirrhotic patients with or without hepatocellular carcinoma who were admitted to Iwate Medical University Hospital were investigated. Serum amino acid concentrations were measured by an enzymatic method. The severity of liver damage was classified into grades A, B, and C based on the Child-Pugh classification. BCAA, branched-chain amino acid (valine + leucine + isoleucine); BTR, BCAA/tyrosine ratio. Each value is shown as the mean ± standard deviation. *P < 0.05, **P < 0.01 (Kruskal-Wallis test). (), number of patients with LC.

damage [57–59]. Plasma adiponectin assumes three forms: low molecular weight, medium molecular weight, and high molecular weight [60–62]. In patients with LC, the high molecular weight form of plasma adiponectin is significantly increased compared with healthy individuals and is correlated with the severity of liver damage [32, 62]. Plasma resistin levels associated with insulin resistance are also correlated with the severity of liver damage in patients with LC [63, 64].

Ghrelin, an orexigenic hormone and stimulator of growth hormone, is mainly found in the gastric wall [65, 66]. Ghrelin plays a role in the hypothalamic centers to regulate feeding and caloric intake [65–67]. Furthermore, ghrelin controls feeding behavior and the long-term regulation of body weight in association with leptin in the hypothalamic centers [66, 67]. The plasma ghrelin level has been considered a marker of pathological conditions such as obesity, insulin resistance, type 2 DM, and hypertension. However, the plasma ghrelin level in patients with LC was controversial in previous reports [68–70]. Our study has shown that the plasma ghrelin level (desacyl form) is higher in LC patients than in healthy controls, while it is not correlated with the severity of liver damage. Rather, the plasma ghrelin level is significantly correlated with BMI, AMC, TSF, and non-protein respiratory quotient (npRQ) [70].

Vitamins (fat-soluble: A, D, E, and K, and water-soluble: thiamine, riboflavin, niacin, $B_6$, $B_{12}$, C, and folate), carnitine (CA), minerals, trace elements (copper, zinc, iron, manganese, and selenium), and hormones (insulin-like growth factor 1, insulin-like growth factor-binding protein 3, reverse triiodothyronine, etc.) need to be examined when assessing the nutritional status of LC patients. In particular, evaluations of serum zinc and CA (total CA, free CA, and acyl-CA) are necessary in LC patients with sarcopenia and hyperammonemia [23–32].

## 2.3. Disturbances of energy metabolism

PEM is a characteristic state of malnutrition in advanced LC and is closely associated with the survival rate, the carcinogenic risk, and the outcome of liver transplantation in patients with LC. The serum Alb concentration is generally a marker of protein malnutrition. The npRQ using indirect calorimetry is a marker of energy malnutrition [71]. Therefore, indirect calorimetry would be the best method to assess PEM. The results of REE, npRQ, and the oxidation rates of three nutrients (carbohydrate, protein, and fat) are obtained by indirect calorimetry. Many previous reports indicated that the npRQ decreases, the oxidation rate of fat increases, and the oxidation rate of carbohydrate decreases according to the Child-Pugh classification [5, 72, 73]. It has been considered that a decreased npRQ (<0.85) after an overnight fast predicts a catabolic state and is related to a lower survival rate in LC patients [5]. Decreased carbohydrate oxidation is explained by both the lower production rate of glucose from glycogen in the liver and decreases in peripheral glucose use due to insulin resistance [74]. In fact, patients with LC cannot store sufficient glycogen due to liver atrophy, and their energy generation pattern after an overnight fast is equivalent to that observed in healthy individuals after 2–3 days of starvation [74, 75]. Increased fat oxidation is caused by an increased rate of lipolysis in fat tissue [76]. Our earlier results are generally similar to previous reports (**Figures 3** and **4**). However, because measurement by indirect calorimetry is not easy, it cannot be routinely performed in outpatients with LC. The serum free fatty acid (FAA)
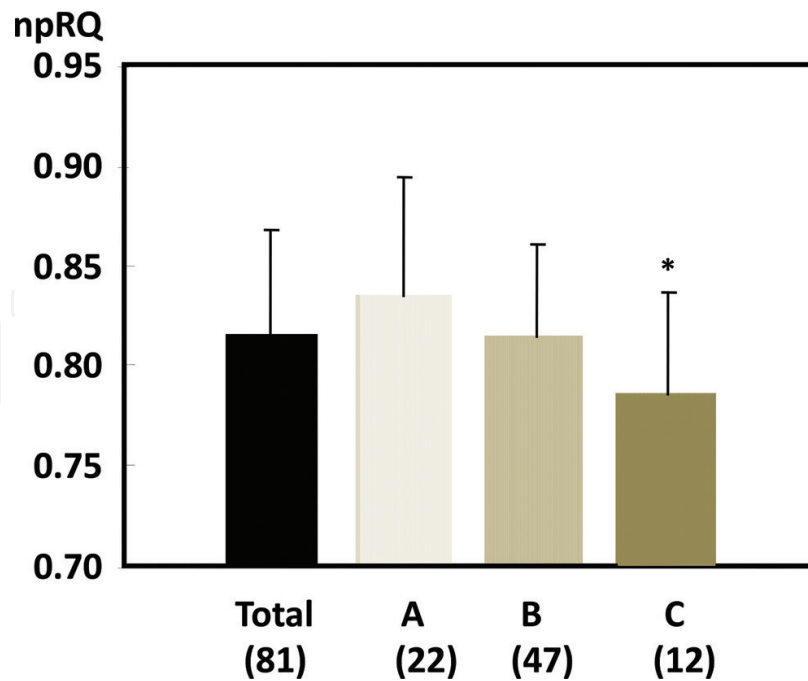
**Figure 3.** Nonprotein respiratory quotients in patients with liver cirrhosis. Eighty-one cirrhotic patients with or without hepatocellular carcinoma who were admitted to Iwate Medical University Hospital were investigated. Energy metabolism was measured by indirect calorimetry (Deltatrac-II Metabolic Monitor, Datax Division Inst. Corp., Helsinki, Finland) in the morning after overnight fasting. npRQ, nonprotein respiratory quotient. Each value is shown as the mean ± standard deviation. *P < 0.05 (compared to grade A). ( ), number of patients with LC.

concentration has recently been reported as an alternative marker to represent npRQ measured by indirect calorimetry to evaluate energy malnutrition in LC [77]. The serum FFA concentration is also a predictor of minimal hepatic encephalopathy diagnosed by computerized neuropsychological testing [78]. Furthermore, our previous study showed that the serum FAA concentration is correlated with the serum acyl-CA to total CA ratio, which would indirectly reflect intracellular mitochondrial function [30]. These findings suggest that the serum FAA concentration in the fasting state may be useful in the assessment of nutritional status in patients with LC.

## 2.4. Glucose intolerance and diabetes mellitus

Glucose intolerance and/or diabetes mellitus is seen in about 30% of patients with LC, though 80% of LC patients have a normal fasting blood glucose level [79]. These manifestations are mainly caused by obesity and increased insulin resistance and hepatitis C virus (HCV) infection. HCV is a major cause of LC and is induced by increased insulin resistance, excess secretion of pancreatic β cells, and portal-systemic shunting [80, 81]. However, insulin resistance improves after eradication of HCV [82]. Age, sex, smoking, excessive alcohol intake, and chronic viral infection (hepatitis B virus and HCV) are established risk factors for HCC [20]. Furthermore, many recent studies have reported that obesity and DM are risk factors for HCC [17–22]. These findings suggest that not only PEM, but also obesity and glucose intolerance or DM might be important factors in the nutritional status that affect the prognosis of LC.
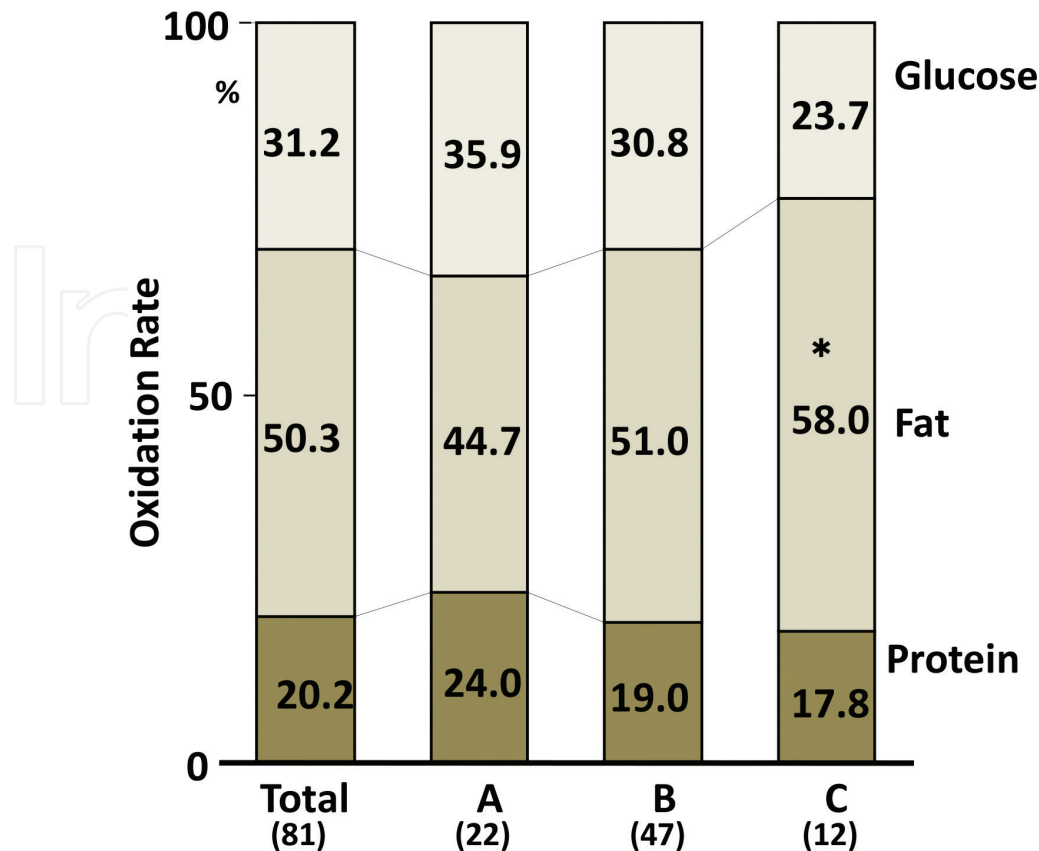
**Figure 4.** Substrate oxidation rates of glucose, fat, and protein using indirect calorimetry in patients with liver cirrhosis. Eighty-one cirrhotic patients with or without hepatocellular carcinoma who were admitted to Iwate Medical University Hospital were investigated. Energy metabolism was measured using indirect calorimetry (Deltatrac-II Metabolic Monitor, Datax Division Inst. Corp., Helsinki, Finland) in the morning after overnight fasting. Each value is shown as the mean. *P < 0.05 (compared to grade A). ( ), number of patients with LC.

## 3. Nutritional management

Based on previous many studies associated with malnutrition including obesity and glucose impairment (DM) in patients with LC, several guidelines on enteral nutrition have been proposed [83–85]. Here, flow chart on nutritional managements for patients with LC shows in **Figure 5**. The recommended dietary managements include energy, protein, fat, sodium chloride, iron, and other nutrient requirement. However, recommended energy intake and protein intake are different between Japan and European Society for parenteral and enteral Nutrition (ESPEN) guidelines (energy intake: 25–35 kcal/kg/day in Japan guideline and 35–40 kcal/kg/day in ESPEN guidelines, and protein intake: 1.0–1.5 g/kg/day in Japan guideline and 1.2–1.5 g/kg/day in ESPEN guidelines). Energy intake should be reduced (25 kcal/kg/day) in patients complicated with DM [85]. Moreover, protein intake involves the protein content of BCAA formulas (BCAA granules or BCAA-enriched nutrient mixture), and it should be reduced to 0.5–0.7 g/kg/day in patients with protein intolerance [85]. Late evening snack (LES) reduces overnight catabolic state in patients with LC
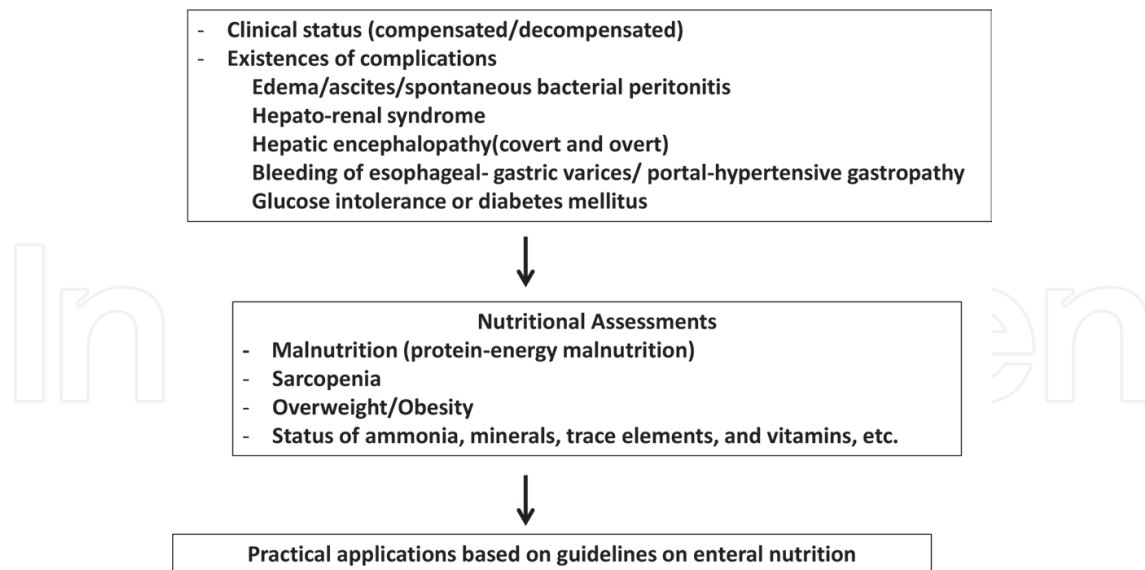
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┌─────────────────────────────────────────────────────────────────────┐
│  -  Clinical status (compensated/decompensated)                       │
│  -  Existences of complications                                       │
│        Edema/ascites/spontaneous bacterial peritonitis                │
│        Hepato-renal syndrome                                          │
│        Hepatic encephalopathy(covert and overt)                       │
│        Bleeding of esophageal- gastric varices/ portal-hypertensive   │
│        gastropathy                                                    │
│        Glucose intolerance or diabetes mellitus                       │
└─────────────────────────────────────────────────────────────────────┘
                                    ↓
┌─────────────────────────────────────────────────────────────────────┐
│                       Nutritional Assessments                         │
│  -  Malnutrition (protein-energy malnutrition)                        │
│  -  Sarcopenia                                                        │
│  -  Overweight/Obesity                                                │
│  -  Status of ammonia, minerals, trace elements, and vitamins, etc.   │
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┌─────────────────────────────────────────────────────────────────────┐
│        Practical applications based on guidelines on enteral nutrition│
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**Figure 5.** Flow chart on nutritional managements for patients with liver cirrhosis.

[86–89]. LES is particularly recommended to the patients with PEM and also useful for managing the blood glucose level in patients with glucose intolerance or DM [90]. As LES, snacks (approximately amounts of 200 kcal) and BCAA-enriched nutrient mixture are usually used. As excess deposition of iron in the liver causes oxidative stress and also promotes hepatocarcinogenesis, so unless severe anemia is observed, an iron-restricted diet 6 mg/kg/day) should be the standard [85, 91]. Zinc supplementation improves the status of hyperammonemia [24–26].

# 4. Conclusion

Nutritional assessment in patients with LC is necessary for the appropriate management of LC patients. PEM, sarcopenia, and obesity are closely associated with adverse outcomes such as liver failure and HCC, as well as graft survival after liver transplantation in patients with LC. However, traditional and newly developed methods of measuring nutritional status are confounded by the changes in metabolism, body composition, and immune function that occur in LC independent of nutritional status. Further studies of precise assessments of malnutrition are needed to improve the prognosis of patients with LC.

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