Prevalence and impact of sarcopenia in non-cirrhotic portal hypertension

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Abstract

Background & Aims: Little is known on nutritional parameters in patients with chronic portal vein thrombosis (PVT) and idiopathic non-cirrhotic portal hypertension (INCPH). The study aims to assess the prevalence and the clinical impact of sarcopenia in patients with non-cirrhotic portal hypertension (NCPH). A control group of cirrhotic patients was also studied. Both groups were followed up to establish the relationship between sarcopenia and clinical outcomes.

Methods: Sixty-seven patients with NCPH (51 PVT and 16 INCPH) were included in the study group and 104 patients with liver cirrhosis in the control group. The axial plane passing through the intersomatic disk between L3 and L4 was evaluated for the quantitative analysis of muscle mass and the skeletal muscle index (SMI) was calculated. The presence of sarcopenia was established according to SMI validated cut off.

Results: Sarcopenia was present in the 38% of patients with INCPH, 35% of patients with chronic PVT, 32% of patients with compensated cirrhosis and 54% of decompensated cirrhotics. During a mean follow-up of 51 ± 62 months, there was no difference in sarcopenic and non-sarcopenic patients with NCPH for incidence of ascites, hepatic encephalopathy, esophageal varices, variceal bleeding and death. However, the incidence of refractory variceal bleeding requiring TIPS placement was significantly higher in comparison with the non-sarcopenic ones (29% vs 7%, P = 0.01 at log-rank test).

Conclusions: In patients with NCPH sarcopenia is similar to that observed in cirrhotic patients. Moreover, the rate of refractory variceal bleeding was higher in sarcopenic patients suggesting a clinical negative impact of muscle depletion.

KEYWORDS
non-cirrhotic portal hypertension, portal vein thrombosis, sarcopenia, skeletal muscle index

Abbreviations: INCPH, idiopathic non-cirrhotic portal hypertension; NCPH, non-cirrhotic portal hypertension; PPG, portal pressure gradient; PVT, portal vein thrombosis; SMI, skeletal muscle index; TIPS, transjugular intrahepatic portosystemic shunt.

Barbara Lattanzi and Stefania Gioia should be considered joint first authors
1 | INTRODUCTION

Malnutrition is common in patients with liver cirrhosis with a prevalence of 65%-90%. The most relevant component of malnutrition in cirrhotic patients is a progressive and generalized loss of muscle mass, quality and strength known as sarcopenia. Sarcopenia may be detected with a prevalence varying from 30% to 90% in liver cirrhosis, depending on the assessment parameter used, and has been reported to be an independent predictor of morbidity and mortality in patients with cirrhosis, associated with a higher prevalence of complications including hepatic encephalopathy (HE). 

Computed Tomography (CT) and Magnetic Resonance image analysis, despite their cost, radiation exposure and logistics, are considered at present the gold standard techniques to quantify muscle mass.

Portal hypertension not due to cirrhosis is mainly caused by chronic portal vein thrombosis (PVT) or by the so-called idiopathic non-cirrhotic portal hypertension (NCPH).

To date for our knowledge, there are no data in the literature concerning the prevalence and the impact of sarcopenia in patients with non-cirrhotic portal hypertension (NCPH).

Our study aims to assess the prevalence of sarcopenia, measured with the skeletal muscle index (SMI) at CT-scan images, and to establish the relationship between sarcopenia and clinical outcomes, in patients with NCPH. A control group of cirrhotic patients was also studied.

2 | PATIENTS AND METHODS

The study retrospectively analysed demographic, clinical and biochemical data prospectively collected in patients with NCPH followed in our department from 2009 to 2013. In our center, the diagnostic workup of patients with NCPH includes a CT scan for the study of the portal vein system, thus all of patients with a NCPH undergoes CT-scan at diagnosis. Portal hypertension was diagnosed in the presence of splenomegaly and esophageal varices or other portal-systemic collaterals and was attributed to chronic PVT when imaging Doppler ultrasound and/or contrast-enhanced CT-scan showed the presence of portal cavernoma. Portal hypertension was attributed to NCPH after having excluded cirrhosis by liver biopsy and portal and hepatic veins obstruction at imaging techniques. Other causes of liver disease (chronic viral hepatitis, alcoholic liver disease, non-alcoholic steatohepatitis, autoimmune hepatitis, haemochromatosis and Wilson disease) were also excluded by a complete diagnostic clinical and laboratory workout.

Patients with liver cirrhosis with at least one abdomen CT scan extended to the axial plane passing through the intersomatic disk between L3 and L4 were enrolled as control. The diagnosis of liver cirrhosis was based on clinical, laboratory and histological features.

2.1 | Patients initial evaluation and follow-up

For each patient a detailed medical history was collected; data including gender, age, height together with the presence of signs and complications of portal hypertension (presence and size of esophageal varices, the presence of ascites or hepatic encephalopathy) were recorded. The clinical and laboratory data were obtained at the moment of the CT scan.

2.1.1 | Assessment of sarcopenia

In each patient, the axial plane passing through the intersomatic disk between L3 and L4 was evaluated for the quantitative analysis of muscle mass. All CT images were analyzed by a trained observer (SDC) with SliceOmatic V4.2 software (Tomovision, Montreal, Quebec, Canada), which enables specific tissue demarcation by using Hounsfield unit (HU) thresholds. Skeletal muscle is identified and quantified by HU thresholds of ~29 to +150. With these specific HU thresholds, measurements of the muscle mass are not influenced by the presence of ascites. Cross-sectional areas (cm²) were automatically computed by summing tissue pixels and multiplying by pixel surface area. Muscle cross-sectional area was normalized for height to obtain the skeletal muscle index (SMI) in cm²/m². Sarcopenia was defined according to previously validated cut-off values in cirrhotic patients awaiting liver transplant: L3 SMI: <39 cm²/m² for females and <50 cm²/m² for males.

2.1.2 | Follow-up

All patients are regularly followed with clinical and laboratory exams and ultrasound evaluation every 6 months. Endoscopic surveillance was made every 12 months, until the evidence of esophageal varices at risk of bleeding needing prophylaxis.

All episodes of new variceal bleeding, ascites, hepatic encephalopathy, TIPS placement and death occurring after the execution of the abdominal CT scan were recorded. The occurrence of variceal bleeding not controllable with an adequate primary endoscopic and pharmacological therapy and thus requiring TIPS placement was defined as refractory variceal bleeding.

All the episodes of bleeding were managed similarly with Terlipressin infusion (2 mg/4 h during the first 48 hours, followed by 1 mg/4 h thereafter), endoscopic therapy (band ligation) and antibiotic prophylaxis. Endoscopic procedures are always performed by selected qualified GI staff.
The purpose of the study was clearly explained to all the patients before obtaining their written informed consent. The “Sapienza” University of Rome Ethical Committee approved the collection of data of the patients for prognostic studies (5068/2018).

2.2 | Statistical analysis

Data are expressed as mean ± SD unless specified otherwise. Comparison between 2 groups was performed by chi-square test or paired and unpaired Student t test, when appropriate. The comparisons between data recorded twice in the same patients (SMI) were performed by Wilcoxon Signed Rank test. Comparison between 3 groups was performed by analysis of variance (ANOVA) and by Newman Keuls multiple comparison post hoc analysis. The occurrence of the clinical endpoint as well as the cumulative survival rate was described by time-dependent survival analysis. The log-rank test was used for the comparison between groups. To determine the independent predictors of refractory bleeding the adjusted Cox regression multivariate analysis was performed.

Due to the small number of events, the predictors at multivariate analysis were selected using clinical considerations. Furthermore, the parameter estimates might be slightly biased as at least 30 events would be needed for the multivariate model.

Families of jointly evaluated hypotheses were assessed by control of the FamilyWise Error Rate through Bonferroni correction. We report multiplicity-adjusted P-values, so that throughout the paper P < 0.05 shall be deemed as (globally) statistically significant.20

The Number Crunche Statistical System (NCSS) and R version 3.4.0 were used for all computations.

### TABLE 1 Clinical and biochemical characteristics of enrolled patients

<table>
<thead>
<tr>
<th>Variables</th>
<th>Idiopathic non-cirrhotic portal hypertension N = 16</th>
<th>Chronic Portal vein thrombosis N = 51</th>
<th>Cirrhosis N = 104</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean ± SD)</td>
<td>51.9 ± 19</td>
<td>48.9 ± 12.6</td>
<td>54.8 ± 13.7a</td>
<td>0.024</td>
</tr>
<tr>
<td>Male gender n(%)</td>
<td>9 (56%)</td>
<td>27 (53%)</td>
<td>80 (77%)a</td>
<td>0.03</td>
</tr>
<tr>
<td>Bilirubin (mg/dL)</td>
<td>1.24 ± 0.6</td>
<td>1.27 ± 1.2</td>
<td>2.7 ± 5.1</td>
<td>NS</td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>4 ± 0.6</td>
<td>4.1 ± 0.4</td>
<td>3.3 ± 0.6a</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>INR</td>
<td>1.3 ± 0.5</td>
<td>1.57 ± 0.6</td>
<td>1.4 ± 0.3</td>
<td>NS</td>
</tr>
<tr>
<td>Platelet (×10^12/μL)</td>
<td>111 ± 75</td>
<td>280±170x</td>
<td>93 ± 46</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Oesophageal varices n (%)</td>
<td>10 (63%)</td>
<td>39 (77%)</td>
<td>73 (70%)</td>
<td>NS</td>
</tr>
<tr>
<td>Ascites n (%)</td>
<td>4 (25%)</td>
<td>14 (27%)b</td>
<td>49 (47%)a</td>
<td>0.06</td>
</tr>
<tr>
<td>Hepatic encephalopathy n (%)</td>
<td>1 (6%)</td>
<td>0</td>
<td>41(39%)a</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>SMI cm^2/m^2</td>
<td>48.1 ± 8.4</td>
<td>48.4 ± 11.2</td>
<td>54.9 ± 43.6</td>
<td>NS</td>
</tr>
<tr>
<td>Sarcopenia n (%)</td>
<td>6 (38%)</td>
<td>18 (35%)</td>
<td>41 (40%)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Abbreviation: SMI, skeletal muscle index.

a Different from the other two groups at Newman-Keuls.
b In 3 patients with PVT ascites was detected with US or CT scan.

### RESULTS

Sixty-seven patients with NCPH were followed in our department from 2009 to 2013 and included in the study group. Since in our center the diagnostic workup of patients with NCPH includes a CT scan for the vascular study, all these patients have a CT-scan available for muscle assessment. Fifty-one were affected by chronic PVT and 16 by INCPH. One hundred and 4 patients with liver cirrhosis were included in the control group.

In 8 patients (50%) affected by INCPH the disease was idiopathic while in the other 8 patients an associated disease has been identified such as myeloproliferative neoplasm (2 patients), prothrombotic state (2 patients), congenital immunodeficiency (1 patient) and in 3 patients NCPH was secondary to oxaliplatin chemotherapy. Among patients with chronic PVT, 17 had a myeloproliferative neoplasm (33%) and 15 patients (29%) had a prothrombotic state.

Concerning the 104 cirrhotic patients, 35% were Child-Pugh class A, the 47% class B, and 18% class C. The main indication for CT-scan in cirrhotic patients was the surveillance of focal lesions (not confirmed as hepatocellular carcinoma in CT-scan) in 55% of patients, evaluation for liver transplantation (27%), vascular study for TIPS placement (15%) or for a suspected vascular shunt (13%).

The clinical and biochemical features of the patients are summarized in Table 1. As expected, mean age was significantly higher in patients with cirrhosis compared to the other 2 groups and gender distribution was different between the 3 groups being male more prevalent in the cirrhotics’ group. Albumin levels were lower in cirrhotic patients while platelets counts were significantly higher in the chronic PVT group, likely due to the presence of myeloproliferative diseases in some of the patients. Signs and complications of portal hypertension (esophageal varices, variceal bleeding, hepatic...
encephalopathy) were equally distributed in the 3 groups of patients. The presence of ascites was more frequent in patients with cirrhosis. Sarcopenia according to SMI was present in the 38% of patients with INCPH, in the 35% of patients with chronic PVT and in the 40% of patients with cirrhosis. When the liver disease was stratified according to MELD score (≥15), the prevalence of sarcopenia in patients with NCPH and compensated cirrhosis (MELD < 15) (36% vs. 32% \( P = 1.00 \)) was similar while cirrhotic patients with MELD ≥ 15 presented a slight higher prevalence of sarcopenia, without reaching statistical significance (36% vs 54% \( P = 0.14 \)) (Figure 1).

In Table 2 the patients NCPH are stratified according to the presence of sarcopenia, identified by the cut-off value of SMI. No significant differences in demographic and laboratory features have been observed between the 2 groups. Twenty-seven patients were on beta-blockers for primary prophylaxis (11 patients) or secondary prophylaxis (16 patients) of variceal bleeding. The use of beta-blockers was equally distributed between patients with and without sarcopenia. During a median follow-up of 29.2 months (IQR 54.8), there was no difference in sarcopenic and non-sarcopenic patients for the incidence of ascites, hepatic encephalopathy, development of oesophageal varices and death. The number of patients with variceal bleeding was also similar between the 2 groups; the number of bleeding episodes per patients was slight higher without reaching the significance in the sarcopenic than in non-sarcopenic group (1.7 ± 0.6 vs 1.3 ± 0.5, \( P = 0.098 \)). Moreover, 7 patients in the sarcopenic group and 3 in the non-sarcopenic group presented a variceal bleeding which was refractory to standard treatment and required a TIPS placement (29% vs 7%, \( P = 0.02 \) at log-rank test). The TIPS was successfully placed in all patients with a reduction in portal pressure gradient from 18.3 ± 10.6 to 5.2 ± 3.4 and avoided further bleeding.

**TABLE 2** Characteristic of patients with non-cirrhotic portal hypertension according to the presence of sarcopenia

<table>
<thead>
<tr>
<th>Variables</th>
<th>Sarcopenic patients (N = 24)</th>
<th>Non-sarcopenic patients (N = 43)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Etiology (INCPH/PVT)</td>
<td>6 (25%)/18 (75%)</td>
<td>10 (23%)/33 (74%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Follow-up</td>
<td>51.3 ± 59</td>
<td>50.2 ± 64</td>
<td>1.00</td>
</tr>
<tr>
<td>Age (mean ± SD)</td>
<td>51.2 ± 14.1</td>
<td>48.7 ± 14.5</td>
<td>1.00</td>
</tr>
<tr>
<td>Male gender n (%)</td>
<td>15 (62%)</td>
<td>22 (51%)</td>
<td>0.74</td>
</tr>
<tr>
<td>Bilirubin (mg/dL)</td>
<td>1 ± 0.8</td>
<td>1.05 ± 0.8</td>
<td>1.00</td>
</tr>
<tr>
<td>Cholinesterasis (UI/L)</td>
<td>6277 ± 2492</td>
<td>6806 ± 2410</td>
<td>0.92</td>
</tr>
<tr>
<td>INR</td>
<td>1.48 ± 0.5</td>
<td>1.52 ± 0.6</td>
<td>1.00</td>
</tr>
<tr>
<td>Esophageal varices no. of pts. (%)</td>
<td>18 (75%)</td>
<td>31 (72%)</td>
<td>0.52</td>
</tr>
<tr>
<td>( \beta )-blockers use</td>
<td>10 (41%)</td>
<td>17 (39%)</td>
<td>0.2</td>
</tr>
<tr>
<td>Clinical manifestation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ascites no. of pts. (%)</td>
<td>11 (41%)</td>
<td>13 (33%)</td>
<td>0.6</td>
</tr>
<tr>
<td>Hepatic encephalopathy no. of pts. (%)</td>
<td>1 (4%)</td>
<td>4 (10%)</td>
<td>0.4</td>
</tr>
<tr>
<td>Variceal bleeding no. of pts. (%)</td>
<td>9 (33%)</td>
<td>14 (35%)</td>
<td>1.0</td>
</tr>
<tr>
<td>No. of bleeding episodes/patient</td>
<td>1.7 ± 0.6</td>
<td>1.3 ± 0.5</td>
<td>0.098</td>
</tr>
<tr>
<td>Refractory variceal bleeding no. of pts. (%)</td>
<td>7 (29%)</td>
<td>3 (7%)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

**DISCUSSION**

This is for our knowledge the first study that analyses the prevalence and the impact of sarcopenia in patients affected by NCPH. The first
important result of our study is that 36% of NCPH patients were sarcopenic according to SMI cut-offs. This prevalence was similar to those observed in compensated cirrhotic patients (with MELD score <15) and lower, although not significantly, of that observed in de-compensated cirrhosis (Figure 1). As NCPH patients have a very mild liver damage, these results may suggest that portal hypertension per se may play a role in the development of sarcopenia.

The role of portal hypertension in the pathogenesis of sarcopenia is not known. A protein-losing enteropathy has been described in cirrhotic patients with portal hypertension but its role is not so clear. Indeed, the amelioration of the nutritional status observed after the resolution of portal hypertension induced by TIPS, support a link between portal hypertension and sarcopenia. Finally, portal hypertension leading to episodes of gastrointestinal bleeding or ascites may determine hospitalizations and states of illness that can determine a worsening in nutritional status and muscle mass.

The second important result of our study is that sarcopenic patients seem to be more prompt to develop complication related to portal hypertension. Sarcopenia resulted to be the main predictor of refractory variceal bleeding in the follow-up and resulted to be independent on well-known predictors of portal hypertension severity such as the variceal size and use of beta blockers. This result is of great importance considering that in patients with NCPH, the most important complication observed in the follow-up is represented by the variceal bleeding and re-bleeding; indeed, it is observed that in these patients, variceal progression is more rapid and bleeding more frequent than in cirrhotic patients. Considering refractory bleeding as an expression of a higher grade of PH, from our results we can speculate that sarcopenia is linked with a worsen portal hypertension. While there was no clinical indication, our patients did not undergo a measure of portal pressure.

In conclusions, our study shows a high rate of sarcopenia in patients with NCPH, similar to that observed in cirrhotic patients, indicating a role of portal hypertension in the pathogenesis of sarcopenia. Moreover, in our series, we observed a higher rate of refractory variceal bleeding in sarcopenic patients suggesting a clinical negative impact of this figure in patients with NCPH.

From a clinical point of view, our results suggest the importance of nutritional assessment in patients with NCPH and, in case of detection of sarcopenia, measures finalized to the amelioration in nutritional status should be taken into consideration.

CONFLICT OF INTEREST
None.

AUTHOR CONTRIBUTIONS
Barbara Lattanzi: study concept and design acquisition of data, analysis and interpretation of data; manuscript preparation; Stefania Gioia: study concept and design acquisition of data, analysis and interpretation of data; manuscript preparation; Simone Di Cola: acquisition of data: analysis and interpretation of data; Daria D’Ambrosio: acquisition of data; Silvia Nardelli: acquisition of data; Daniele Tavano: acquisition of data; Alessio Farcomeni: supervision of statistical analyses and performance of part of the statistical analyses; Manuela Merli: study concept and design, analysis and interpretation of data; manuscript preparation; final drafting of the manuscript; Oliviero Riggio: study concept and design, analysis and interpretation of data; manuscript preparation; final drafting of the manuscript; study supervision.

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