Effect of sarcopenia on liver cirrhosis with complicating esophageal and gastric varices after endoscopic therapy

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Effect of sarcopenia on liver cirrhosis with complicating esophageal and gastric varices after endoscopic therapy

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Abstract

Background: Several investigators have reported that sarcopenia is common in patients with cirrhosis. However, few studies have discussed the association between sarcopenia and liver cirrhosis complicated with esophageal and gastric variceal bleeding (LC-EGVB). We aimed to investigate the impact of sarcopenia on rebleeding after endoscopic therapy in patients with LC-EGVB.

Method: CT images from the 3rd lumbar vertebrae were selected to analyze body composition, including SMT VAT and SAT, by SliceOmatic software. Sarcopenia was defined according to validated cutoff values for patients with cirrhosis: 44.77 cm^2/m^2 for males and 32.50 cm^2/m^2 for females.

Results: A total of 187 LC-EGVB patients and 309 donors were included. The rate of sarcopenia in donors (17.4%) was significantly lower than that in LC-EGVB patients (41.2%). LC-EGVB patients with sarcopenia have a high prevalence of portal vein thrombosis and rebleeding rate at 1 year. The rate of sarcopenia in the rebleeding group was significantly higher than that in the non-rebleeding group. Univariate and multivariate analyses showed that sarcopenia was an independent risk factor for rebleeding within 1 year in LC-EGVB patients.

Conclusion: LC-EGVB patients have a high prevalence of sarcopenia. Sarcopenia is an independent risk factor for rebleeding within 1 year.

Key words: liver cirrhosis; esophageal and gastric variceal bleeding; sarcopenia; rebleeding

Abbreviations: liver cirrhosis complicated with esophageal and gastric variceal bleeding, LC-EGVB; BMI, body mass index; PVT, portal venous thrombosis; HE, hepatic encephalopathy; HCC, hepatocellular carcinoma; RCS, red color signs; EVG, esophageal varices grading; SMT, skeletal muscle tissue; VAT, visceral adipose tissue; SAT, subcutaneous adipose tissue.

Introduction

With the development of computed tomography (CT) examination, a second analysis of CT images in the 3rd lumbar vertebra was considered an objective and the gold standard for determining the body composition of visceral adipose tissue (VAT), subcutaneous adipose tissue (SAT), and skeletal muscle tissue (SMT)[1]. Previous studies have demonstrated that an increase in VAT is an independent risk factor for metabolic syndrome, which includes diabetes, hypertension and coronary artery disease[2, 3]. We also found that VAT and SMT were influential factors for the severity and prognosis of patients with acute pancreatitis. Patients should have a proper diet and exercise program after discharge to reduce VAT and strengthen muscle function to improve prognosis [4].

Sarcopenia is recognized as a syndrome that is characterized by the progressive and systemic loss of skeletal muscle mass and strength[5, 6]. Several studies have found that sarcopenia is correlated with poor survival in cancer patients[7, 8]. In the last decade, several investigators have reported that sarcopenia is common in patients with cirrhosis and is an independent prognostic factor for mortality in cirrhosis patients[9]. Zeng et al. found that cirrhosis was significantly associated with sarcopenia, and sarcopenia patients had relatively poor liver function[10]. Topan and colleagues found that sarcopenia was a significant risk factor for the occurrence rate of ascites, hepatocellular carcinoma, urinary tract infection and spontaneous peritonitis[11]. A recent study found that sarcopenia was associated with minimal hepatic encephalopathy (HE) and the risk of overt HE in patients with cirrhosis, and this association may reduce the metabolism of ammonia[12].

However, few studies have discussed the association between sarcopenia and liver cirrhosis complicated with esophageal and gastric variceal bleeding (LC-EGVB). In

this study, we studied the impact of sarcopenia on the outcomes of LC-EGVB patients after endoscopic therapy.

Method

Patients and donors

A total of 206 patients with LC-EGVB treated at PLA Rocket Force Characteristic Medical Center from March 2017 to July 2018 were selected. All patients received endoscopic therapy for EGVB. Seven of 206 patients did not receive a CT examination 1 week after the first endoscopic therapy. Twelve of 199 patients were lost to follow-up 1 year after endoscopic therapy. Finally, a total of 187 LC-EGVB patients were included in this study. The detailed information of the included patients is shown in Table 1. A total of 309 donors were also selected, and these donors were diagnosed with gastrointestinal polyps, mild gastroesophageal reflux disease, chronic gastritis, or dyspepsia as previously described[4]. The study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Ethics Committee of PLA Rocket Force Characteristic Medical Center.

CT image analysis

All patients and donors received CT scans. A CT image from the 3rd lumbar vertebrae was selected. SliceOmatic software (version 5.0; Tomovision, Magog, Canada) was used to quantify the body composition, which enables specific tissue demarcation using previously reported Hounsfield unit (HU) thresholds. SMT ranged from -29 to +150 HU, VAT ranged from -150 to -50 HU, and SAT ranged from -190 to -30 HU. As shown in Figure 1, SMT is marked in red, VAT in yellow and SAT in green. The area and mean attenuation (HU) of different tissues were calculated automatically. The cross-sectional skeletal muscle area was normalized to height (cm^2/m^2) to evaluate the skeletal muscle index (SMI). Sarcopenia was defined according to validated cutoff values in patients with cirrhosis. For males, it was 44.77 cm^2/m^2, and for females, it was 32.50 cm^2/m^2.[10]

Endoscopic findings for EGVB and follow-up

All patients received endoscopic therapy, including endoscope band ligation,

endoscopic cyanoacrylate injection or endoscopic lauromacrogol injection. The grade of esophageal varices and red color signs were defined as previously described. All patients were followed-up for at least 1 year. Patients with rebleeding at the 1-year follow-up received endoscopic examination and therapy if necessary.

Statistical analysis

We used SPSS statistical software 26 (version 26.0; IBM Corp., Armonk, NY, UAS) to analyze the data and make tables. A two-sided $P < 0.05$ was considered statistically significant, and a $P < 0.1$ was considered marginally significant. For continuous data with normal and nonnormal distributions, variables are expressed as the mean ± standard deviation or median (interquartile range), respectively. The Kolmogorov–Smirnov test was used to analyze whether the data were normally distributed. The significance of the differences between the two groups was analyzed by two-sample t test or Mann–Whitney U test. Categorical variables are expressed in numbers (%) and were compared between these variables using the chi-square test and Fisher's exact test. Univariate and multivariate logistic regression analyses were used to evaluate the risk factors for severe esophageal varices. When P values were less than 0.1 in univariate analysis, they were considered statistically significant and were included in multivariate analysis. Univariate and multivariate Cox regression analyses were used to evaluate the risk of gastroesophageal variceal rebleeding.

Results

The basic characteristics of the included patients

As shown in Table 1, a total of 187 patients who were diagnosed with LC-EGVB were included in this manuscript. Among these patients, 121 were male. The etiology of the majority of cirrhosis patients was viral infection (56.7%), and others included alcohol (15%) and autoimmune disease (12.3%). These patients also had a few complications, such as ascites (59.9%), portal vein thrombosis (PVT) (29.9%), splenomegaly (75.9%), HCC (10.7%), hepatic encephalopathy (31.0%) and sarcopenia (41.2%). The body composition features are listed in Table 1.

Body composition in LC-EGVB patients and donors

In this study, we included 309 donors, who were described previously[4]. The rate of sarcopenia in the donors was 17.4%, which was significantly lower than that in LC-EGVB patients (41.2%). We selected BMI-matched and sex-matched individuals and measured body composition. The results showed less SMT, VAT and SAT in LC-EGVB patients than donors (Figure 1). As shown in Table 2, no difference in BMI was found in LC-EGVB patients and donors by sex. The rate of sarcopenia in male LC-EGVB patients was significantly higher than that in male donors (47.11% vs. 27.60%, $p<0.001$). However, the rate of sarcopenia in female LC-EGVB patients was not significantly different from that in donors (30.30% vs. 17.95%, $p=0.054$). The reason for this may be the relatively small population of LC-EGVB patients. Body composition analysis showed that male patients with EGVB had less SMT, VAT and SAT than male donors. The female patients with EGVB had less SMT and SAT than the female donors, but VAT was not significantly different.

Sarcopenia and clinical outcomes in EGVB patients

In this study, we focused on the association between sarcopenia and the outcomes of LC-EGVB. The 187 LC-EGVB patients were divided into a sarcopenia group and a non-sarcopenia group. BMI values in the sarcopenia group were significantly lower than that in the non-sarcopenia group (Table 3). Significant differences in PVT (44.2% vs. 20%, $p<0.001$) and the rebleeding rate at 1 year (42.9% vs. 16.4%, $p<0.001$) were also found between the two groups. We also found differences in the endoscopy results, including the grade of gastroesophageal varices (92.2% vs. 76.4% $p<0.01$) and the prevalence of red color signs (89.6% vs. 76.4%, $p<0.05$). In contrast, no significant differences were found for ascites, splenomegaly, HCC rate and hepatic encephalopathy.

Sarcopenia was a risk factor for rebleeding after 1 year in LC-EGVB patients

As shown in Table 1, 51 of 187 LC-EGVB patients experienced rebleeding within 1 year. These patients were divided into a rebleeding group and a non-rebleeding group. As shown in Table 4, the rate of sarcopenia in the rebleeding group was 64.7% (33/51),

which was significantly higher than that in the non-rebleeding group (32.4%, 44/136). Univariate and multivariate analyses showed that sarcopenia was an independent risk factor for rebleeding at the 1-year follow-up of LC-EGVB patients (Table 5).

Discussion

Previous studies have reported that the prevalence of sarcopenia in cirrhosis ranges from 30%-70%[13]. These results are consistent with those in this manuscript. While the prevalence in LC-EGVB patients was relatively high (41.2%), the reason for this may be that all the cirrhosis patients were complicated with EGVB. Moreover, sarcopenia was more prevalent in male patients with cirrhosis. In this study, we also found that the prevalence of sarcopenia was higher in male patients with EGVB than in female patients (47.11% vs. 30.30%). The pathogenesis of sarcopenia in cirrhosis is complex and multifactorial. A few studies have found that the imbalance between muscle breakdown and formation may play important roles[14]. The mechanisms contributing to sarcopenia may include reduced nutrient and energy intake, maldigestion, malabsorption, altered macronutrient metabolism, inhibited muscle growth, elevated myostatin levels, increased muscle breakdown and physical activity[15-17].

Esophageal and gastric varices are the most common complications in liver cirrhosis patients. The bleeding of esophageal and gastric varices is considered an urgent emergency, and nearly 1% of patients with liver cirrhosis die of EGVB[18]. It was demonstrated that the risk factors for EGVB include varices located in the critical area, high portal pressure, large varices, blue coloration, red-colored signs and advanced stages of liver disease[19, 20]. However, few studies have discussed the association between sarcopenia and LC-EGVB. Ishizu and colleagues found that the prevalence of low skeletal mass had no association with either death or rebleeding within 5 days in liver cirrhosis complicating esophageal and gastric varices. Nevertheless, low skeletal mass is an independent risk factor for 6-week mortality[21]. Lattanzi et al. found that sarcopenia patients with noncirrhotic portal hypertension had a higher rate of refractory variceal bleeding than non-sarcopenia patients[22]. In this study, we demonstrated that the rebleeding rate of liver cirrhosis complicated by EGV in the sarcopenia group

(33/77, 42.9%) was significantly higher than that in the non-sarcopenia group (18/110, 16.4%). The prevalence of sarcopenia in the rebleeding group at 1 year was significantly higher than that in the non-rebleeding group. Univariate and multivariate analyses showed that sarcopenia was a risk factor for rebleeding of EGV within 1 year.

This study has two potential limitations. First, the number of patients included in this study was relatively small. A study of a large number of patients needs to be conducted to confirm our results. Second, the cutoff of SMI for defining sarcopenia is from research with a large number of donors, and more studies are needed to confirm the cutoff.

In conclusion, our study demonstrated a high prevalence of sarcopenia in LC-EGVB patients. Further research found that a higher rate of rebleeding within 1 year and PVT patients were found in the sarcopenia group of LC-EGVB patients, and a relatively higher BMI was found in the non-sarcopenia group. Univariate and multivariate analyses showed that sarcopenia was an independent risk factor for rebleeding of LC-EGV within 1 year.

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Table Legend:

Table 1: Characteristics of included patients

Table 2: Body composition features of donors and patients with LC-EGVB by sex

Table 3: Comparison of characteristics between patients with sarcopenia group and non-sarcopenia group

Table 4: Comparison of characteristics between patients with rebleeding group and non-rebleeding group

Table 5: Univariate and multivariate analyses of factors linked to rebleeding

Figure Legend:

Figure 1: Computed tomographic scans showing areas of body composition in LC-EGVB patients and donors. Example of body composition features in a (A) male patient with LC-EGVB, (B) male donor, (C) female patient with LC-EGVB, and -(D) female donor. Muscle, subcutaneous, and visceral adipose tissue are shown in red, green, and yellow, respectively.

Author Contributions: Hao NB and Li CZ designed the study. Zhou Y, Li X, Zhang D and Hao NB collected and analyzed data. Hao NB, Hu WW and Xie J wrote the manuscript. All authors have read and agreed to the published version of the manuscript.

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Data Availability Statement: Data are available from the corresponding author upon reasonable request.

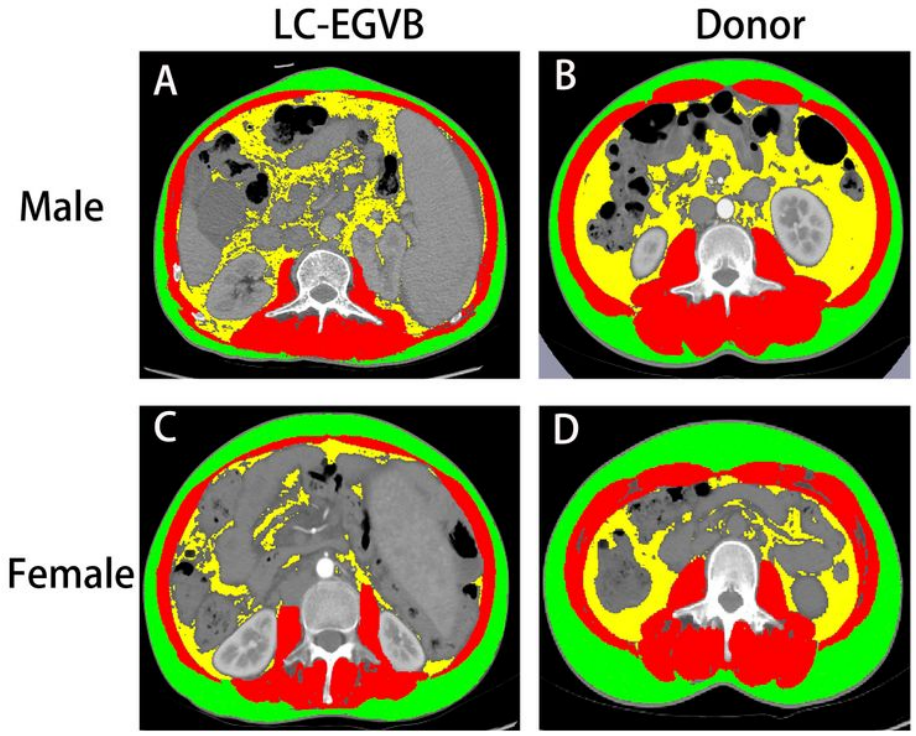
Conflicts of Interest: The authors declare that they have no conflict of interest with the contents of this article.

Availability of data and materials: The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethical approval and consent to participate: The study was approved by the Institutional Ethics Committee of PLA Rocket Force Characteristic Medical Center and due to the retrospective nature of the data analysis, the requirement for informed consent from the patient's parents was waivered.

Figures



	LC-EGVB	Donor
BMI	21.30	21.30
SMT	104.80	139.63
VAT	78.61	103.30
SAT	51.09	74.33

	LC-EGVB	Donor
BMI	20.70	20.70
SMT	71.37	110.08
VAT	26.36	43.97
SAT	84.15	120.90

Figure 1

Computed tomographic scans showing areas of body composition in LC□EGVB patients and donors. Example of body composition features in a (A) male patient with LC-EGVB, (B) male donor, (C) female patient with LC-EGVB, and -(D) female donor. Muscle, subcutaneous, and visceral adipose tissue are shown in red, green, and yellow, respectively.

Supplementary Files

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