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

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List of investigators

Study site	Principal Investigator	Associate Investigator	No. patients enrolled
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Ferrara	Simone Loredana		44
Milan	Pietro Lampertico	Massimo Iavarone Giulia Tosetti Paola Serri Mariangela Bruccoleri	42
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Messina	Sergio Maimone	Veronica Nassisi	28
Verona	Antonio Colecchia	Alberto Ferrarese	23
Ancona	Gianluca Svegliati Barone		18
Turin	Carlo Alessandria	Ilaria Giovo	16
Milan	Alessio Aghemo	Chiara Masetti Nicola Pugliese Michele Campigotto	13
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Naples	Luigi Elio Adinolfi	Riccardo Nevola	11
Bari	Maria Rendina		11
Catania	Gaetano Bertino		9
Caltanissetta	Marcello Maida		7
L'Aquila	Clara Balsano	Nerio Iapadre	7

Verona	David Sacerdoti	Leonardo Antonio Natola	7
Salerno	Carolina Ciacci	Antonella Santonicola	6
Milan	Anna Ludovica Fracanzani	Annalisa Cespiati	5
Castellana Grotte	Raffaele Cozzolongo		5
Lamezia Terme	Lorenzo Antonio Surace		5
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Rome	Antonio Grieco	Giuseppe Marrone	3
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Promotion and funding

This was a prospective observational study, performed on behalf of the *Italian Association for the Study of the Liver* (AISF). No funding was available for this study.

Supplementary tables

Table S1 . *Patients characteristics at inclusion according to the presence or absence of myosteatosis**

	Whole cohort	No Myosteatosis	Myosteatosis
Number	433	130 (30)	303 (70)
Age	57.1 (8.9)	56.7 (3.9)	61.0 (8.2) [0.0001]
Sex M	308 (71.1)	113 (85.6)	196 (64.7) [0.0009]
Etiology			
Alcohol	225 (51.9)	66 (50)	160 (52.8)
HCV	109 (25.2)	40(30,3)	69 (22.8)
HBV	27 (6.23)	11(7,6)	16 (5.3)
NASH	70 (16.5)	22 (16,7)	49 (16.2)
Autoimmune/Biliary disease	9 (2.1)	2 (1.5)	7 (2.3)
Others or undefined	60 (13.8)	15 (11.4)	45 (14.9)
Metabolic			
Diabetes	138 (31.8)	41 (31.1)	97 (32.0)
Arterial hypertension	160 (36.9)	40 (30.3)	121 (39.9)
Dyslipidemia	75 (17.3)	22 (16.7)	54 (17.8)
Clinical features			
Ascites	214 (49.4)	54 (40.9)	161 (53.1) [0.01]
E-G Varices╫	277 (63.9)	91 (68.9)	186 (61.4)
I-Prophylaxis ╞	221 (51)	74 (56.1)	147 (48.5)
NSBB	109 (25.2)	36 (27.7)	73 (24.1)
EBL	41 (9.5)	13 (10)	28 (9.24)
II-Prophylaxis §	71 (16.4)	25 (19.2)	46 (15.2)
Overt Hepatic encephalopathy	82 (18.9)	27 (20.5)	55 (18.5)
ANT [n=348]╪	17.1 (6.13)	18,5 (6.17)	16,4 (6.11) [<0.001]
AKI	19 (4.38)	4 (3.0)	16 (5.3)
Episodes of infection	55 (12.7)	7(5.3)	48 (15.8) [<0.001]
Severity of liver disease			
Child-Pugh			
A ┤	162 (37.4)	56 (43.1)	106 (35)
B ┤	196 (45.3)	58 (44.6)	139 (45.9)
C ┤	75 (17.3)	18 (13.8)	58 (19.1)
MELD score	12.99 (4.32)	12.0 (4.46)	13.47 (4.43) [<0.001]
MELD-Na score	14.3 (4.72)	13.0 (5.11)	14.9 (5.08) [<0.001]
MELD score < 15	303	108 (35.7)	195 (64.3)

MELD score ≥ 15	145	37 (25.5)	108 (74.5)
Bilirubin mg/dL	2.88 (4.52)	2.35 (4.53)	3.12 (4.52) [0.05]

*Data are presented as number of patients or means and % or SD in brackets, as appropriate, computed by the Student's t test for means and by the chisquare test for proportions.

^ The percentage is calculated based on the number of patients with alcoholic etiology.

¶ p value for significant differences from patients without muscle changes

╫ Esophago-Gastric varices

╪ANT= animal naming test, available in 348 patients

╞ Primary prophylaxis for variceal bleeding

§ Secondary prophylaxis for variceal bleeding, mostly NSBB+EVL

┤ Child-Pugh class A, B, C.

Abbreviations: MELD, model for end stage liver disease; NSBB, non-selective beta blockers; EVL, endoscopic variceal ligation;

Table S2. Univariable analysis for death, hospitalization and new decompensation by the Fine and Gray model.

Variable	Score	Sub-Hazard Ratio	p	95% Confidence Interval	
Death (LT competing)					
Sarcopenia	No=0; sarco=1	1.21	0.492	0.69	2.11
Myosteatosis	No=0; myo=1	2.86	0.010	1.28	6.41
Combined sarcopenia and myosteatosis	No=0; combined sarco-myo=1	1.39	0.011	1.07	1.79
Bilirubin	Continuous values	1.07	0.001	1.03	1.11
INR	Continuous values	2.98	<0.0001	1.89	4.71
Albumin	Continuous values	0.37	<0.0001	0.24	0.57
Creatinine	Continuous values	1.35	<0.0001	1.23	1.47
Age	Continuous values	1.01	0.327	0.98	1.04
Gender		1.06	0.841	0.58	1.95
OHE	No=0; yes=1	3.40	<0.001	1.95	5.94
Ascites	No=0; yes=1	4.34	<0.001	2.18	8.62
MELD	Continuous values	1.15	<0.001	1.10	1.21
Child-Pugh	5 tp 15 points	1.61	<0.001	1.40	1.84
Hospitalization (death and LT competing)					
Sarcopenia	No=0; sarco=1	1.01	0.907	0.78	1.31
Myosteatosis	No=0; myo=1	1.36	0.034	1.02	1.80
Combined sarcopenia and myosteatosis	No=0; combined sarco-myo=1	1.14	0.017	1.02	1.28
Bilirubin	Continuous values	0.99	0.659	0.96	1.02
INR	Continuous values	1.25	0.188	0.89	1.72
Albumin	Continuous values	1.06	0.590	0.85	1.31
Creatinine	Continuous values	1.33	<0.001	1.22	1.44
Age	Continuous values	1.00	0.546	0.99	1.01
Gender		1.11	0.445	0.84	1.45
OHE	No=0; yes=1	1.39	0.027	1.04	1.86

Ascites	No=0; yes=1	1.32	0.026	1.03	1.69
MELD	Continuous values	1.03	0.025	1.00	1.06
Child-Pugh	5 tp 15 points	1.10	0.006	1.03	1.18
First or further decompensation (death and LT competing)					
Sarcopenia	No=0; sarco=1	1.48	0.019	1.07	2.06
Myosteatosis	No=0; myo=1	1.29	0.166	0.89	1.87
Combined sarcopenia and myosteatosis	No=0; combined sarco-myo=1	1.07	0.268	0.94	1.23
Bilirubin	Continuous values	1.01	0.382	0.98	1.04
INR	Continuous values	1.36	0.055	0.99	1.86
Albumin	Continuous values	0.76	0.044	0.58	0.99
Creatinine	Continuous values	1.17	0.134	0.95	1.44
Age	Continuous values	1.00	0.997	0.98	1.01
Gender		0.98	0.937	0.68	1.41
OHE	No=0; yes=1	1.94	<0.001	1.67	2.77
Ascites	No=0; yes=1	2.99	<0.001	2.10	4.26
MELD	Continuous values	1.07	<0.001	1.04	1.10
Child-Pugh	5 tp 15 points	1.29	<0.001	1.19	1.39

Abbreviations: INR= international normalized ratio; OHE overt hepatic encephalopathy

Table S3. Significant risk predictors for death, hospitalization and new decompensation by the Fine and Gray model, and including MELD-Na.

Variable	Score	Sub-Hazard Ratio	p	95% Confidence Interval	
Including MELD-Na and excluding relevant single components					
Death (LT competing)					
Muscle changes ¶	No=0; I-sarco=1, I-myo =2; sarco-myo=3	1.33	0.086	0.95	1.84
MELD-Na	Continuous values	1.12	<0.0001	1.07	1.18
OHE	No=0; yes=1	2.08	0.011	1.18	3.66
Ascites	No=0; yes=1	2.51	0.010	1.24	5.09
Hospitalization (death and LT competing)					
Muscle changes ¶	No=0; I-sarco=1, I-myo =2; sarco-myo	1.18	**0.014**	1.03	1.35
MELD-Na	Continuous values	1.02	0.191	0.98	1.05
Albumin	g/L	1.28	0.047	1.00	1.63
Ascites	No=0; yes=1	1.39	0.054	0.99	1.95
First or further decompensation (death and LT competing)					
Muscle changes ¶	No=0; I-sarco=1, I-myo =2; sarco-mio=3	1.03	0.70	0.89	1.18
MELD-Na	Continuous values	1.03	0.039	1.00	1.06
Ascites	No=0; yes=1	2.52	<0.0001	1.73	3.67
OHE	No=0; yes=1	1.48	0.038	1.02	2.14

¶ In these analyses, each of the assessed muscle changes (i.e I-sarcopenia, I-myosteatosis, sarco-myosteatosis) were scored as absent/present: when 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, combined sarcopenia and myosteatosis=3.

Table S4. Adjusted prognostic role of muscle changes, by the Fine and Gray model, for death, hospitalization and new liver decompensation, including Child–Pugh score.

Variable	Score	Sub-Hazard Ratio	p	95% Confidence Interval	
Including Child-Pugh 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	1.77	0.077	0.97	1.79
Child–Pugh score	5 tp15 points	1.59	<0.0001	1.38	1.83
Creatinine	mg/dL	1.29	<0.0001	1.19	1.41
Hospitalization (death and LT as competing events)					
I-Myosteatosis	No=0; yes=1	1.39	0.034	1.02	1.88
Child–Pugh score	5 tp15 points	1.1	0.022	1.01	1.18
Creatinine	mg/dL	1.31	<0.0001	1.20	1.43
Non elective hospitalization (death and LT as competing events)					
I-sarcopenia	No=0; yes=1	1.80	0.092	0.91	3.57
Child–Pugh score	5 tp15 points	1.35	<0.0001	1.22	1.50
New decompensation (death and LT as competing events)					
Muscle changes¶	No=0; I-sarco=1, I-myo =2; sarco-myo=3	0.94	0.44	0.80	1.10
Child–Pugh score	5 tp15 points	1.21	0.022	1.10	1.31

¶ 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.

Table S5. Significant risk predictors for death, hospitalization and new decompensation by the Fine and Gray model¶.

Variable	Score	Sub-Hazard Ratio	p	95% Confidence Interval	
Death (LT competing)					
Muscle changes	No=0; I-sarco=1, I-myo =2; sarco-myo	1.4	0.20	0.83	2.37
INR	Continuous values	3.06	0.002	1.53	6.11
Albumin	g/L	0.63	0.028	0.43	0.95
Creatinine	mg/dL	1.33	<0.0001	1.16	1.52
OHE	No=0; yes=1	2.39	0.003	1.33	4.29
Ascites	No=0; yes=1	3.25	0.005	1.44	7.3
Hospitalization (death and LT competing)					
I-Myosteatosis	No=0; yes=1	1.44	0.20	1.06	1.95
Creatinine	mg/dL	1.36	<0.0001	1.25	1.48
Ascites	No=0; yes=1	1.39	0.031	1.03	1.88
New decompensation (death and LT competing)					
Muscle changes	No=0; I-sarco=1, I-myo =2; sarco-mio	1.12	0.22	0.93	1.37
OHE	No=0; yes=1	2.38	<0.0001	1.47	3.87
Ascites	No=0; yes=1	3.04	<0.0001	1.85	5.01

¶ Models including model for end stage liver disease and Child-Pugh score are included in separate analyses shown in table 3 and supplementary table 4.

Abbreviations: I-sarco= isolated sarcopenia; I-myo= isolated myosteatosis; sarco-myo: sarcopenia and myosteatosis. INR= international normalized ratio; OHE hepatic encephalopathy

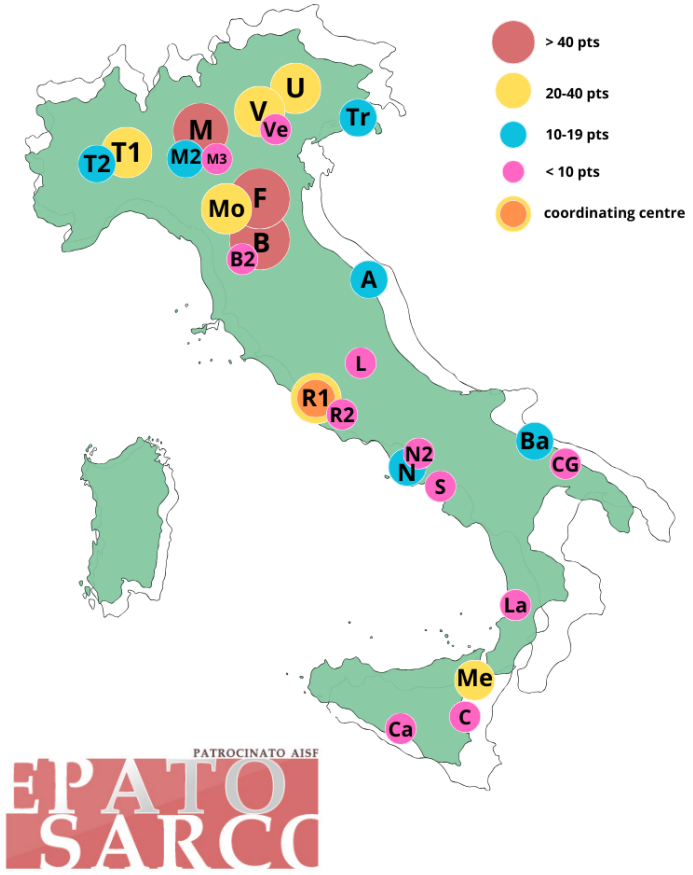
Table S6. Principal indications for abdominal CT-scan in our cohort.

CT-scan indication	**number (whole cohort 433 pts)**
Study of liver parenchyma (exclusion of HCC, US unreliable due to patients conformation …)	300
Evaluation of portal hypertension	44
Evaluation of splanchnic vein thrombosis	37
Miscellanea (feasibility of TIPS placement, abdominal pain, other …)	52

Abbreviations: HCC hepatocellular carcinoma; US, ultrasound; TIPS, Transjugular Intrahepatic Portosystemic Shunt

Supplementary figures

Fig. S1. Geographical distribution and details of centers involved in EpatoSarco multicenter study



Cod	City	Hospital	n
		NORTH OF ITALY	
B	BOLOGNA	Alma Mater Studiorum - University of Bologna	
F	FERRARA	Arcispedale S.Anna	
M	MILAN	Foundation IRCCS Ca' Granda Ospedale Maggiore Policlinico	
U	UDINE	Hepatology and Liver Transplantation Unit, Azienda Sanitaria Universitaria Friuli Centrale, University of Udine	
T1	TURIN	Gastrohepatology Unit AOU Città della Salute e della Scienza di Torino	
Mo	MODENA	Azienda Ospedaliero-Universitaria of Modena	
V	VERONA	Gastroenterology, Verona University Hospital, Ospedale Borgo Trento	
T2	TURIN	Division of Gastroenterology and Hepatology, Città della Salute e della Scienza Hospital, University of Turin	
M2	MILAN	IRCCS Humanitas Research Hospital, Rozzano	
Tr	TRIESTE	Clinica Patologie del Fegato, Azienda Sanitaria Universitaria Giuliano Isontina, Trieste, Italy	
Ve	VERONA	Liver Unit, Department of Medicine, University and Azienda Ospedaliera Universitaria Integrata of Verona	
M3	MILAN	General Medicine and Metabolic Diseases, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico	
B2	BOLOGNA	Internal Medicine Unit for the Treatment of Severe Organ Failure, IRCCS Azienda Ospedaliero-Universitaria di Bologna	
		CENTER OF ITALY	
R1	ROME	Department of Translational and Precision Medicine, Sapienza University of Rome	
A	ANCONA	Liver Injury and Transplant Unit, Ospedali Riuniti	
R2	ROME	Internal and Liver Transplant Medicine Unit, Fondazione Policlinico Universitario Agostino Gemelli IRCCS	
		SOUTH OF ITALY	
Me	MESSINA	Division of Medicine and Hepatology, University Hospital of Messina, Messina,	
N	NAPLES	AOU Vanvitelli, Napoli, Piazza Miraglia, UOC di Medicina Interna	
Ba	BARI	Section of Gastroenterology, Department of Emergency and Organ Transplantation, University of Bari	
C	CATANIA	Hepatology Unit Department of Clinical and Experimental Medicine University of Catania, Policlinico "Rodolico"	
Ca	CALTANISSETTA	Gastroenterology and Endoscopy Unit, S. Elia-Raimondi Hospital	
L	L'AQUILA	Department of Life, Health, Environmental Sciences, School of Emergency and Urgency Medicine	
S	SALERNO	Department of Medicine, Surgery and Dentistry, "Scuola Medica Salernitana", University of Salerno	
CG	CASTELLANA GROTTE	Division of Gastroenterology, National Institute of Gastroenterology S De Bellis	
La	LAMEZIA TERME	Traveler and Migration Medicine Center, ASP Catanzaro	
N2	NAPLES	Department of Clinical and Experimental Medicine, Second University of Naples	

Fig. S2. Different distribution of muscle alterations (red, isolated sarcopenia; blue, isolated myosteatosis; yellow, combinated sarco-myosteatosis; grey , no muscle alterations) between male and females

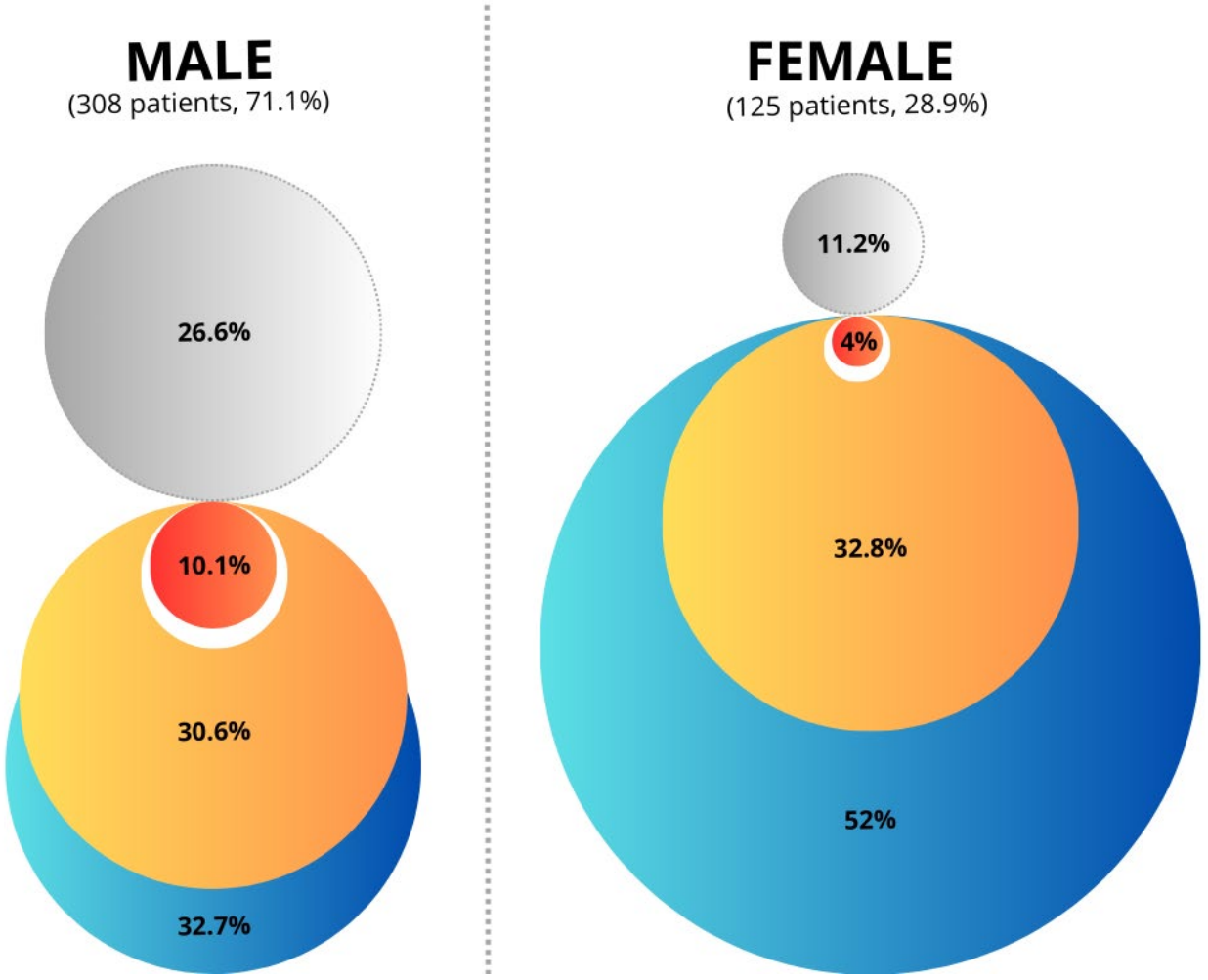


Fig. S3. Relationship between functional tests and frailty index with L3-SMI and muscle attenuation on CT scans. Each of the 4 panels represent the distribution of the assessed parameters in single patients (solid circles) and the corresponding fitted regression line. R 2 and p values refer to the corresponding regression analysis. Panel A: hand-grip test measured in Kilograms vs muscle surface in squared cm measured at the level of third or fourth lumbar vertebra. Panel B: hand- grip test vs muscle attenuation at CT scan, measured in Hounsfield units (HU). Panel C: up and go test measured in seconds vs muscle attenuation, HU. Panel D: frailty index vs muscle attenuation (HU)