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1 **Evaluation of the impact of sarcopenia in patients with acute mesenteric ischemia**

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Abstract

Introduction: Sarcopenia has been identified as a prognostic factor in several diseases. The aim of this study was to investigate the impact of sarcopenia in patients with acute mesenteric ischemia.

Material and methods: Consecutive patients admitted for an acute mesenteric ischemia were retrospectively included at the University Hospital of Nice. Sarcopenia was assessed by the measurement of total psoas area normalized for height (TPA/H) on CT-scan and was defined as a TPA/H inferior to the lowest sex-specific quartile. The management of the patients and the 30-day outcomes were compared between sarcopenic and non-sarcopenic patients. Correlations between the TPA/H and biological characteristics were investigated.

Results: Among the 80 patients included, the lowest quartile of TPA/H that defined sarcopenia was 406.1 mm²/m² for men and 307 mm²/m² for women. The rate of revascularization or the need of intestinal resection did not significantly differ between sarcopenic and non-sarcopenic patients (10.5% vs 26.2%, P=0.214 and 26.3% vs 47.5%, P=0.118 respectively). The 30-day mortality did not significantly differ between the two groups (63.2% vs 47.5%, P=0.297). The TPA/H was significantly negatively correlated with the neutrophil, thrombocyte and monocyte counts (r=-0.283; -0.288, -0.225, P<0.05) and positively correlated with the hemoglobin concentration and the glomerular filtration rate (r=0.368; 0.261, P<0.05).

Conclusion: Further studies on longer follow-up period would be of interest to fully understand the prognostic value of sarcopenia in patients with acute mesenteric ischemia.

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55

56 **Introduction**

57 Acute mesenteric ischemia is defined as a sudden interruption of the blood supply to a
58 segment of the small intestine, leading to ischemia and secondary inflammatory changes
59 potentially extending to the large intestine. If untreated, the disease can lead to intestinal
60 necrosis and death (1). Despite advances over the past few years, the disease is still associated
61 with extremely high rates of mortality and morbidity (2, 3). Several prognostic factors have
62 been identified such as the duration of the ischemia, the grade of the vascular occlusion or the
63 presence of collateral blood flow (4). The elevation of biological parameters such as lactate,
64 C-reactive protein, acidosis or leukocyte count have been identified to be associated with
65 increased mortality (3, 5-7). General characteristics of patients including the age or presence
66 of comorbidities (6, 8, 9) may also impact on the prognosis. Sarcopenia corresponds to a loss
67 of the skeletal muscle mass and is considered as a general marker of frailty. Its interest as a
68 predictor of post-operative complications and overall survival has been proposed in several
69 visceral surgical procedures including pancreatic resection, nephrectomy, hepatectomy or
70 colon resection (10-13). However, its impact during acute mesenteric ischemia has been so far
71 poorly investigated. The aim of this study was to investigate the impact of sarcopenia in
72 patients with acute mesenteric ischemia.

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74

75 **Material and methods**

76

77 *Population*

78 Consecutive patients who were diagnosed with an acute mesenteric ischemia were
79 retrospectively included at the University Hospital of Nice between January 2011 and
80 February 2019. The patients were referred to the surgeons with the diagnoses of acute
81 mesenteric ischemia in the emergency room or in the intensive care unit. The diagnosis of
82 acute mesenteric ischemia was based on the association of clinical symptoms and biological
83 and imaging analyses (1). Patients without CT-scan images or diagnosed with a chronic
84 mesenteric ischemia or an infectious colitis were excluded from this study. Clinical
85 characteristics were collected and included demographic data and the presence of
86 cardiovascular risk factors. Biological parameters at in-hospital admission were collected. The
87 neutrophil to lymphocyte ratio (NLR) was calculated by dividing the absolute value of
88 neutrophils to lymphocytes; the platelet to lymphocyte ratio by dividing the absolute value of
89 platelets to lymphocytes (PLR). The glomerular filtration rate was calculated according to the
90 Chronic Kidney Disease EPIdemiology collaboration (CKD-EPI) equation. CT-scan images
91 were retrospectively analyzed by three independent observers to identify the localization of
92 the vascular thrombosis. Procedural characteristics were collected including the need of a
93 revascularization and/ or an intestinal resection. Non-operative approach was defined as the
94 absence of revascularization or intestinal resection. The 30-day outcomes including all-cause
95 mortality or complications were recorded.

96

97 *Data Collection*

98 Clinical and procedural characteristics as well as biological parameters were collected using
99 manual and electronic medical records (Clinicom®). The diagnostic code K. K55.0 “Acute
100 vascular disorders of intestine” was used to extract patients. Imaging data were recorded and
101 extracted from the softwares Picture Archiving and Communication Systems (PACS) and
102 Aquarius iNtuition Edition® version 4.4.8 (TeraRecon, Inc. San Mateo). Sarcopenia was

103 assessed by the measurement of the cross-sectional area of the right and left psoas muscles
104 (Total Psoas Area: TPA) on CT-scan images (Figure 1). The horizontal sections of the CT
105 images were created by adjusting the sagittal and coronal sections using the software
106 Aquarius. The TPA was measured at the level of the third lumbar vertebra using the software
107 Aquarius® by 3 independent blinded operators. The correlation of the measurement between
108 observers was checked (Supplemental Table 1 and Supplemental Figure) and the average was
109 calculated. The TPA was then normalized for height (TPA/H mm^2/m^2) as a convention for
110 body composition measurement. To date, there is no clear consensus on the cut-off for the
111 TPA value used to define sarcopenia (14). In order to use cut-off values adapted to our
112 population, sarcopenia was defined as the presence of a TPA/H inferior to the lowest sex-
113 specific quartile (406.1 mm^2/m^2 for men and 307 mm^2/m^2 for women), as described in
114 previously published studies (10, 11, 13, 15-17).

115

116 *Study end points*

117 To evaluate the impact of sarcopenia in patients with acute mesenteric ischemia, clinical
118 characteristics as well as 30-day outcomes were compared among the groups. Correlations
119 between the TPA/H and other clinical and biological characteristics were investigated.

120

121 *Statistical analysis*

122 Categorical data were expressed as the number of patients and percentage and continuous
123 variables were expressed as the median with interquartile range. Group differences were
124 compared using Fisher's exact test for categorical data and Mann-Whitney test for continuous
125 variables. Correlations were determined by Pearson's correlation coefficient. The
126 reproducibility of TPA/H measurements were evaluated using a graphic analysis with the

127 Bland-Altman plot. A P value <0.05 was considered as significant. Statistical analyses were
128 performed using GraphPad Prism® software (version 7.00, La Jolla California USA).

129

130 **Results**

131 In total, 80 patients with acute mesenteric ischemia were included in the study (Table 1). The
132 median of the age was 73 years (60 – 83) and 41 patients (51.3%) were men. The vascular
133 thrombosis was located in the celiac trunk for 9 patients (11.3%), the superior mesenteric
134 artery for 62 cases (77.5%), the inferior mesenteric artery for 9 patients (11.3%) and the
135 mesenteric vein for 1 patients (1.3%). The etiologies of the acute mesenteric ischemia were
136 embolic in 24 patients (30%), atherosclerosis-related in 34 cases (42.5%) and undetermined in
137 22 cases (27.5%). The median body mass index was 22.4 kg/m² (20.1 – 25.9). The median of
138 the TPA was 1183.5 mm² (928.8 – 1845). The median of the TPA normalized for height
139 (TPA/H) was 479.2 mm²/m² (365.1 – 657.4). The lowest quartile of the TPA/H that defined
140 sarcopenia was 406.1 mm²/m² for men and 307 mm²/m² for women. The initial characteristics
141 were compared between sarcopenic and non-sarcopenic patients (Table 2). No significant
142 difference was identified regarding age, sex, the presence of diabetes, arterial hypertension,
143 dyslipidemia or smoking between the two groups. Patients with sarcopenia had a lower body
144 mass index compared to non-sarcopenic patients (23.9 kg/m² vs 19.7, P=0.0022).
145 The procedural characteristics were compared between patients with sarcopenia and those
146 without sarcopenia in order to identify potential confounding factors on 30-day outcomes
147 (Table 3). The localization of the thrombosis did not differ between the two groups; nor did
148 the etiologies. There was no difference regarding the management of the acute mesenteric
149 ischemia. The rate of revascularization was 10.5% in patients with sarcopenia and 26.2% in
150 patients without sarcopenia, P=0.214. An intestinal resection was required in 5 patients
151 (26.3%) with sarcopenia and in 29 patients (47.5%) without sarcopenia, P=0.118. In the

152 whole cohort, a non-operative approach was decided for 32 patients (40%), among whom 29
153 received palliative care. No significant difference was observed regarding the rate of non-
154 operative approach between sarcopenic and non-sarcopenic patients (57.9% vs 34.4%,
155 $P=0.106$). The presence of sarcopenia did not significantly impact on the 30-day outcomes.
156 No significant difference was observed between the two groups for the 30-day mortality
157 (63.2% vs 47.5%, $P=0.297$). The 30-day all-cause complications was 31.6% vs 44.3%,
158 $P=0.427$. When only patients who underwent a surgical intervention were considered, no
159 significant difference was observed between sarcopenic and non-sarcopenic patients
160 regarding the 30-day post-operative outcomes (Supplemental Table 2).
161 To better understand the link between sarcopenia and patients' characteristics, the correlations
162 between the TPA/H and the clinical and biological parameters were investigated (Figure 2).
163 The TPA/H was significantly negatively correlated with the neutrophil and thrombocytes
164 counts ($r=-0.283$, $P=0.013$ and -0.288 , $P=0.011$, respectively). An inverse correlation was also
165 found with the monocytes count ($r=-0.225$, $P=0.049$), but not with the lymphocytes ($r=-0.005$,
166 $P=0.968$). The TPA/H was significantly negatively correlated with the NLR ($r=-0.234$,
167 $P=0.041$) and there was a tendency for the PLR ($r=-0.215$, $P=0.061$). A positive correlation
168 between the TPA/H and the hemoglobin concentration was also observed ($r=0.368$,
169 $P=0.0009$). The TPA/H was positively correlated with the glomerular filtration rate ($r=0.261$,
170 $P=0.023$) and negatively correlated with the age of patients ($r=-0.294$, $P=0.011$).

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172

173 **Discussion**

174 To the best of our knowledge, this is the first study which aimed to explore the impact of
175 sarcopenia during acute mesenteric ischemia. The 30-day mortality rate tended to be higher in
176 sarcopenic patients although it did not reach statistical significance. The prognostic value of

177 sarcopenia has been investigated in several digestive cancers. Sarcopenia was associated with
178 short and long-term outcomes following resection of pancreatic adenocarcinoma, with
179 sarcopenic patients having a 63% increased risk of death at 3 years (10, 15). Sarcopenia was
180 also identified to be a predictor for worse overall survival after open colon resection for
181 cancer (12). Interestingly, it has also been identified as an independent predictor of post-
182 operative complications such as anastomotic leakage after colorectal resection (18). The
183 impact of sarcopenia has been further investigated in context of abdominal surgery. A first
184 study demonstrated a significant association between TPA and post-operative morbidity,
185 increased length of stay and 90-day mortality in patients who underwent an emergency
186 abdominal surgery (19). However, the authors did not identify a significant association
187 between TPA and 30-day mortality ($P=0.26$). Another study in elderly patients undergoing
188 emergency abdominal surgery also revealed that sarcopenic patients had a higher 90-day
189 mortality compared to non-sarcopenic patients, corresponding to an odds ratio of 2.66
190 ($P=0.01$) (20). The effect of sarcopenia may predominate in the first post-operative year (21)
191 and other studies also reported a difference between the 30-day and the 90-day mortality in
192 patients who underwent abdominal surgery (10, 22).

193 In our study, we did not identify differences on the procedural characteristics between
194 sarcopenic and non-sarcopenic patients. Compared to other studies, the rate of intestinal
195 resection was relatively small in our cohort (23) and could be, at least partly, explained by the
196 high rate of palliative treatment. This cohort involved elder patients with comorbidities, some
197 admitted with multi-organ failure, which could explain the high rate of palliative treatment. A
198 multimodal management strategy would be of interest to propose an early revascularization
199 and improve the prognosis of patients (24). Interestingly, patients with sarcopenia were less
200 likely to be offered surgery, probably due to their baseline frailty. The difference did not

201 reach statistical significance but the statistical power of this analysis was limited due to the
202 size of the cohort. Further studies on larger cohorts are required to confirm the results.

203 In this study, the TPA/H negatively correlated with neutrophil, thrombocyte and monocyte
204 counts. The neutrophil to lymphocyte ration (NLR) and the platelet to lymphocyte ratio (PLR)
205 have been proposed as inflammatory markers in several diseases including mesenteric
206 ischemia and other cardiovascular pathologies (25-30). Our results suggest a relationship
207 between systemic inflammatory response and sarcopenia in patients with acute mesenteric
208 ischemia. Similarly to our findings, a positive correlation between sarcopenia and NLR or
209 PLR was found in patients undergoing surgery for gastric cancer (31). An increase of NLR
210 and PLR can be observed in both chronic and acute inflammatory state, and this inflammatory
211 response may contribute to changes in the body composition, increasing the metabolic
212 demand, reducing the body strength and favoring sarcopenia.

213 While the TPA/H correlated with neutrophils, monocytes and platelets, no correlation was
214 observed for lymphocytes. Lymphopenia is a common feature of inflammatory process and
215 mainly results from increased apoptosis of lymphocytes associated with their redistribution
216 within the lymphatic system (32). As inflammatory state is most often associated with a
217 decrease of lymphocyte count, it could partly explain why no direct correlation was observed
218 between lymphocyte count and sarcopenia.

219 Besides the inflammatory markers, a positive correlation between the TPA/H and the
220 hemoglobin concentration was found. Other authors observed that hemoglobin concentration
221 was independently associated with grip strength (33) and that low hemoglobin concentration
222 was associated with sarcopenia (34). Anemia can be caused by either inflammation or
223 nutritional deficiency, two pathologic states which can favor the development of sarcopenia.

224 In this cohort, rectal hemorrhage may also have contributed to decrease the hemoglobin
225 concentration. As expected, age was inversely correlated with the TPA/H. The association

226 between sarcopenia and age has been extensively reported (35). Muscle mass and strength
227 decreases with age and beyond 50 years, the loss of leg muscle mass is estimated to be 1-2%
228 per year (14, 36). Finally, the renal function assessed by the glomerular filtration rate
229 correlated with the TPA/H. Several studies have highlighted that the loss of skeletal muscle
230 was significantly associated with the decline of the glomerular filtration rate (37, 38). During
231 chronic kidney disease, the uremic environment impacts on both skeletal muscle regeneration
232 and catabolism and may favor sarcopenia (39). However, in this cohort, the duration of the
233 ischemia as well as the patients' hemodynamic parameters may potentially have impacted on
234 the renal function and act as confounding factors. It would be of interest to address it in future
235 studies.

236 This study presents some limitations. First, calculating the TPA on CT-scan images using a
237 manual outline of the psoas is a simple, fast and inexpensive method to assess sarcopenia but
238 it may be less precise than using an automated imaging-analysis software (15). In this study,
239 the measurement of the TPA/ H was performed by 3 independent operators and the
240 reproducibility within the operators was checked to limit bias. As no consensus on the cut-off
241 values to define sarcopenia exist, we used the lowest sex-specific quartile, as previously
242 described (10, 11, 15). The cut-off values were lower in our cohort and this could be, at least
243 partly, explained by the fact that our cohort involved older patients. Second, this was a
244 retrospective single-center study. The size of the cohort may have limited the statistical power
245 to identify a significant impact of sarcopenia on 30-day post-operative outcomes. In addition,
246 follow-up on longer period is necessary to fully understand the impact of sarcopenia during
247 acute mesenteric ischemia. Prospective multi-centre studies would be of interest to address it.
248 This would be useful to explore more deeply specific post-operative complications such as the
249 rate of anastomotic leakage or the need of a re-intervention. In addition, it could provide a
250 more detailed analysis of the clinical and procedural characteristics of the patients including

251 the duration of the ischemia, the length of fasting, the hemodynamic conditions or the drugs
252 used, which could potentially impact on the results. Finally, several plasma biomarkers are
253 currently used for the diagnosis of acute mesenteric ischemia, even though none of them are
254 perfectly accurate (40). D-dimer has a high sensitivity, making it an excellent exclusion test,
255 but the specificity is low. Plasma lactate concentration has also demonstrated a high
256 sensitivity, but a low specificity in the early diagnosis of intestinal ischemia (41). Due to the
257 retrospective nature of the study, the D-dimer and lactate concentration was not available for
258 all patients. Further studies would be of interest to investigate the potential correlation
259 between these biomarkers and sarcopenia.

260

261

262 **Conclusion**

263 Acute mesenteric ischemia is associated with high rates of mortality and morbidity and risk
264 assessment may help to improve care provided to patients. To the best of our knowledge, this
265 is the first study to address the link between sarcopenia and acute mesenteric ischemia. No
266 significant difference on 30-day outcomes was found between sarcopenic and non-sarcopenic
267 patients. A positive correlation was found between the TPA/H and inflammatory markers.
268 Other clinical characteristics of patients including the age, the renal function as well as the
269 hemoglobin concentration significantly correlated with the TPA/H. These results suggest that
270 the TPA/H could be an interesting risk predictive marker reflecting the general state of
271 patients. Further studies on larger cohorts and longer follow-up period are required to fully
272 understand the prognostic value of sarcopenia in patients with acute mesenteric ischemia.

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275

276 **Author contribution**

277 All authors confirm they contributed to the intellectual content of this article including
278 conception and design. They revised the manuscript and approved the final version.

279

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281

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283

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285

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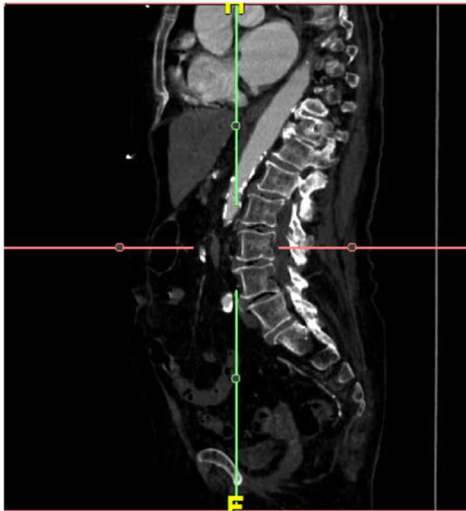
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A



B

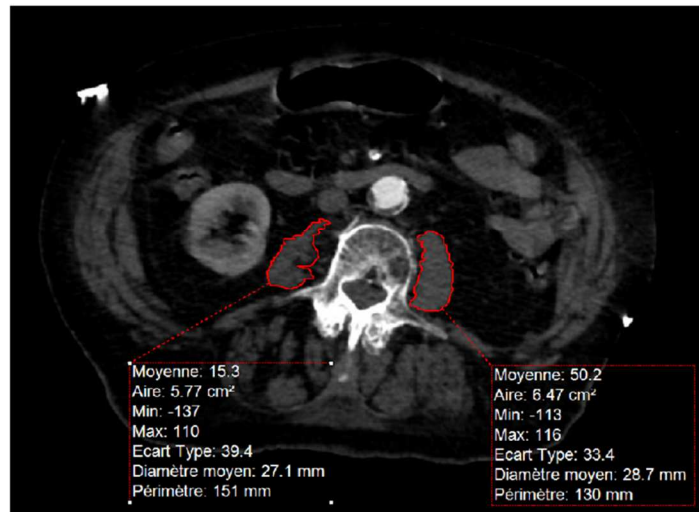


Figure 1: Representative images of the measurement of the Total Psoas Area. (A) The third lumbar vertebra was identified by counting from the sacral bone. The axial image at the L3 level in which both transverse processes were visualized was selected. (B) The measurement of the TPA was performed by manual outlining of the right and left psoas muscle borders.

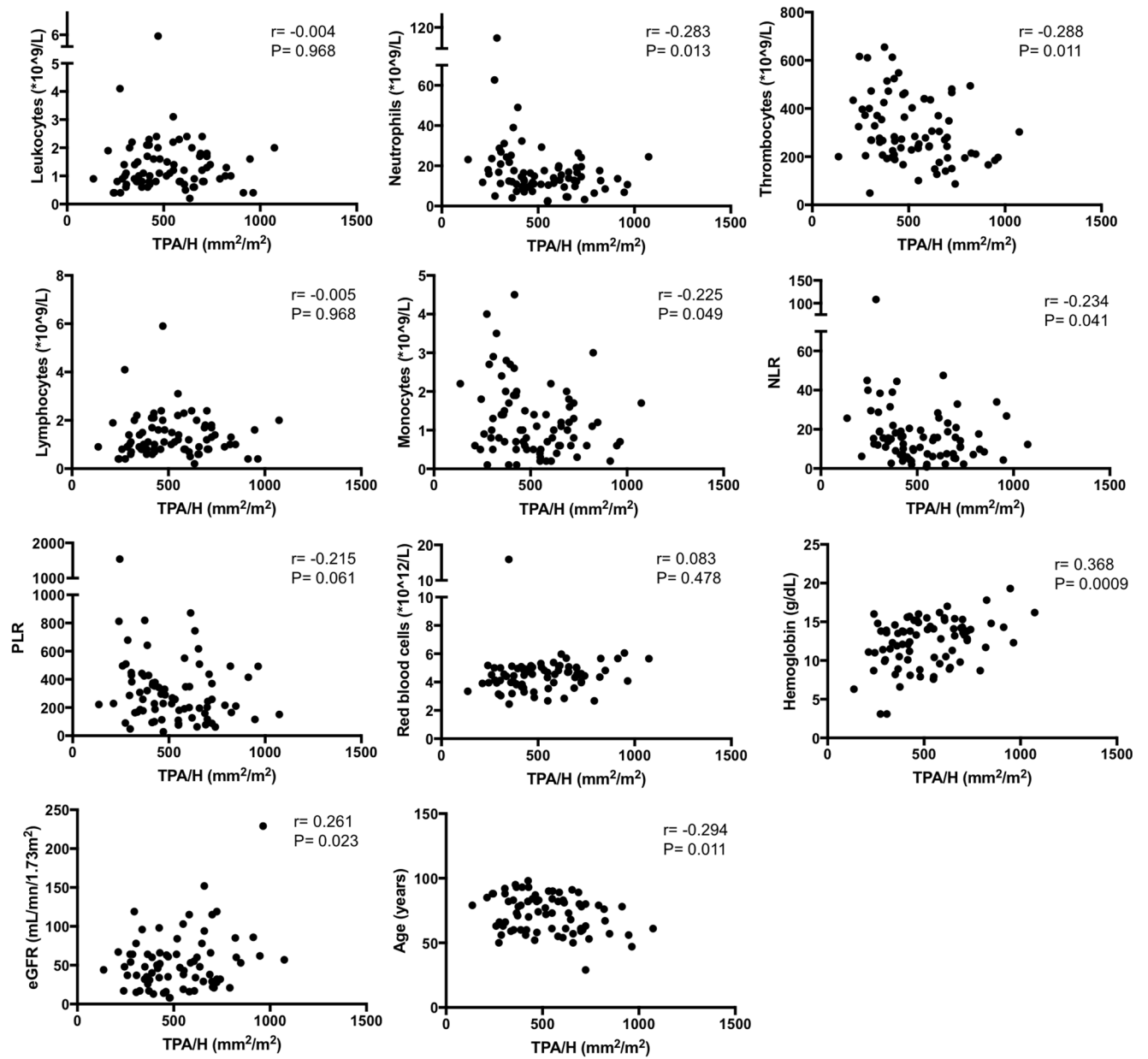


Figure 2: Correlation between index of sarcopenia and biological or clinical parameters

TPA/H: Total psoas area normalized for height (mm²/m²)

Patients characteristics (n= 80)	Data
General characteristics	
. Age	73 (60 – 83)
. Male sex	41 (51.3%)
. Weight (kg)	62.7 (53.5 – 70)
. Height (m)	1.65 (1.58 – 1.72)
. Body mass index (kg/m ²)	22.4 (20.1 – 25.9)
. Diabetes	20 (25%)
. Arterial hypertension	48 (60%)
. Dyslipidemia	9 (11.3%)
. Smoking (active or weaned)	31 (38.8%)
. History of inflammatory chronic disease	7 (8.8%)
. History of cancer	12 (15%)
. TPA (mm ²)	1183.5 (928.8 – 1845)
. TPA/ H (mm ² /m ²)	479.2 (365.1 – 657.4)
Treatment	
. Antiplatelet	33 (41.3%)
. Anticoagulant	14 (17.5%)
Localization of the thrombosis	
. Celiac trunk	9 (11.3%)
. Mesenteric superior artery	62 (77.5%)
. Mesenteric inferior artery	9 (11.3%)
. Mesenteric vein	1 (1.3%)
Etiology of the acute mesenteric ischemia	
. Embolism	24 (30%)
. Atherosclerosis	34 (42.5%)
. Undetermined	22 (27.5%)

Clinical symptoms	
. Intestinal angina	4 (5%)
. Pain	65 (81.3%)
. Vomiting	23 (28.8%)
. Peritonitis	24 (30%)
. Shock	32 (40%)
. Rectal hemorrhage	21 (26.3%)
Biological parameters at in-hospital admission	
. Red blood cells (* 10 ¹² /L)	4.5 (3.8 – 5)
. Hemoglobin (g/dL)	13.2 (10.1 – 14.6)
. Thrombocytes (*10 ⁹ /L)	270 (200 – 403)
. Leukocytes (*10 ⁹ /L)	16.8 (11.7 – 23.2)
. Neutrophils (*10 ⁹ /L)	13.6 (10.1 – 19.7)
. Lymphocytes (*10 ⁹ /L)	1.1 (0.8 – 1.8)
. Monocytes (*10 ⁹ /L)	1 (0.6 – 1.8)
. NLR	14.2 (7.1 – 20.7)
. PLR	258.8 (164.7 – 427)
. AST (U/L)	46.5 (28 – 100.3)
. ALT (U/L)	27.5 (17 – 48.8)
. Creatinine concentration (μmol/L)	115 (87 – 184)
. eGFR (mL/mn/1.73m ²)	48 (29 – 64)

Table 1: General characteristics of patients with acute mesenteric ischemia

Values are median (interquartile range) or n (%).

AST: aspartate transaminase

ALT: alanine aminotransferase

eGFR: estimated glomerular filtration rate

NLR: neutrophil to lymphocyte ratio

PLR: platelet to lymphocyte ratio

TPA: Total psoas muscle area

TPA/H: Total psoas area normalized for height

General characteristics	Patients with sarcopenia (n=19)	Patients without sarcopenia (n=61)	P value
Age	78 (63 – 88)	73 (60 – 82.5)	0.3946
Male sex	10 (52.6%)	31 (50.8)	0.8903
Weight (kg)	53 (40.1 – 62.2)	66 (56 – 72)	0.0144
Height (m)	1.7 (1.6 – 1.8)	1.6 (1.6 – 1.7)	0.1306
Body mass index (kg/m ²)	19.7 (15 – 21.4)	23.9 (21 – 28.5)	0.0022
Diabetes	5 (26.3%)	15 (24.6%)	0.1517
Arterial hypertension	11 (57.9%)	37 (60.7%)	0.2145
Dyslipidemia	2 (10.5%)	7 (11.5%)	0.9090
Smoking (active or weaned)	8 (42.1%)	23 (37.7%)	0.7310
History of inflammatory chronic disease	1 (5.3%)	6 (9.8%)	0.1386
History of cancer	5 (26.3%)	7 (11.5%)	0.1137
Antiplatelet	8 (42.1%)	25 (41%)	0.9309
Anticoagulant	2 (10.5%)	12 (19.7%)	0.3596
TPA/ H (mm ² /m ²)	295.3 (244.9 – 350.1)	580.5 (437.7 – 699.4)	<0.0001

Table 2: Comparison of initial characteristics between patients with sarcopenia and those without sarcopenia

	Patients with sarcopenia (n=19)	Patients without sarcopenia (n=61)	P value
Localization of the vascular thrombosis			
. Celiac trunk	2 (10.5%)	7 (11.5%)	0.9090
. Superior mesenteric artery	16 (84.2%)	46 (75.4%)	0.4224
. Inferior mesenteric artery	0 (0%)	9 (14.8%)	0.0755
. Mesenteric vein	0 (0%)	1 (1.3%)	0.5744
Etiology of the acute mesenteric ischemia			
. Embolism	5 (26.3%)	19 (31.1%)	0.6882
. Atherosclerosis	10 (52.6%)	24 (39.3%)	0.3063
. Undetermined	5 (26.3%)	17 (27.9%)	0.8947
Management of the acute mesenteric ischemia			
. Revascularization	2 (10.5%)	16 (26.2%)	0.214
- Vascular bypass	1 (5.3%)	4 (6.6%)	0.999
- Endovascular repair	0 (0%)	4 (6.6%)	0.568
- Thrombectomy	1 (5.3%)	10 (16.4%)	0.445
. Intestinal resection	5 (26.3%)	29 (47.5%)	0.118
- Jejunum resection	2 (10.5%)	5 (8.2%)	0.668
- Ileum resection	3 (15.8%)	19 (31.1%)	0.247
- Colon resection	3 (15.8%)	20 (32.8%)	0.245
. Non-operative approach	11 (57.9%)	21 (34.4%)	0.106
30-day outcomes			
. All-cause death	12 (63.2%)	29 (47.5%)	0.297
. All-cause complications	6 (31.6%)	27 (44.3%)	0.427

Table 3: Comparison of procedural characteristics and outcomes between patients with sarcopenia and those without sarcopenia