Original Article

Oral nutritional supplements (ONSs) for cirrhotic patients undergoing liver resection assessed by ultrasound measurement of rectus femoris and anterior tibialis muscles thickness. Randomized clinical trial

ABSTRACT

Purpose: We evaluated the effects of postoperative administration of (ONSs) on the liver function and the outcome of cirrhotic patients using ultrasound (US) assessment of rectus femoris (RF) and anterior tibialis (AT) muscles.

Patients and Methods: Forty-three malnourished adult hepatic patients who underwent major liver resections were recruited in this study. In the conventional diet (CD) group, the patients took water at postoperative day (POD) 0 and routine soft diet starting from POD1. In the ONS group, a commercially elemental diet was started from POD1 for 7 days postoperatively, with a target endpoint of 35-40 kcal/kg and 1.2-1.5 g/kg of protein per day. US assessment of the RF and AT muscles was done preoperatively and at POD3 and 7, including anterior-posterior (AP) diameter, lateral–lateral (LL) diameter, and cross-sectional area (CSA). Muscles' echogenicity was defined by the Heckmatt scale. The outcome of the patients was also recorded.

Results: Consumption of ONS preserved the measured RF and AT characteristics (AP and LL diameters and CSA) in the ONS group at POD3 and 7 compared to the CD group. Heckmatt scale was significantly increased at POD3 and 7 in the CD group compared to the ONS group. Both total protein and albumin levels at POD3 and 7 were significantly lower in the CD group compared to the ONS group [P = (0.02, 0.03) and (0.05, 0.04), respectively]. Serum phosphate was significantly lower at POD7 in the ONS group than the CD group (p = 0.04). There were significant decreases in the ICU stay and time of passing flatus (h) in the ONS group comparing with the CD group (P = 0.045 and *P* = 0.00, respectively).

Conclusions: ONS maintains muscle mass and echogenicity of RF and AT along with better liver function and intestinal function recovery.

Key words: Liver resection; muscles ultrasound; ONS

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Introduction

Malnutrition in hepatic patients results from a variable combination of decrease intake, altered macronutrient metabolism, maldigestion, malabsorption, and hyper metabolic state.[1] Hepatic patients, particularly with decompensated cirrhosis, usually experience weight loss and muscle wasting as well as protein-energy malnutrition, which often result in sarcopenia. Muscle mass loss leads to muscle weakness, which interferes with postoperative weaning from mechanical ventilation and results in poor outcome.[2] In chronic liver disease, severe protein-calorie malnutrition adversely affects liver regeneration after liver resection surgeries; however, perioperative oral nutritional supplement (ONS) in patients with impaired liver function play a fundamental rule in the outcome,[3] encourage postoperative enteral nutrition, preserve the immunity, and maintain the integrity of the gastrointestinal tract.[4] European Society for Clinical Nutrition and Metabolism encourages the use of ONS if the patients are unable to safeguard appropriate oral intake.[5] Using nutritional assessment tools, such as anthropometric and biometric measures, in patients with advanced liver diseases is difficult owing to complications such as ascites and inflammation. Measuring muscle mass by ultrasound (US) techniques is a reliable, accessible, low-cost, and applicable technique.[6] In this study, we estimated the influence of early postoperative ONS in malnourished cirrhotic patients undergoing liver resection via US evaluation of the mass and morphological alteration of anterior tibialis (AT) and rectus femoris (RF) muscles. We also evaluated the impact of ONS on liver function, infectious complications, and outcome.

Patients and Methods

This prospective double-blind trial was conducted in the Department of Anesthesia and Intensive Care at the National Liver Institute, Menoufia University. The study protocol was approved by the National Liver Institute Review Board (IRB number 00156/2019) and registered in the Pan African Clinical Trial Registry (www.pactr.org; No.: PACTR 201907570828748). Written consent was obtained from all the recruited patients. There were 43 adult hepatic patients, categorized as Child-Pugh A or B, undergoing major liver resections for liver tumors (either primary or secondary), with a modified BMI below 23 with mild ascites or 22 with no ascites, and triceps skinfold (TSF) and mid-arm muscle circumference (MAMC) below the 5^{th} percentile, i.e., who were considered malnourished. Three patients dropped out of the study as the surgery was aborted since the patients were inoperable. Exclusion criteria included refusal of the patient to be involved in the study, treatment with corticosteroids, and neuromuscular diseases. Participants were randomized to either receiving conventional diet (CD group) or oral nutritional supplementation (ONS group). Using randomization table generated by permuted block technique with variable block size.

In the CD group, the patients took some water at postoperative day (POD) 0 and started with soft routine diet at POD1, after assessment of the abdominal sound on the morning of POD0.

In the ONS group, after the assessment of abdominal sound, ONS was started from the morning of POD1 for at least 7 days postoperatively. The target endpoint for ONS was 35-40 kcal/kg and 1.2-1.5 g/kg of protein per day.[5] We started with small volume of ONS and gradually increased it according to the patient's tolerance. A commercially available elemental diet was supplemented with high energy, high protein ONS, high energy to meet the energy needs in a low volume of diet and allow optimum fluid restriction (2 kcal/mL), and high protein to meet the elevated protein requirement in a low volume of diet (10 g protein/100 mL).

For all patients, general anesthesia was induced using 2 mg/kg propofol, 2–4 μg/kg fentanyl, and 0.6 rocuronium, and maintained using a balanced anesthetic technique, involving sevoflurane at 0.7–1 minimum alveolar concentration (MAC), and a/mixture of air and oxygen (FiO_2: 0.4). The central venous catheter was inserted with ultrasound guidance (Sonosite, Nanomex, UK) through the right internal jugular approach. We administered crystalloid solution (6 mL/kg/h) to maintain the central venous pressure (CVP) at 5 cm H_2O or less to reduce the blood loss. At the end of the surgery, the patients were extubated after fulfillment of the criteria of extubation. Standard low molecular weight (LMW) heparin used as a prophylactic against deep vein thrombosis. The hemodynamic parameters were recorded before induction, intraoperatively, and postoperatively. Blood samples were taken for routine biochemistry analysis, including the liver function tests. The rate of infectious complications, ICU stay, and intestinal function recovery, postoperative abdominal distention, postoperative nausea and vomiting, and time of flatus passing were also recorded.

Nutritional status was evaluated preoperatively using subjective global assessment (SGA), TSF, body mass index (BMI), and MAMC. For all patients, US assessment of the RF and AT muscles was conducted preoperatively and at POD3 and 7. We used a US device with a 5- to 7.5-MHz linear probe. The US technique used in this study was based on that used previously by Pasta G *et al*.[7] Lateral-lateral (LL) diameter, cross-sectional area (CSA), and anterior-posterior (AP) diameter were recorded for both muscles. Qualitative parameter (echogenicity) was determined using the Heckmatt scale (Normal echogenicity corresponds to score of 1; a higher grade of echogenicity and higher score correlates with a higher severity of myopathy).[8]

Statistical analysis

The Kolmogorov–Smirnov test was used to assess the normality of the data. Data were represented as mean ± SD, with 95% confidence intervals (95%CI) where appropriate. SPSS version 15 (SPSS Inc., Chicago, IL, USA) was used to conduct all the statistical analyses. Independent t-test was used for comparisons between the two studied groups. P value < 0.05 was considered as statistically significant. Fisher's exact test and Chi-square test were used to compare the qualitative variables.

Sample size and power of the study

We are planning a study of a continuous response variable from independent control and experimental subjects with 1 control(s) per experimental subject. In a previous study, the response within each subject group was normally distributed with standard deviation (1.384).[9]

If the true difference in the experimental and control means is (1.537) cm^2, in the primary outcome which is the cross-sectional area of the (Rectus Femoris) assessed by the US between the experimental group (ONS) and control group (CD) group we will need to study 18 experimental subjects and 18 control subjects to be able to reject the null hypothesis that the population means of the experimental and control groups are equal with probability (power) 90%. The Type I error probability associated with this test of this null hypothesis is 0.05.[9]

Results

Forty patients completed the study, with 20 patients in each group. Three patients were dropped out of the study [Figure 1]. All patients were fully complied with the required oral supplement dose according to there corresponding group. The gender and age distribution were comparable between the two study groups. Child score, lobe resected, and SGA were comparable with no statistically significant difference. With respect to the anthropometric data, we observed no significant differences between the BMI of both groups at all periods of measurements; however, we observed a significant decrease in the values of MAC, TSF, and HGS for the CD group at POD7 (P = 0.04, 0.01, and 0.06, respectively; Table 1). Preoperative levels of total protein and albumin were comparable between the studied groups. Postoperatively, the total protein and albumin levels were significantly lower

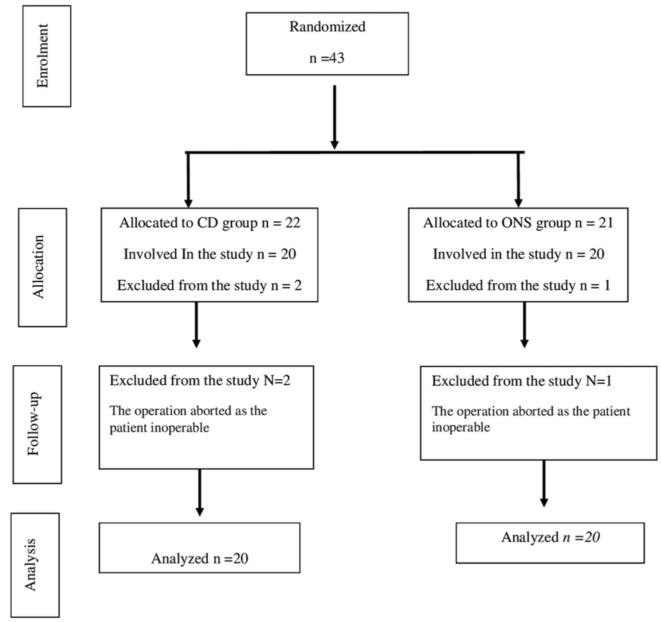

Figure 1: Flow chart, CD (conventional diet), ONS (oral nutritional supplement group)

in the CD group compared to the ONS group. Preoperative and postoperative levels of blood urea nitrogen (BUN) and transferrin were comparable between the two study groups [Table 2]. Preoperative serum phosphate level was comparable between the two groups until POD7 when it decreased significantly in the ONS group compared with the CD group.

Preoperative CSA and AP and LL diameters of the RF muscles were comparable between the two study groups; however, at POD7, these values were significantly reduced in the CD group. In addition, at POD3, the CSA of the RF muscles was significantly lower in the CD group. The preoperative Heckmatt scores for RF muscles was comparable between both the groups; however, at POD3 and POD7, the CD group exhibited significantly higher Heckmatt scores than the ONS group ($p = 0.000$ and 0.003, respectively). Preoperative CSA and AP and LL diameters of the AT muscle were comparable between both the groups; however, these values were significantly reduced in the CD group at POD7. The preoperative Heckmatt scores for AT muscles were comparable between both the groups; however, at POD3, these scores were significantly higher for the CD group than the ONS group ($p = 0.00$; Table 3).

Compared to the CD group, the ONS group exhibited significantly lower values for ICU stay and time of passing flatus (h) ($P = 0.045$ and $P = 0.00$, respectively; Table 4). There was no statistically significant difference between the two groups with respect to the number of patients suffering from infection and postoperative nausea and vomiting. None of the patients suffered from abdominal distention after feeding [Table 4].

Table 1: Anthropometric data the in studied groups

Variable	Time	Mean ± SD		*P* value
		CD group (*n* = 20)	ONS group (*n* = 20)	
BMI (kg/m²)	T0	27.25 ± 4.57	26.08 ± 3.61	0.38 NS
	T1	27.39 ± 4.53	26.64 ± 3.66	0.56 NS
	T2	27.04 ± 4.63	26.41 ± 3.64	0.64 NS
MAC (cm)	T0	28.40 ± 4.22	28.65 ± 3.63	0.84 NS
	T1	28.55 ± 3.46	28.80 ± 2.93	0.81 NS
	T2	25.80 ± 5.12	28.65 ± 2.96	0.04*
TSF (mm)	T0	18.95 ± 4.12	19.35 ± 3.75	0.75 NS
	T1	19.20 ± 3.44	19.05 ± 3.52	0.89 NS
	T2	16.60 ± 3.05	18.95 ± 2.65	0.01*
HGS (kg)	T0	41.25 ± 12.29	43.30 ± 8.80	0.55 NS
	T1	28.35 ± 10.99	33.70 ± 13.21	0.17 NS
	T2	30.85 ± 15.95	39.65 ± 12.93	0.06*

CD: Conventional diet group, ONS group: Oral nutritional supplement group; T0; preoperative; T1; post-operative day3 (POD3); T3; POD7; S.D: Standard deviation; NS: Not significant;*significance with other group; ($P < 0.05$); BMI: body mass index; TSF: Triceps skin fold; MAC: Mid arm circumference; HGS Hand grip strength

Table 2: Laboratory data in studied groups

Variable	Time	Mean ± SD		*P* value
		CD group (*n* = 20)	ONS group (*n* = 20)	
Total protein (gm/l)	T0	7.15 ± 1.24	7.67 ± 0.99	0.15 NS
	T1	5.51 ± 0.73	6.01 ± 0.60	0.02*
	T2	5.69 ± 0.83	6.19 ± 0.61	0.03*
Albumin (g/dL)	T0	3.74 ± 0.548	4.07 ± 0.61	0.08 NS
	T1	2.76 ± 0.47	3.06 ± 0.45	0.05*
	T2	2.89 ± 0.46	3.18 ± 0.39	0.04*
BUN (mg/dl)	T0	14.90 ± 4.53	16.61 ± 4.92	0.26 NS
	T1	15.90 ± 4.52	15.70 ± 3.46	0.88 NS
	T2	15.70 ± 4.43	15.75 ± 4.06	0.97 NS
PO_4 (mg/dl)	T0	3.96 ± .56	3.93 ± .711	0.86 NS
	T1	3.55 ± .76	3.21 ± .69	0.15 NS
	T2	3.53 ± .42	3.18 ± .60	0.04*
Transferritin (µg/L)	T0	36.89 ± 8.26	38.55 ± 7.28	0.50 NS
	T1	14.45 ± 2.62	16.47 ± 5.51	0.15 NS
	T2	13.07 ± 2.85	13.58 ± 3.11	0.59 NS

CD: Conventional diet group, ONS group: Oral nutritional supplement group; T0; preoperative; T1; post-operative day3 (POD3); T3; POD7; S.D: Standard deviation; NS: Not significant.;; PO4: Serum phosphate; BUN: Blood urea nitrogen; *significance with other group; ($P < 0.05$); NS: not significant

Figure 2: Ultrasound images of the RF muscle using the superficial linear transducer in a patient fed with oral nutritional supplement (ONS) (a) and another patient fed with conventional diet (CD) (b) the picture was taken at POD3. The echogenicity visible as a starry night appearance (Grade I based on Heckmatt's rating scale) in a patient fed with oral nutritional supplement (ONS) (a). Elevated echogenicity (Grade III) in a patient fed with CD (b). The RF CSA of a patient fed with oral nutritional supplement (ONS) (a) was greater than that of a patient (b) fed with conventional diet (CD).

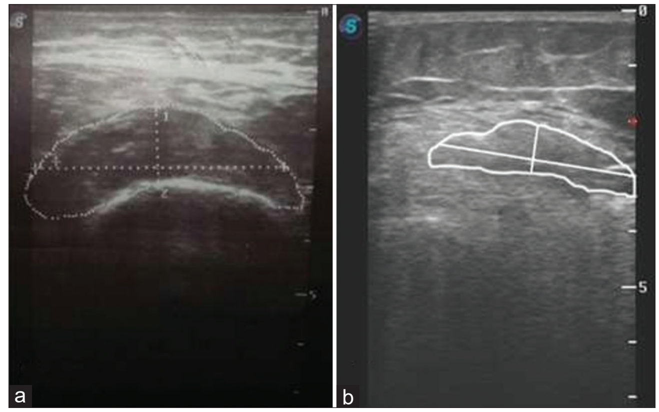

Figure 2: Ultrasound images of the rectus femoris muscle using the superficial linear transducer in a patient on oral nutritional supplement (ONS) (a) and another patient on conventional diet (CD) (b) the picture was taken at POD3

The images were taken in the ICU Department of the National Liver Institute, Menoufia University.

Discussion

We evaluated the effects of postoperative ONS versus CD in hepatic patients who underwent hepatic resection using US assessment of the quantitative and qualitative changes in the RF and AT muscles. The main outcome of our study was the ability of ONS to maintain muscle mass and echogenicity of RF and AT muscles with better liver function and intestinal function recovery, which corroborated the results of previous clinical studies on ICU patients.[2,10]

Patients with liver cirrhosis exhibit insufficient glycogen reserves, due to liver dysfunction, along with an increased consumption of amino acids, which enhances the release of amino acids from the skeletal muscles, which, in turn, leads to sarcopenia. Another contributing cause of sarcopenia in these patients is hyperammonemia.[11]

Proteins such as prealbumin, transferrin, and albumin are negative acute-phase proteins. Their levels alter due to different stress levels. So, they are not a good marker for assessment of the nutrition status.[12] Anthropometric measurements are unreliable and inaccurate tools for assessment of the nutrition state of cirrhotic patients with edema and ascites.[13] On the other hand, bioelectrical impedance analysis (BIA) correlated well with the patient's Child-Pugh score.[14] SGA for the assessment of nutritional state is commonly used to assess malnutrition in hepatic patients. Being a subjective tool, its interpretations vary across different examiners.[15] In cirrhotic patients, handgrip Strength (HGS) has been shown to provide better assessment than the SGA.[16] Ultrasonography has a better correlation with the MRI and the CT scan findings,[17] with the merit of being less expensive and involving no radiation exposure.[2] Pathological muscle changes, such as fatty infiltration, atrophy, and intramuscular fibrosis, can be assessed using ultrasound. These morphological derangements in the muscle may occur due to muscle edema from capillary leak or inflammation, which occurs initially due to fibrosis and fatty degeneration, followed by loss of muscle myofibrils and muscle contour, along with a decline in the performance of the muscle.[18]

Table 3: Muscle ultrasound in the studied groups

Variable	Time	Mean ± SD		*P* value
		CD group (*n* = 20)	ONS group (*n* = 20)	
RF:CSA (cm²)	T0	4.479 ± 1.38	4.85 ± 1.53	0.42 NS
	T1	3.78 ± 1.25	4.75 ± 1.45	0.029*
	T2	3.71 ± 1.33	4.74 ± 1.47	0.027*
RF:AP diam. (mm)	T0	1.51 ± 0.51	1.50 ± 0.29	0.91 NS
	T1	1.32 ± 0.43	1.48 ± 0.31	0.21 NS
	T2	1.25 ± 0.41	1.49 ± 0.27	0.04*
	T0	3.96 ± 0.59	4.18 ± 0.63	0.26 NS
RF:LL diam. (mm)	T1	3.73 ± 0.61	4.00 ± 0.63	0.18 NS
	T2	3.57 ± 0.51	3.99 ± 0.69	0.03*
	T0	1.20 ± 0.41	1.05 ± 0.22	0.16 NS
RF: Echogenicity	T1	2.15 ± 0.49	1.50 ± 0.51	0.000*
	T2	2.40 ± 0.94	1.60 ± 0.59	0.003*
	T0	7.524 ± 1.61	7.516 ± 1.22	0.99 NS
AT:CSA (cm²)	T1	6.83 ± 1.32	7.50 ± 1.25	0.10 NS
	T2	6.52 ± 1.34	7.37 ± 1.33	0.05 *
AT:AP diam. (mm)	T0	2.20 ± 0.58	2.21 ± 0.49	0.98 NS
	T1	1.87 ± 0.51	2.15 ± 0.49	0.08 NS
	T2	1.79 ± 0.51	2.11 ± 0.49	0.05*
AT:LL diam. (mm)	T0	4.61 ± .53	4.84 ± .62	0.21 NS
	T1	4.39 ± .52	4.72 ± .62	0.08 NS
	T2	4.23 ± .53	4.73 ± .61	0.009*
AT: Echogenicity	T0	1.20 ± .41	1.05 ± .22	0.16 NS
	T1	2.25 ± .64	1.55 ± .51	0.00*
	T2	2.25 ± .79	1.80 ± .69	0.06 NS

CD: Conventional diet; ONS: Oral nutritional supplement; T0; preoperative; T1; post-operative day3 (POD3); T3; POD7; S.D: Standard deviation;*significance with other group; ($P < 0.05$) NS: Not significant.; RF: Rectus femoris;. AT; anterior tibialis (CSA-AP-LL) cross section area anterio- posterior and lateral diameter;*significance with other group; ($P < 0.05$); NS: not significant

Using US technique, we detected a significant loss in the muscle mass (AT and RF) and increase in the echogenicity score in CD group than the ONS group. These observations were associated with a prolonged ICU stay. Our results corroborated those of Puthucheary ZA *et al*., who reported that alterations in muscle architecture correlated with increased ICU stay and bad outcome.[2] Grimm A *et al*. used the US technique for muscle assessment in patients with severe sepsis and concluded that the use of US technique holds great potential for muscle examination and can be used to obtain data about morphological derangement of muscles in these types of patients. They also reported that US is more preferable than invasive methods, such as muscle biopsy.[18] Gruther W *et al*. reported that decrease in muscle mass was negatively correlated with ICU stay.[19]

Providing nutrition to critically ill patients is aimed at preserving their muscle mass. Thus, it is essential to find an easily applicable method to measure the changes in the muscle mass during this critical period.[20] Ultrasonography can be used to measure muscle mass even in the presence of edema and fluid retention.[21] Here, we evaluated the efficiency of the US technique as a novel tool for the assessment of the nutritional status and muscle mass while providing nutrition support in hepatic patients. Puthucheary ZA demonstrated that US-assisted measurement of significant decrease in the muscle mass is associated with myofiber necrosis and muscular fascia inflammations.[2] Mourtzakis M and Wischmeyer P encouraged the use of the US technique for the assessment of skeletal muscles to quantify muscle wasting.[22,23] Lower limb muscles facilitate a better muscle mass assessment compared with upper limbs owing to the type of their fiber, which shows early changes.[24] For our study, we selected the RF and AT muscles.

Our study demonstrated that the administration of ONS improved liver function and intestinal function recovery. It has

Table 4: Patients characteristic and outcome

Variable	CD group (*n* = 20)	ONS group (*n* = 20)	*P* value
Age (years)	57.25 ± 5.821	54.50 ± 6.60	0.17 NS
Sex (M/F)	17/3	16/4	1 NS
RT/LT	15/5	17/3	0.69 NS
Child A/B	15/5	15/5	NA
SGA A/B	17/3	19/1	0.31 NS
Surgery time (hrs.)	4.55 ± 0.841	4.25 ± 1.164	0.36 NS
Operative blood loss (ml)	918.50 ± 464.48	1006.50 ± 227.81	0.45 NS
PRBCs unit transfusion	1.15 ± 1.22	1.10 ± 1.29	0.90 NS
Time of pass flatus (hrs.)	17.50 ± 4.174	11.10 ± 2.94	0.00*
pts.(n) of infection	7/13	4/16	0.48 NS
PONV (No. of pts.)	6/14	8/12	0.74 NS
ICU stay (days)	3.40 ± 1.569	2.55 ± 0.94	0.045*

Data expressed as mean ± SD; CD: Conventional diet group, ONS group: Oral nutritional supplement group, RT: Right lobe; LT; Left lobe; SGA: Subjective global assessment. PRBCs: Packed red blood cell transfusion. PONV: Postoperative nausea and vomiting; NA: Not applicable.; S.D: Standard deviation;*significance with other group; ($P < 0.05$); NS: not significant previously been shown that perioperative supplementation of branched-chain amino acid in HCC patients undergoing liver resection improved the liver function.[25] Chen L *et al*. previously reported that administration of ONS improved the outcome of the patients.[26]

Our results showed that ONS administration helped in maintaining muscle mass and echogenicity. In contrast to our findings, Casaer MP *et al*. demonstrated that decrease in lean body mass is not affected by type of nutritional support.[27]

Furthermore, our results showed the ONS group exhibited lower serum phosphate levels, which might indicate better liver regeneration. Hypophosphatemia occurs after hepatectomy as phosphate anion is essential for nucleotide synthesis and hepatocellular growth.[28]

Nutritional supplements provided after liver resection as additives of an ordinary diet improve the nutritional status and plays a fundamental role in hepatic regeneration and outcome. Enteral feeding maintains the integrity of the gastrointestinal tract, so it is often preferred over parenteral nutrition. Richter *et al*. demonstrated better outcomes in post-hepatic resection patients who received enteral feeding.[29]

As liver regeneration is affected by the nutritional status, sufficient nutritional intake can be indispensable for liver regeneration and outcome after major hepatectomy.[30]

There were certain limitations of our study. First, the follow-up period for our patients was very short. The elongation of the follow-up period could assist in assessment of long-term effects of ONS on the muscle mass. Second, we did not compare ultrasound parameters with other tools, such as BIA.

From our study, we concluded that early ONS administration following liver resection in hepatic patients facilitates maintenance of muscle mass. A better liver function may indicate proper regeneration as well as reduced ICU stay with better intestinal function recovery. US technique holds great potential for qualitative and quantitative measure of the muscles, which could, in turn, be used as a tool for nutritional assessments in hepatic patients.

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Nil.

Conflicts of interest
There are no conflicts of interest.

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