Research Article
Cirrhosis and Liver Failure

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Myosteatosis is closely associated with sarcopenia and significantly worse outcomes in patients with cirrhosis

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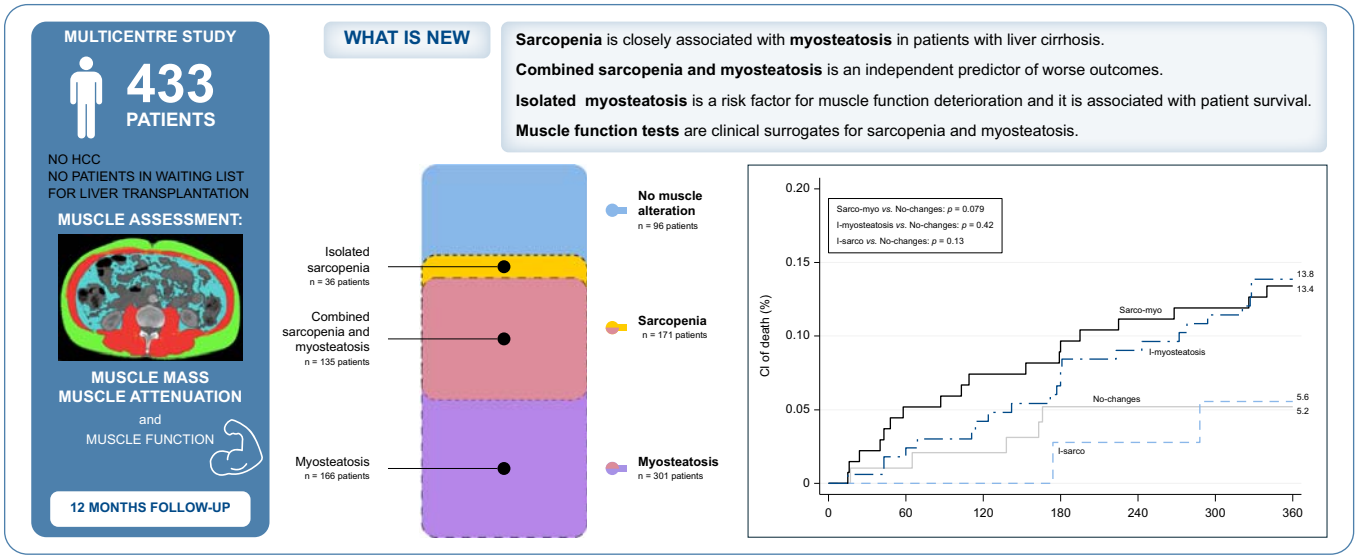
Graphical abstract



Highlights

- Sarcopenia is closely associated with myosteatosis in patients with cirrhosis.
- The combination of sarcopenia and myosteatosis is an independent predictor of worse outcomes.
- Isolated myosteatosis is a risk factor for decline in muscle function and is associated with patient survival.
- Muscle function tests are clinical surrogates for sarcopenia and myosteatosis.

Impact and implications

This study investigates the prognostic role of muscle changes in patients with cirrhosis. The novelty of this study is its multicentre, prospective nature and the fact that it distinguishes between the impact of individual muscle changes and their combination on prognosis in cirrhosis. This study highlights the prognostic role of myosteatosis, especially when combined with sarcopenia. On the other hand, the relevance of sarcopenia could be mitigated when considered together with myosteatosis. The implication from these findings is that sarcopenia should never be evaluated individually and that myosteatosis may play a dominant role in the prognosis of patients with cirrhosis.

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Myosteatosis is closely associated with sarcopenia and significantly worse outcomes in patients with cirrhosis

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Background & Aims: Sarcopenia and myosteatosis are common in patients with cirrhosis. This study aimed to determine the prevalence of these muscle changes, their interrelations and their prognostic impact over a 12-month period.

Methods: We conducted a prospective multicentre study involving 433 patients. Sarcopenia and myosteatosis were evaluated using computed tomography scans. The 1-year cumulative incidence of relevant events was assessed by competing risk analysis. We used a Fine-Gray model adjusted for known prognostic factors to evaluate the impact of sarcopenia and myosteatosis on mortality, hospitalization, and liver decompensation.

Results: At enrolment, 166 patients presented with isolated myosteatosis, 36 with isolated sarcopenia, 135 with combined sarcopenia and myosteatosis and 96 patients showed no muscle changes. The 1-year cumulative incidence of death in patients with either sarcopenia and myosteatosis (13.8%) or isolated myosteatosis (13.4%) was over twice that of patients without muscle changes (5.2%) or with isolated sarcopenia (5.6%). The adjusted sub-hazard ratio for death in patients with muscle changes was 1.36 (95% CI 0.99–1.86, $p = 0.058$). The cumulative incidence of hospitalization was significantly higher in patients with combined sarcopenia and myosteatosis than in patients without muscle changes (adjusted sub-hazard ratio 1.18, 95% CI 1.04–1.35). The cumulative incidence of liver decompensation was greater in patients with combined sarcopenia and myosteatosis ($p = 0.018$) and those with isolated sarcopenia ($p = 0.046$) than in patients without muscle changes. Lastly, we found a strong correlation of function tests and frailty scores with the presence of muscle changes.

Conclusions: Myosteatosis, whether alone or combined with sarcopenia, is highly prevalent in patients with cirrhosis and is associated with significantly worse outcomes. The prognostic role of sarcopenia should always be evaluated in relation to the presence of myosteatosis.

Introduction

Malnutrition is a frequent occurrence in patients with cirrhosis, with prevalence varying from 5% to 99% depending on the studied population and the diagnostic tools applied.[1–4] Several factors contribute to nutritional changes in these patients, including inadequate dietary intake, altered nutrient absorption and substrate utilisation modifications due to liver disease.[5] Moreover, a variety of disease-related acute and chronic complications can reduce a patient's ability to maintain their food intake[6] and/or increase their energy expenditure. Ultimately, malnutrition is associated with an increased risk of mortality, a higher incidence of complications related to portal hypertension and infections, and a longer hospital stay.[7–12]

Sarcopenia, a progressive and generalized loss of muscle mass and strength, is a significant feature of malnutrition in patients with cirrhosis.[13–16] Many studies have shown that sarcopenia is an independent predictor of morbidity and mortality,[11–13,17] and its inclusion in the evaluation of patients on liver transplantation (LT) waiting lists has been reported.[18] In obese patients with cirrhosis, loss of skeletal muscle can lead to a condition known as "sarcopenic obesity", which is associated with even worse prognosis and outcome.[17]

Muscle impairment in these patients is characterised not only by reduced muscle mass but also by changes in normal

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tissue structure and composition. Intramuscular fat accumulation, or myosteatosis, is known to reduce muscle quality.[17,19] Myosteatosis is more common in obese and elderly patients, but can also occur in normal weight individuals, reflecting a chronic inflammatory state.[20] Myosteatosis is associated with metabolic abnormalities and decreased muscle strength, and may lead to worsened median survival.[17,21]

Several studies have been conducted to investigate the role of sarcopenia and myosteatosis in the natural course of cirrhosis.[13,17,21] However, the available literature does not provide comprehensive information for various reasons. Firstly, most studies were retrospective. Second, the methods used to assess sarcopenia and myosteatosis, as well as the cut-offs used to define them, were heterogeneous.[13] Thirdly, most studies focus on patients with severe liver disease on LT waiting lists, while data on patients with less severe disease are still scarce.[22] Finally, the extent to which different muscle abnormalities coexist and impact patient prognosis and outcomes has not been previously defined.

To address this knowledge gap, we planned a multicentre prospective Italian study under the aegis of the Italian Association for the Study of the Liver.

Patients and methods

Study aims and design

The primary aim of the study was to investigate the impact of sarcopenia and myosteatosis, alone or in combination, on mortality, the need for hospitalization, and first or further liver decompensation. The secondary aim was to explore the correlations among muscle function, frailty and sarcopenia and myosteatosis in the subgroup of patients with available data.

Consecutive patients with cirrhosis from 26 Italian centres (see Fig. S1) were prospectively enrolled between January 2019 and December 2021 and followed-up for 1 year. The onset of the SARS-CoV-2 pandemic during the enrolment period significantly limited recruitment resources, especially from smaller centres. The cumulative incidence of the outcome of interest was calculated by competing risk analysis, and the prognostic role of muscle changes was assessed by multivariable analysis adjusted for major known prognostic indicators.

Eligibility and inclusion criteria

All patients with cirrhosis aged 40-75 years who underwent an abdominal computed tomography (CT) scan of the third lumbar (L3) vertebra for any clinical indication were eligible for the study. The cut-off age for inclusion was an arbitrary decision to reduce the potential confounding effect of age-related muscle abnormalities. We excluded patients on LT waiting lists or who had hepatocellular carcinoma (HCC), a history of LT, concomitant neuromuscular disease, current malignancy other than non-melanocytic skin cancer, a history of serious extrahepatic diseases, or HIV infection. Each patient was enrolled at the time of abdominal CT scan.

Patient characteristics and follow-up

Patient characterisation at inclusion was based on the following data: age, sex, liver disease aetiology, the presence and grade of ascites according to the International Club of Ascites, presence and grade of overt hepatic encephalopathy (OHE) according to the West Haven criteria, animal naming test (ANT) result of patients without OHE, oesophageal varices and size (according to the American Association for the Study of Liver Disease classification), history of gastrointestinal bleeding, and model for end-stage liver disease (MELD), MELD-Na and Child–Pugh scores.

Anthropometric data (including dry weight for patients with ascites and fluid retention) and hand grip test (HGT), liver frailty index (LFI) and 'timed up and go' (TUG) test results were also recorded.

Clinical visits to the outpatient clinic and biochemical exams were repeated at 6 and 12 months or more frequently when needed. During follow-up, data on hospitalizations and episodes of liver decompensation were collected during inpatient and outpatient visits, as well as through phone calls or emails.

The first episode of liver decompensation was defined as the presence of ascites, OHE, or variceal bleeding in a previously compensated patient. 'Further decompensation' was defined as the worsening of previous decompensation with recurrent, refractory, or complicated ascites; acute kidney injury; spontaneous bacterial peritonitis; variceal bleeding; or worsening of OHE. Death from any cause and LT were also recorded during the observation period.

Assessment of muscle changes

The assessment of sarcopenia and myosteatosis on CT images was centralised at the coordinating centre. All CT scans were assessed for sarcopenia and myosteatosis by two trained experts (S.DC. and L.L.).

According to the consensus statement of the EWGSOP (European Working Group on Sarcopenia in Older People),[23] abdominal muscle area was always evaluated by CT at the third or fourth lumbar vertebra in the present study. The Hounsfield unit (HU) limits used for assessing skeletal muscle mass ranged from -29 to +150 HU. The muscle area was normalised for height, resulting in a ratio (cm^2/m^2) known as the L3–L4 skeletal mass index (L3–L4 SMI). Patients were classified as having sarcopenia according to the validated SMI cut-off (<50 cm^2/m^2 for men and < 39 cm^2/m^2 for women).[24]

To assess myosteatosis across the entire muscle area, we computed the mean muscle attenuation in HU, which reflects the fat infiltration of muscles. We used the same CT image used for the SMI calculations. Patients were classified as having myosteatosis according to the following cut-off values: <41 HUs for patients with a BMI <24.9 kg/m^2 and <33 HU for those with a BMI ≥25 kg/m^2.[25]

The adipose tissue located within the peritoneal cavity was identified using HU thresholds for visceral adipose tissue ranging from -150 to -50 HU.[26] Subcutaneous adipose tissue was detected in the layer of adipose tissue beneath the skin and above the parietal peritoneal lining, using HU thresholds ranging from -190 to -30 HU.[27]

Assessment of muscle function and frailty

Assessment of patient muscle function at enrolment was based on the TUG test[28] and the HGT.[29] Patient frailty was assessed using the LFI.[30] Patients with LFI ≥4.5 were categorised as *frail*, those with LFI ≥3.2 and <4.5 were categorised as *prefrail*, and those with LFI <3.2 as *non-frail.*

Study approval and informed consent

The Local Ethical Committee of the Coordinator Center approved the study protocol and data collection (EC n° 94/19, 30/01/19), and each collaborating centre provided its own ethical committee approval. All patients provided informed consent to participate in the study.

Statistical analysis

Baseline patient characteristics are reported as proportions or means and standard deviations. The chi-square test assessed differences between proportions, and the Student's *t* test evaluated differences between means. We calculated the incidence rates of the events of interest as the number of observed events/100 patient-years of follow-up.

We assessed the cumulative incidence function (CIF) of death by competing risk analysis,[31] with LT as a competing event. Death and LT were considered competing events when assessing the CIF of first and further liver decompensation and of new hospitalizations. CIF differences were assessed by Gray's test.[32] Time zero for analyses of time to events (death, first or further decompensation and new hospitalization) was the date of the index CT for muscle assessment.

One-year incidence plots are shown. Throughout the text and figures, probabilities are expressed as percentages.

We assessed the adjusted impact of muscle damage on outcomes by a multivariable Fine-Gray model for competing risks.[33] We used Robust (sandwich) variance estimation for multivariable models.[34,35] The analysis included the following known prognostic indicators: sarcopenia, myosteatosis, serum bilirubin, INR, serum albumin, serum creatinine, age, sex, and the presence of OHE or ascites. The MELD[36] and Child-Pugh scores[37] were included in separate analyses excluding their individual components to avoid redundancy. A variable indicating participating centre was included in all multivariable models to account for between-centre heterogeneity. We performed variable reduction for the final multivariable models by a backwards procedure, based on the importance of risk predictors, clinical judgement and statistical significance. We included the number of variables in the multivariable models ≤1 per 10 observed outcome events.

In a subgroup of patients with available information on muscle function, we explored the relationships between HGT, TUG test and LFI results with muscle surface and muscle attenuation at the time of CT scan using regression analyses.

Statistical analyses were performed using STATA 16.1 (©2019 Stata Corporation, College Station, TX).

Results

Patient characteristics at inclusion and type of skeletal muscle damage

A total of 447 patients were eligible for the study, 14 of whom were excluded due to incomplete data, leaving 433 patients with available data for analysis. The mean follow-up (±SD) was 349±89 days.

The characteristics of the patients in the total population and in the subgroups according to the type of muscle changes are shown in Table 1.

The most common aetiology of cirrhosis was alcohol-related (39.9%), followed by hepatitis C (15.5%) and metabolic (15.0%). At enrolment, 158 patients were compensated, and 275 patients were decompensated, owing to ascites, OHE or portal hypertensive bleeding alone or in various combinations. The mean MELD score was 13±4.95 points, and the mean Child–Pugh score was 7.45±2.0 points; 162 patients (37.4%) were in class A, 196 (45.3%) in class B, and 75 (17.3%) in class C.

Isolated sarcopenia (I-sarcopenia) was diagnosed in 36 patients (8.3%), isolated myosteatosis (I-myosteatosis) in 166 patients (38.3%) and combined sarcopenia and myosteatosis in 135 patients (31.2%), while only 96 patients (22.2%) had no evidence of muscle damage (Fig. 1). Muscle changes were significantly more common in females than in males (88.8% *vs.* 73.4%, p <0.0001), mainly due to a significantly greater prevalence of I-myosteatosis in females (52.0% *vs.* 32.8%, p <0.0001) (Fig. S2). Overall, patients with any muscle changes had more advanced disease, with significantly greater Child–Pugh scores (7.6±2.0 *vs.* 7.0±1.8 points, p = 0.01) and a greater prevalence of ascites (53.4% *vs.* 36.5%, p = 0.003).

Myosteatosis was the most frequent muscle change, detected in 301 patients (69.5%). Compared to I-sarcopenia patients and patients without muscle changes, patients with myosteatosis were significantly older (60.8±8.8 *vs.* 57.2±9.1 years, p = 0.0001) and had significantly higher MELD (13±5 *vs.* 12±4 points, p = 0.006), Child–Pugh (7.6±2.1 *vs.* 7.0±1.8 points, p = 0.006) and ANT (18.5±5.5 *vs.* 16.5± points, p = 0.0037) scores. Comparisons between patients with and without myosteatosis, independent of the presence of sarcopenia, are shown in Table S1.

Patients with I-myosteatosis also had greater visceral and subcutaneous adiposity than patients with myosteatosis and sarcopenia (170±100 cm/m^2 *vs.* 131±79 cm/m^2, p = 0.0005) (Table 2).

Muscle function assessment was not always available, as some centres did not have a suitable handgrip dynamometer, which preventing LFI assessment in many patients. Specifically, we collected HGT results for 274 patients (63.3%), TUG test results for 228 patients (52.6%), and LFI results for 249 patients (57.5%). Compared to patients without myosteatosis, those with myosteatosis, either alone or associated with sarcopenia, had worse TUG test (13.3±5.7 *vs.* 9.4±3.8 points, p value <0.0001) and HGT (32.5±16.4 *vs.* 36.8±15.9 points, p = 0.049) results and were more frequently diagnosed as frail (33% *vs.* 13%, p = 0.002).

Impact of muscle changes on mortality

During the follow-up period, 51 deaths occurred, 45 of which were liver related. The major outcome events and corresponding incidence rates/100 patient-years are shown in Table 1. The incidence of death was higher in patients with muscle changes than in those without muscle changes. The difference was statistically significant for patients with I-myosteatosis (p = 0.015) and those with combined sarcopenia and myosteatosis (p = 0.012). The corresponding 1-year cumulative incidences of death with LT as a competing risk were 5.6% for patients without muscle changes, 5.2% for patients with I-sarcopenia, 13.8% for patients with I-myosteatosis and 13.4% for patients with combined sarcopenia and myosteatosis (Fig. 2). The differences between patients in each muscle change group and patients without muscle changes were,

Table 1. Patient characteristics at inclusion and major clinical outcomes.

	Whole cohort*	No muscle changes	I-sarco*	I-myo*	Combined sarco-myo*
Patients, n (%)	433	96 (22.2)	36 (8.3)	166 (38.3)	135 (31.1)
Age, years	57.1 (8.9)	56.7 (8.9)	58.6 (9.2)	60.8 (8.7) [0.0003]	60.7 (9.0) [0.0009]
Sex, M	308 (71.1)	82 (85.4)	31 (86.1)	101 (60.8) [<0.0001]	94 (69.6) [0.005]
Aetiology					
Alcohol	173 (39.9)	37 (38.5)	10 (27.7)	67 (40.4)	59 (43.7)
HCV	67 (15.5)	18 (18.8)	10 (27.7)	22 (13.2)	17 (12.6)
HBV	19 (4.4)	7 (7.3)	0	6 (3.6)	6 (4.4)
Alcohol+virus	38 (8.8)	12 (12.5)	1 (2.8)	12 (7.2)	13 (9.6)
NASH	65 (15.0)	12 (12.5)	8 (22.2)	31 (18.7)	14 (10.4)
Autoimmune/biliary disease	9 (2.1)	0	2 (5.6)	4 (2.4)	3 (2.2)
Others or undefined	62 (14.3)	10 (10.4)	5 (13.9)	24 (14.5)	23 (17.0)
Metabolic					
BMI, kg/m^2	27.8.7 (5.5)	28.7 (4.5)	24.4 (4.2) [<0.001]	28.6 (6.0)	24.6 (4.6) [<0.001]
Diabetes	138 (31.9)	33 (34.4)	8 (22.2)	61 (36.7)	36 (26.7)
Hypertension	160 (36.9)	30 (31.3)	10 (27.8)	72 (43.4) [0.05]	48 (35.6)
Dyslipidemia	75 (17.3)	17 (17.7)	5 (13.9)	36 (21.7)	17 (12.6)
Laboratory/clinical					
INR	1.4 (0.38)	1.34 (0.23)	1.34 (0.27)	1.43 (0.41) [0.036]	1.42 (0.41)
Albumin, g/L	35.8 (0.72)	37.4 (7.91)	37.7 (7.51	35.7 (7.0)	34.3 [0.0015]
Bilirubin, mg/dl	2.9 (4.5)	2.3 (2.4)	2.6 (4.0)	2.5 (3.0)	3.9 (6.7) [0.02]
Creatinine, mg/dl	0.90 (0.53)	0.88 (0.36)	0.83 (0.18)	0.87 (0.32)	0.97
Hb, g/dl	11.9 (2.4)	12.5 (2.3)	12.0 (2.4)	11.9 (2.3) [0.05]	11.3 [0.0001]
Oesophagogastric varices	277 (64.4)	68 (71.6)	23 (63.9)	105 (64.0)	81 (60)
Ascites	215 (49.7)	35 (36.5)	19 (52.8)	72 (43.4)	89 (65.9) [<0.0001]
OHE	86 (19.9)	17 (17.7)	10 (27.8)	36 (21.7)	23 (17.0)
ANT [n = 348]	17.1 (6.18)	18.4 (5.3)	18.8 (6.1)	16.2 (6.2) [0.01]	16.8 (6.5) [0.03]
Child–Pugh score	7.5 (2.0)	7.0 (1.78)	7.2 (1.9)	7.4 (2.1)	7.9 (2.0) [0.0009]
Child-Pugh A	162 (37.4)	44 (45.8)	12 (33.3)	68 (41.0)	38 (28) [0.018]
Child-Pugh B	196 (45.3)	40 (41.7)	18 (50)	68 (41.0)	70 (51.9) [0.018]
Child-Pugh C	75 (17.3)	12 (12.5)	6 (16.7)	30 (18.0)	27 (20) [0.018]
MELD score	12.9 (4.9)	12.2 (3.9)	11.6 (5.2)	12.9 (4.8)	13.9 (5.5) [0.007]
MELD-Na score	14.3 (5.4)	13.2 (4.3)	12.5 (6.3)	14.3 (5.2)	15.6 (5.9) [<0.001]
Ongoing therapies					
Primary prophylaxis†	221 (51)	52 (54.2)	22 (61.1)	79 (47.6)	68 (50.4)
NSBB	109 (25.2)	24 (25)	12 (33.3)	41 (24.7)	32 (23.7)
EVL	41 (9.5)	11 (11.5)	2 (5.6)	15 (9.0)	13 (9.6)
Secondary prophylaxis‡	71 (16.4)	17 (17.7)	8 (22.2)	23 (13.9)	23 (17.0)
Rifaximin	99 (24.5)	26 (27.7)	10 (31.2)	40 (26.0)	23 (18.6)
Lactulose	181 (44.8)	44 (46.8)	16 (50)	73 (47.4)	48 (38.7)
Albumin	59 (14.6)	15 (15.9)	4 (12.5)	24 (15.6)	16 (12.9)
Outcome events, N (incidence rate per 100 patient-years)					
Follow-up, patient-years	414	95	36	158	125
Death	51 (12.3)	5 (5.2)	2 (5.6)	24 (15.2) [0.015]	20 (16.0) [0.012]
Liver transplant	42 (9.7)	10 (10.5)	8 (22)	10 (6.3)	14 (11.2)
New hospitalization	207 (50.0)	33 (34.7)	17 (47.2)	88 (55.7) [0.0012]	69 (55.2) [0.0025]
All decompensation#	143 (31.4)	24 (25.3)	11 (30.6)	45 (28.5)	50 (40.0) [0.023]

Data are presented as number of patients or means and % or SD in brackets, as appropriate; between group differences were assessed by the Student's *t* test for means and Chi-square test for %, respectively.

ANT, animal naming test; EVL, endoscopic variceal ligation; INR, international normalised ratio; MELD, model for end-stage liver disease; NASH, non-alcoholic steatohepatitis; NSBB, non-selective beta blocker; OHE, overt hepatic encephalopathy.

*p value for significant differences from patients without muscle changes.

†Primary prophylaxis for variceal bleeding.

‡Secondary prophylaxis for variceal bleeding, mostly NSBB+EVL.

#All decompensation includes first or further decompensation.

however, not significant, although the increase in mortality in patients with combined sarcopenia and myosteatosis approached significance (p = 0.079).

Impact of muscle changes on hospitalization

During the 1-year follow-up, 207 liver-related hospitalizations were reported. The hospitalization incidence rate/100 patient-years in patients with combined sarcopenia and myosteatosis and I-myosteatosis was 55.7 and 55.2, respectively, both significantly higher (p = 0.0012 and 0.025, respectively) than that in patients without muscle changes (34.7). In patients with I-sarcopenia, the corresponding incidence rate was 47.2, which was not significantly different from that in patients without muscle changes (Table 1). The 1-year cumulative incidence of new hospitalization with death and LT as competing events

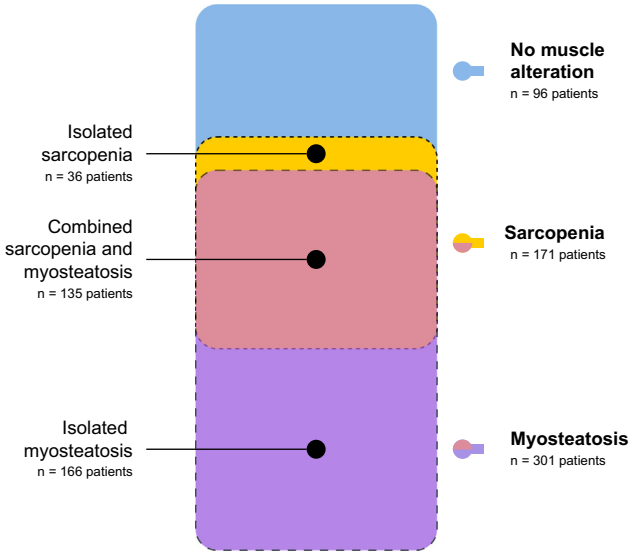


Fig. 1. Proportions and interactions of muscle abnormalities in our cohort. No muscle alterations (light blue), isolated sarcopenia (yellow), isolated myosteatosis (purple) and combined sarcopenia and myosteatosis (pink). (This figure appears in color on the web.)

was also significantly greater in patients with any type of muscle change than in those without muscle changes (Fig. 3).

Impact of muscle changes on first and further liver decompensation

At the start of the study, 158 patients with compensated cirrhosis were included, 43 without muscle changes, 12 with I-sarcopenia, 66 with I-myosteatosis and 37 with combined sarcopenia and myosteatosis.

Overall, decompensation occurred for the first time during follow-up in 5 of the 43 patients without muscle changes and 19 of the 115 patients with any type of muscle changes, with corresponding incidence rates per 100 patient-years of 11.3 and 16.7, respectively ($p = 0.39$). Among the 275 patients with decompensated cirrhosis at inclusion, 119 developed further decompensation: 19 of 53 without muscle changes, 11 of 24 with sarcopenia, 45 of 100 with myosteatosis, and 44 of 98 with combined sarcopenia and myosteatosis. The corresponding incidence rates per 100 patient-years were 37.6, 46.4, 50, and 48.9, respectively (p was not significant for differences between each type of change *vs.* no changes). In the overall population, the 1-year cumulative incidence of any decompensating event (either first or further, with death and liver transplant as competing events) was 39% for patients with combined sarcopenia and myosteatosis, 36% for those with I-sarcopenia, 34% for those with I-myosteatosis, and 30% for those with no muscle changes (Fig. 4). Compared with patients with no changes, the difference was significant for those with combined sarcopenia and myosteatosis ($p = 0.018$) and for those with I-sarcopenia ($p = 0.046$).

Adjusted prognostic role of muscle changes

Univariate analysis for death, hospitalization, and first or further decompensation is shown in Table S2. To investigate whether muscle changes had an independent impact on outcomes, we performed multivariable analyses. Multivariable models exploring the prognostic impact of muscle changes including MELD are shown in Table 3, while those including MELD-Na and Child-Pugh scores are shown in Table S3 and Table S4, respectively. The corresponding analyses excluding the MELD score and including its individual components are shown in Table S5.

Muscle changes had a significant effect on the incidence of hospitalization ($p = 0.012$) and tended to increase mortality ($p = 0.058$) but had no effect on first or further liver decompensation ($p = 0.60$). The c-statistic of the attenuation index for mortality was 0.69 (CI 0.62-0.76). In models including the individual components of the MELD score (ascites, OHE, and albumin) (Table S2), no independent prognostic effect of muscle changes was observed.

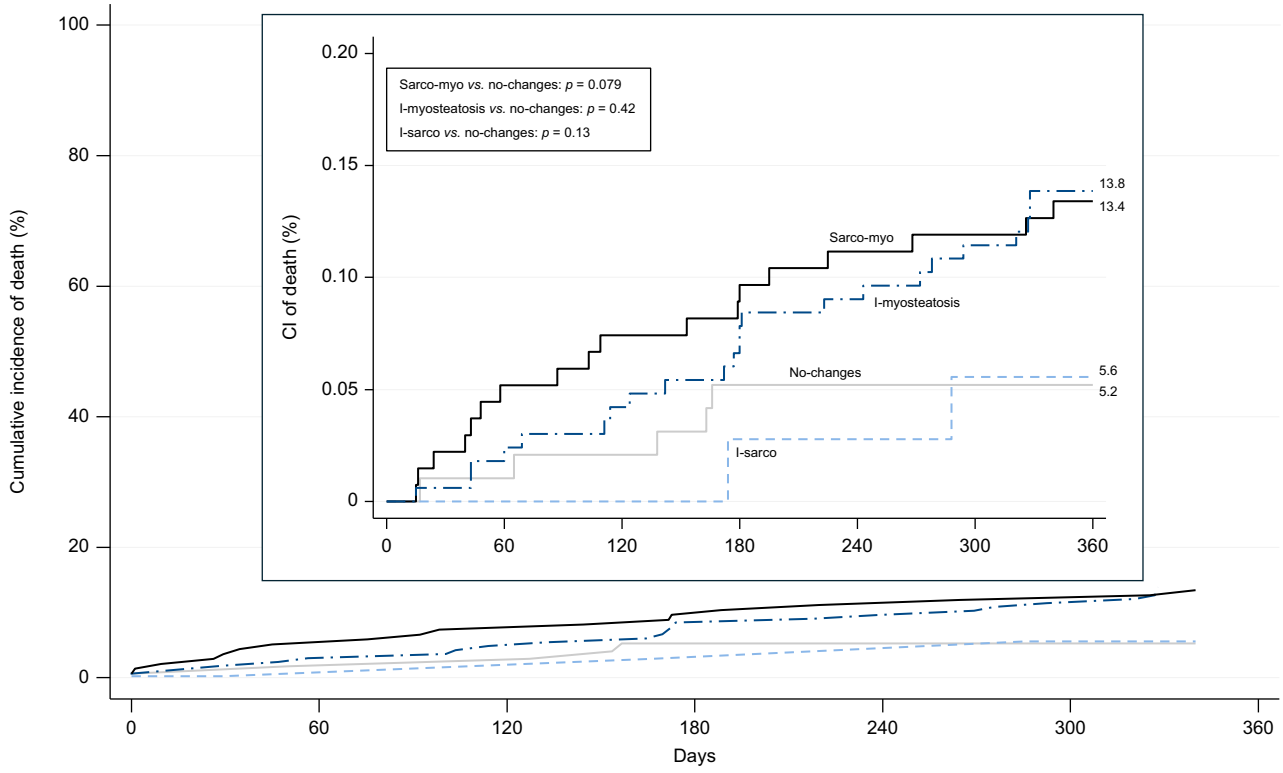
Correlations between muscle function and sarcopenia and myosteatosis

The frailty index was assessed in 238 patients, and the mean frailty index score was 3.7±0.85 points. A total of 65 patients were classified as frail, and 117 as prefrail. The mean frailty index score was significantly higher in patients with combined sarcopenia and myosteatosis (3.96±0.84) or I-myosteatosis (3.83±0.88) than in patients with I-sarcopenia (3.5±0.6) or no muscle changes (3.49±0.82). Differences in the same direction were found for HGT and TUG test results (Table 2). The HGT values correlated with the SMI ($r = 0.11$, $p < 0.0001$) but not with the HU (muscle attenuation utilised for the diagnosis of myosteatosis as a continuous value), while the TUG test and LFI did not correlate with the SMI but were inversely correlated with the HU (Fig. S3).

Table 2. Function tests and CT parameters of the whole population and of patient subgroups according to the type of muscle changes.

Parameter	Whole cohort	No muscle changes	I-sarco*	I-myo*	Combined sarco-myo*
Function tests, mean (SD)					
Frailty liver index (n = 238)	3.77 (0.85)	3.49 (0.82)	3.50 (0.60)	3.83 (0.88) [0.021]	3.96 (0.84) [0.0022]
Hand grip, kg (n = 263)	33.87 (16.3)	38.26 (17.33)	31.99 (8.88)	34.78 (17.03)	29.71 (15.17) [0.0021]
Up & go test, sec (n = 226)	11.8 (5.4)	9.9 (3.9)	8.0 (2.9)	13.3 (5.7) [0.0002]	12.6 (5.5) [0.003]
Computed tomography parameters, mean (SD)					
Patients, n	433	96	36	166	135
L3 SMI	50.3 (10.9)	59.1 (8.8)	43.4 (5.3) [<0.0001]	54.2 (9.4) [<0.0001]	41.2 (6.6) [<0.0001]
Muscle attenuation, %HU	31.6 (8.4)	39.8 (5.1)	40.1 (6.0)	27.8 (6.8) [<0.0001]	28.2 (6.7) [<0.0001]
VAT, cm/m^2	150.8 (91.8)	158.5 (87.7)	111.6 (80.7) [0.006]	170.2 (100.1)	131.9 (79.8) [0.017]
SAT, cm/m^2	196.8 (120.6)	213.5 (106.7)	137.5 (89.5) [0.0002]	236.1 (132.9)	152.8 (99.9) [<0.0001]

HU, Hounsfield unit; SAT, subcutaneous adipose tissue; SMI, skeletal muscle index; VAT, visceral adipose tissue.
*p value for significant differences compared with patients without muscle changes, computed by the Student's t test.



N° at risk							
No changes	96	94	92	87	86	85	84
I-sarco	36	34	33	30	29	28	26
Sarco-myo	135	123	117	112	107	105	103
I-myosteatosis	166	163	158	152	146	140	133

Fig. 2. Cumulative incidence of death with liver transplantation as a competing risk in four patient subgroups according to the type of muscle damage. The inset shows the same data on a larger scale. The numbers below the abscissa are the number of patients at risk. The numbers next to the curves are the cumulative incidence of death % at the end of the observation period. *p* values were computed by the Gray's test. I-myosteatosis, isolated myosteatosis; I-sarco, isolated sarcopenia; No changes, no muscle changes; Sarco-myo, sarcopenia combined with myosteatosis.

Discussion

In the present study, we aimed to assess the prognostic relevance of muscle alterations in a large prospective cohort of patients with cirrhosis and varying degrees of liver impairment.

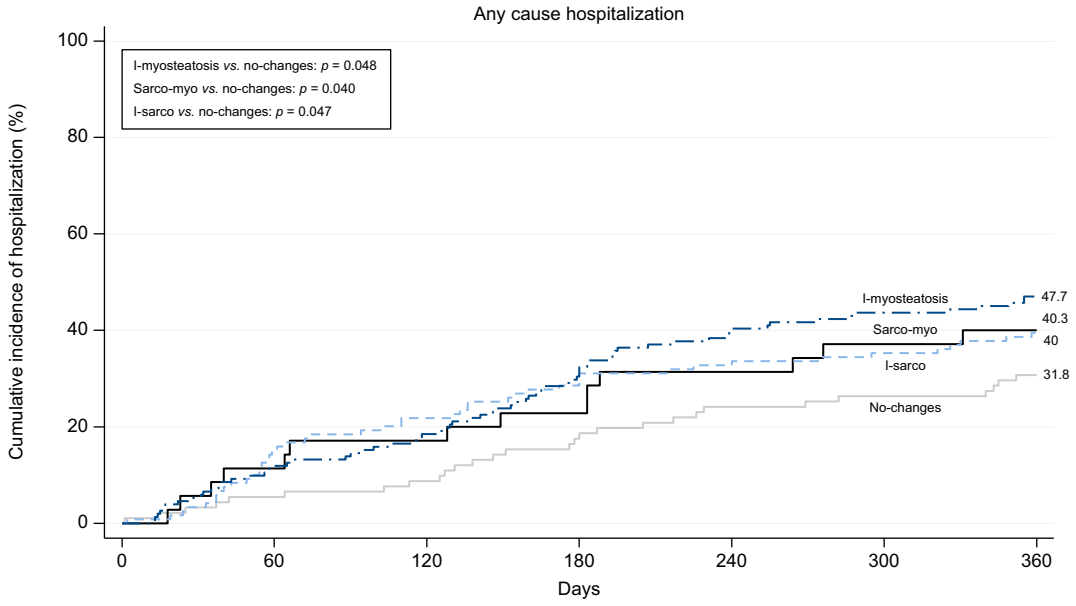
Seventy-eight percent of patients had some muscle changes at the time of enrolment. In our cohort, myosteatosis was the main muscle alteration affecting a significant proportion of the study population, while sarcopenia was rarely present in the absence of myosteatosis. In a retrospective cohort, Tachi *et al.*[38] reported a prevalence of myosteatosis of 82% and sarcopenia of 36%, with 93% of patients with sarcopenia having concomitant myosteatosis. Only a small proportion of patients had sarcopenia alone, as in our study. A recent study[39] examined the combination of reduced muscle function, quality, and quantity in 197 patients and suggested that myosteatosis may precede the onset of other muscle abnormalities. There may be a physiological explanation for this observation. Chronic hyperammonaemia, present in cirrhosis, induces mitochondrial dysfunction and a subsequent reduction in lipid oxidation, leading to intramuscular fat infiltration (myosteatosis).[40] Intramuscular fat, often associated with insulin resistance, has been linked to the development of a lipotoxic profile associated with the secretion of fatty acids and inflammatory adipokines, the latter having a detrimental effect on myocyte function.[41]

In our cohort, patients with myosteatosis, with or without sarcopenia, were generally older, more often female, had more visceral and subcutaneous fat, and had more advanced liver disease (see Table 1 and Table S1). In addition, these patients exhibited lower cognitive performance (as measured by the ANT) and were more likely to have ascites and bacterial infections. Functional performance was also impaired in these patients, as evidenced by lower TUG test scores and a greater tendency to frailty.

The role of myosteatosis, which has not always been evaluated in previous studies, was relevant in blunting that of sarcopenia, which has always been considered an important predictor of clinical outcomes in patients with cirrhosis.

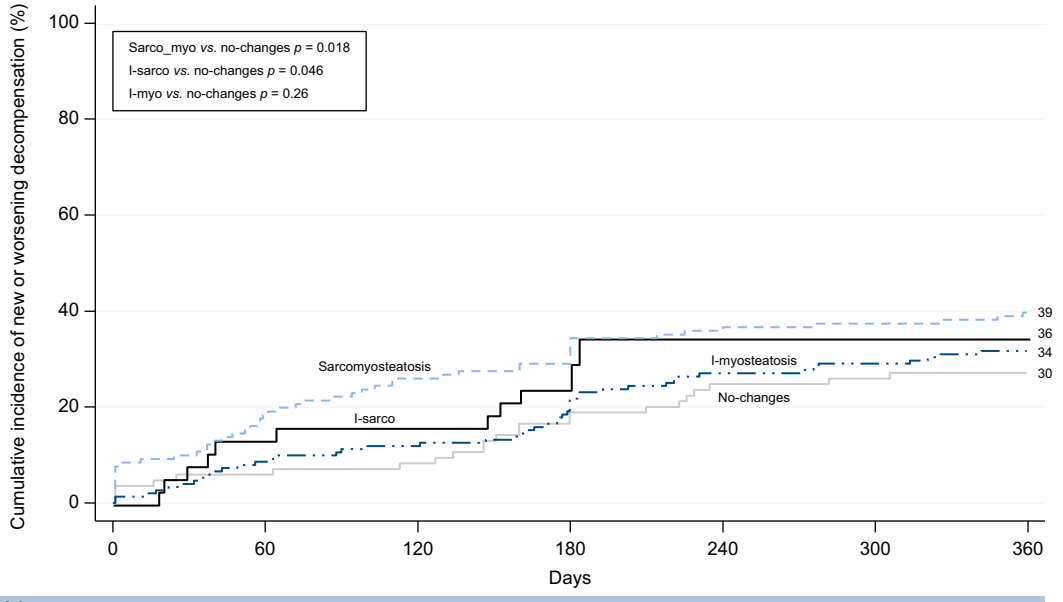
Indeed, a diagnosis of myosteatosis, even if not associated with sarcopenia, was a predictor of a greater risk of death (Fig. 2) and hospitalization (Fig. 3).

On the other hand, I-sarcopenia was not an independent predictor of mortality or hospitalization in our cohort. This finding may be influenced by the limited number of patients diagnosed with I-sarcopenia.



N° at risk							
No changes	96	87	83	73	67	65	61
I-sarco	36	29	26	22	18	16	15
Sarco-myo	135	95	85	74	67	64	59
I-myosteatosis	166	140	129	108	89	82	75

Fig. 3. Cumulative incidence of hospitalization, with death and liver transplantation as competing risks, in four patient subgroups according to type of muscle damage. The numbers below the abscissa are the number of patients at risk. The numbers next to the curves are the cumulative incidence of death % at the end of the observation period. *p* values were computed by the Gray test. I-myosteatosis, isolated myosteatosis; I-sarco, isolated sarcopenia; No changes, no muscle changes; Sarco-myo, sarcopenia combined with myosteatosis.



N° at risk							
No changes	96	90	87	76	69	68	67
I-sarco	36	29	27	23	18	17	17
Sarco-myo	135	103	91	84	74	72	68
I-myosteatosis	166	153	146	130	114	108	100

Fig. 4. Cumulative incidence of new liver decompensation (first or further) with death and liver transplantation as competing risks in four patient subgroups according to type of muscle damage. The numbers below the abscissa are the number of patients at risk. The numbers next to the curves are the cumulative incidence of death % at the end of the observation period. *p* values were computed by the Gray test. I-myosteatosis, isolated myosteatosis; I-sarco, isolated sarcopenia; No changes, no muscle changes; Sarco-myo, sarcopenia combined with myosteatosis.

Table 3. Adjusted prognostic role of muscle changes, by the Fine and Gray model, for death, hospitalization and liver decompensation, including the MELD score.

Variable	Score	Sub-hazard ratio	*p* value	95% CI	
Including the MELD score and excluding relevant single components					
Death (LT as a competing event)					
Muscle changes[†]	No = 0; I-sarco = 1, I-myo = 2; sarco-myo = 3	1.36	0.058	0.99	1.86
MELD	Continuous values	1.12	<0.0001	1.06	1.86
OHE	No = 0; yes = 1	2.09	0.011	1.18	3.69
Ascites	No = 0; yes = 1	2.73	0.005	1.35	5.52
Hospitalization (death and LT as competing events)					
Muscle changes[†]	No = 0; I-sarco = 1, I-myo = 2; sarco-myo	1.18	0.012	1.04	1.35
MELD[*]	Continuous values	1.36	0.191[*]	0.99	1.06
Albumin	g/L	1.28	0.052	0.998	1.65
Ascites	No = 0; yes = 1	1.86	0.062	0.98	1.91
Non-elective hospitalization (death and LT competing)					
Muscle changes[†]	No = 0; I-sarco = 1, I-myo = 2; sarco-myo = 3	1.12	0.25	0.92	1.36
MELD[*]	Continuous values	1.02	0.31[*]	0.98	1.07
HE	No = 0; yes = 1	2.26	0.001	1.38	3.72
Ascites	No = 0; yes = 1	2.86	<0.0001	1.67	4.87
First or further decompensation (death and LT as competing events)					
Muscle changes[†]	No = 0; I-sarco = 1, I-myo = 2; sarco-mio = 3	1.04	0.60	0.90	1.20
MELD	Continuous values	1.04	0.02	1.01	1.07
Ascites	No = 0; yes = 1	2.49	<0.0001	1.72	3.62
OHE	No = 0; yes = 1	1.48	0.038	1.02	2.15

LT, liver transplantation; MELD, model for end-stage liver disease; OHE, overt hepatic encephalopathy.
*MELD was forced in this analysis to show the effect of the other variables adjusted for MELD.
[†]In these analyses, each of the assessed muscle changes (*i.e.* I-sarcopenia, I-myosteatosis, and sarco-myosteatosis) was scored as absent/present; if none of them was significant, we included in the model a discrete variable scored as follows: no changes = 0, I-sarcopenia = 1, I-myosteatosis = 2, and combined sarcopenia and myosteatosis = 3.

Our study highlights that the occurrence of muscle changes, regardless of the type, represents a significant moment in the natural history of cirrhosis and adversely affects numerous outcomes. Multivariate analyses of competitive risk factors for mortality (with LT as a competing event), including the presence and type of muscle abnormalities, the MELD score and the presence of OHE or ascites (Table 3), showed that the presence of muscle changes negatively affected survival and hospitalization rates.

Altered muscle function and frailty have been shown to affect quality of life,[42] self-autonomy and prognosis of patients with cirrhosis.[43] In our study, many patients were categorised as frail or prefrail (76.5% in total). The correlation between frailty and TUG test results and muscle attenuation suggests that these tests, which are easy to perform, may be useful surrogates that overcome the need for imaging to assess changes in muscle quality.

The strengths of the present study include its prospective design, multicentre structure, use of CT scans (the gold standard for detecting muscle changes) in all patients, and detailed analysis of various types of muscle abnormalities.

Our study has several limitations. Nutritional assessment was only performed at baseline, without considering changes that may have occurred during follow-up. The different centres' policies regarding patient care in day services or in hospitals may have influenced the hospitalization rate, and laboratory data were not centralised. Muscle function tests were not performed in any of the centres participating in the study. Furthermore, although CT scans are widely used in patients with cirrhosis for various reasons (see Table S6), the availability of CT scans as an inclusion criterion may have introduced a baseline selection bias. Moreover, the prevalence of muscle alterations was sex dependent. Indeed, male patients represented 70% of the population, which could have impacted the overall cohort's distribution averages. Consequently, the study outcomes may not fully represent both sexes, highlighting the need for future larger studies designed with this in mind.

In conclusion, our study has shown that a comprehensive and integrated assessment of muscle changes is crucial for understanding their role in the natural history of cirrhosis. Our analyses revealed that myosteatosis is the most frequent alteration and has a significant impact on the course of liver disease. Many previous studies have focused on the assessment of sarcopenia, but concomitant myosteatosis is likely to play a major prognostic role. This may resize the predictive role of sarcopenia in favour of a more comprehensive consideration of muscle changes.

Our study suggests that muscle function tests could serve as a valuable and practical bedside tool for estimating prognosis and identifying patients at greater risk of mortality.

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Abbreviations

ANT, animal naming test; CIF, cumulative incidence function; CT, computed tomography; HGT, hand grip test; HU, Hounsfield unit; I-myosteatosis; isolated myosteatosis; I-sarcopenia; isolated sarcopenia; LFI, liver frailty index; LT, liver transplantation; MELD, model for end-stage liver disease; OHE, overt hepatic encephalopathy; SMI, skeletal muscle index; TUG, timed up and go.

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Conflict of interest

The authors declare that they have no competing interests.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

Manuela Merli: study concept and protocol, data collation, study supervision, analysis, results interpretation, and drafting and revision of the manuscript for important intellectual content.

Simone di Cola: study protocol, data coordinator, analysis plan, results interpretation, and drafting and revision of the manuscript. Gennaro D'Amico: analysis, results interpretation, revision of the manuscript for important intellectual content. Paolo Caraceni and Filippo Schepis: centre supervision, results interpretation, manuscript revision for important intellectual content. Simone Loredana, Pietro Lampertico, Massimo Iavarone, Pierluigi Toniutto, Silvia Martini, Sergio Maimone, Antonio Colecchia, Gianluca Svegliati-Barone, Alessio Aghemo, Saveria Lory Crocè;, Luigi Elio Adinolfi, Maria Rendina, Enrico Pompili, Federica Indulti, Dario Saltini, Giulia Tosetti, Paola Serri, Mariangela Bruccoleri, Carolina Martelletti, Veronica Nassisi, Alberto Ferrarese, Carlo Alessandria, Ilaria Giovio, Chiara Masetti, Nicola Pugliese, Michele Campigotto, Riccardo Nevol: centre supervision, results interpretation, manuscript revision. Gaetano Bertino, Clara Balsano, Nerio Lapadre, Marcello Maida, David Sacerdoti, Leonardo Antonio Natola, Carolina Ciacci, Antonella Santonicola, Raffaele Cozzolongo, Lorenzo Antonio Surace, Anna Ludovica Fracanzani, Annalisa Cespiati, Alessandro Federico, Mario Romeo, Antonio Grieco, Giuseppe Marrone, and Luca Vizioli: Patient selection and inclusion, follow-up, and data collection.

Data availability statement

The data that support the findings of this study are available from the corresponding author, M.M., upon reasonable request.

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Supplementary data

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