Low Skeletal Muscle Index and Myosteatosis as Predictors of Mortality in Critically Ill Surgical Patients

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Research article

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Abstract

Background

Low muscle mass and other specific body composition indexes, assessed by computed tomography (CT), are associated with adverse outcomes after elective surgery, such as an increased risk of postoperative complications and higher mortality. However, limited information is available about the role of these indexes on short- and long-term outcomes in surgical patients admitted to the intensive care unit (ICU). The aim of the study was to assess the association of body composition indexes with 90-days mortality in this specific patient cohort.

Methods

We performed a retrospective study including adult surgical patients admitted to the ICU between 2014 and 2018 who underwent a CT scan at the time of admission. Total Muscle Area (TMA), Total Fat Area (TFA), Visceral fat area (VFA) and Intramuscular fat area (IMFA) were measured. Skeletal Muscle Index (TMA/m2), MyoSteatosis (IMFA/TMA), Sarcopenic Obesity (VFA/TMA) were then calculated. We analyzed the impact of these indexes on mortality.

Results

204 patients were included. Overall 90-day mortality was 28%. Log rank test and cox multivariate analysis on 90-day mortality showed a significant association of low SMI and myosteatosis with 90-days mortality. Myosteatosis was also significantly associated with prolonged mechanical ventilation and increased ICU length of stay.

Conclusions

Specific body composition indexes may predict mortality in surgical patients admitted to the ICU. Low skeletal muscle index and myosteatosis were independently associated with increased 90-day mortality.

Introduction

In recent years, there has been a growing interest on the association between body composition and surgical outcomes. Specific indexes assessed by computed tomography (CT) accurately identify subgroups of patients at risk of complications after major elective surgery [1–5].

Most of the prognostic scoring systems adopted in ICU [6] focus on disease severity at presentation, organ failures and comorbidities, whereas none of them include body composition parameters. Sarcopenia – defined as loss of skeletal muscle mass and function [7] – is a surrogate index of

advanced age, frailty, and protein catabolism [7]. These conditions have shown to be valuable predictors of poor prognosis in critically ill patients [8, 9]. A strong association between CT-assessed body composition and increased mortality in ICU trauma [10, 11] and septic patients [12–14] has been also established.

Recent studies [15, 16] reported a correlation between a single parameter of body composition (low skeletal muscle index) and decreased survival in surgical critically ill patients. Moreover, the results of a large multicenter trial [17] demonstrated that a low baseline phase angle (reflecting fat-free mass loss), measured by bioelectrical impedance analysis, was associated with higher 28-day mortality in a mixed population of ICU patients.

However, sparse literature exists on the association of other specific body composition indexes (i.e. myosteatosis and sarcopenic obesity) and outcomes in this subset of ICU patients.

The aim of the present study was to investigate the association of body composition parameters, specifically skeletal muscle index, myosteatosis and sarcopenic obesity, with 90-days mortality of patients admitted to the ICU after complicated abdominal surgery.

Methods

Patients and study design

We evaluated surgical patients admitted to a tertiary-level ICU between June 2014 and December 2018.

Inclusion criteria were the following: age ≥ 18 years; ICU admission after urgent abdominal surgery or reoperation for complicated elective major abdominal surgery (gastrointestinal, gynecologic or urologic procedures); patients who underwent an abdominal CT within 30 days before and 48 hours after the admission in intensive care. We excluded patients admitted to ICU following trauma, intraoperative medical complications (e.g. cardiac arrhythmia) or patients with planned ICU admission for monitoring after elective surgery.

Ethics statement

The study was reviewed and approved by the Institutional Review Board (Comitato Etico ASST Monza). Written informed consent was waived. Results are reported according to Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement.

CT scan and Body Composition measurement

Body composition indexes were measured and calculated from the CT scan closest in time to the admission (from 72 hours before to 24h after the admission to the ICU). A multidetector CT scan was performed with 256-slice CT scanners (Brilliance iCT or iCT-elite, Philips Medical Systems, Eindhoven, Netherlands) and an unenhanced scan was acquired in every study protocol. The raw data were

reconstructed with Hybrid-Iterative Reconstruction algorithm (iDose4), in order to obtain the same image quality between the two different CT scanners; subsequently, all the scans were transferred to an image workstation (Intellispace portal 8.0; Philips Medical Systems) to evaluate, select, anonymize and save the image for the analysis in DICOM format. The analysis was performed on the axial CT 5mm-image through L3 with the open-source image analysis software ImageJ (developed by the National Institutes of Health; available from http://rsbweb.nih.gov/ij/download.html), which produces comparable results to other software for body composition analysis [18].

Two different radiologists, blinded to patient information and using the selected CT image, drew multiple regions of interests (ROI) in the outer and inner perimeter of abdominal muscles, and analyzed pixels with densities between -20 Hounsfield units (HU) to +150 HU for muscles and with densities in the -190 HU to -30 HU range for fat-tissue. The radiologists then calculated total muscle area (TMA, which estimates the total muscle mass) [19], total fat area (TFA), visceral fat area (VFA) and intramuscular fat area (IMFA). Subcutaneous fat area (SFA) was obtained by subtracting VFA from TFA and intramuscular fat area (IMFA) was obtained subtracting VFA from the ROI of the outer abdominal muscle perimeter.

Body composition indexes were normalized for height in meters squared [1,18], and expressed as cm2/m2. We used TMA and VFA to calculate Skeletal Muscle Index (SMI=TMA/m2) and Sarcopenic Obesity (SO=VFA/TMA). We also determined the grade of MyoSteatosis through the intramuscular adipose tissue content (MS=IMFA/TMA) [20]. Tertiles were estimated for each index according to sex [21,22].

Data collection

The following parameters were retrieved from the medical records: demographics (age, sex, height, weight, and body mass index [BMI]), Charlson Comorbidity Index (CCI), Simplified Acute Physiology Score (SAPS) II, Sequential Organ Failure Assessment (SOFA) score on ICU admission, clinical data (use of vasopressor, use of mechanical ventilation, diagnosis of abdominal urgency or type of complication after elective surgery), length of ICU and hospital stay, duration of mechanical ventilation, outcome (hospital discharge or death).

Study endpoints

The primary aim of the present study was to investigate the association of body composition parameters, specifically skeletal muscle index, myosteatosis and sarcopenic obesity, with 90-day mortality.

Secondary aims included exploring the association of the same parameters with ICU, in-hospital and 1-year mortality, mechanical ventilation days and ICU length of stay

Statistical analysis

Continuous variables were described as mean ± standard deviation or median [interquartile range] depending on their distribution, categorical variables as absolute (relative) frequency. The normality of

distribution was assessed using the Shapiro–Wilk test.

Differences in 90-day mortality were tested using a non-parametric test for trend across tertiles of body composition indexes. If the trend was statistically significant, multiple pairwise comparisons among tertiles of indexes were explored using the Chi-square test.

The Kaplan Meier approach was applied to assess the unadjusted probability of survival at 90-days and 1-year follow up. Log-rank test was used to compare curves between 3 groups defined by tertiles of body composition indexes. Mortality at 90-day follow up was then tested into a multivariate Cox-regression model using a stepwise selection approach (cut-off $p < 0.20$ for selection at the univariate analysis).

The association of patient characteristics with outcomes was assessed with univariate logistic regression (for ICU, in-hospital and 1-year mortality) and linear regression (duration of mechanical ventilation and ICU length of stay) analyses. Variables with a $p < 0.20$ were included into a multivariable logistic and linear regression model, respectively, using a stepwise selection approach.

To further explore the interaction of low skeletal muscle index and myosteatosis - we explored the role of combination of low/high levels of SMI with low/high levels of myosteatosis on 90-day hospital mortality. Patients with low or high SMI were defined as the groups of patients with SMI level below or above the 50th percentile, respectively. Equally, patients with low or high myosteatosis were defined as the groups of patients below or above the 50th percentile of myosteatosis, respectively. Furthermore, to evaluate the improvement in the discrimination performance of the multivariate Cox model on the primary end-point (i.e. 90 days mortality) when myosteatosis and skeletal muscle index are combined, we compared its Harrel's C-index to alternate Cox models where only one of the 2 indexes is included.

Statistical significance was considered with a $p < 0.05$ (two-tailed). Statistical analyses and graphs were performed using STATA-16/MP (StataCorp LP, College Station, TX, USA) and GraphPad Prism 8.0.2 (GraphPad Software, San Diego, CA, USA).

Results

During the study period 275 consecutive patients were admitted to ICU after urgent abdominal surgery or reoperation for complicated elective major abdominal surgery. Among them, 204 patients met the inclusion criteria and were included in the analysis.

Table 1 shows the parameters of the study population at baseline and during the ICU stay. Median time from CT exam to ICU admission was 1 day (interquartile range 0–2 days), ranging from 30 days before to ICU admission to 2 days after ICU admission.

Table 1
Characteristics of the study population at baseline and during the ICU course. Data are expressed as mean ± SD or absolute (relative) frequency. BMI, body mass index; SAPS II, simplified acute physiology score; SOFA, sequential organ failure assessment; ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit; RRT, renal replacement therapy.

	All patients (n = 204)
Age, years	68 ± 14
Females, n (%)	78 (38)
Weight, kg	73 ± 19
BMI, kg/m^2	26.0 ± 6.2
Urgent surgery, n, (%)	127 (62)
Complicated elective surgery, n (%)	77 (38)
Oncologic patients	88 (43)
Invasive ventilation at admission	192 (94)
SAPS II	43 ± 15
SOFA	6 ± 4
Charlson comorbidity index, n (%)	67 (33)
● 0−3	68 (33)
● 4−5	69 (34)
● ≥ 6	
ICU	
Use of invasive ventilation, n (%)	194 (95)
Use of non-invasive ventilation, n (%)	18 (9)
Tracheostomy, n (%)	4 (2)
ECMO, n (%)	4 (2)
RRT, n (%)	17 (8)

Mean values for TMA, IMFA, SFA and VFA were 97 ± 21 cm^2, 23 ± 14 cm^2, 153 ± 96 cm^2 and 204 ± 125 cm^2 for females and 124 ± 30 cm^2, 24 ± 13 cm^2, 223 ± 118 cm^2 and 164 ± 91 cm^2 for males, respectively. Mean values for SMI, SO and MS were 37 ± 8 cm2/m2, 1.6 ± 0.9 and 0.25 ± 0.16 for females and 41 ± 10 cm2/m2, 1.9 ± 1.1 and 0.20 ± 0.11 for males, respectively.

Outcomes for the study population are shown in Table 2. One hundred and seventy-two patients (84%) were discharged alive from the ICU, whereas in-hospital and 90-day survival was 73% and 72%, respectively. 131 patients (64%) were alive at 1-year follow up.

Table 2
Patient outcomes. Data are expressed as mean ± SD or absolute (relative) frequency. ICU, intensive care unit.

Primary endpoint	
90-d mortality, n (%)	57 (28)
Secondary endpoints	
ICU mortality, n (%)	32 (16)
Mechanical ventilation, days	6.2 ± 9.3
● All patients	5.1 ± 7.5
● ICU survivors	12.3 ± 14.4
● ICU non survivors	
ICU length of stay, days	7.4 ± 9.9
● All patients	6.5 ± 8.2
● ICU survivors	12.5 ± 15.5
● ICU non survivors	
In-hospital mortality, n (%)	55 (27)
Hospital length of stay, days	35.9 ± 27.6
● All patients	38.7 ± 27.6
● Hospital survivors	28.2 ± 26.1
● Hospital non survivors	
1-year mortality, n (%)	73 (36)

Figure 1 shows the association of single body composition indexes (stratified by tertiles) and 90-day mortality. A lower total muscular area (panel A) was associated with a higher 90-day mortality.

Figure 2 shows the association of composite body composition indexes and 90-day mortality. A low skeletal muscle index (SMI, Panel A) and a higher degree of myosteatosis (MS, Panel C) were associated with a higher 90-day mortality.

Figure 3 displays the impact of skeletal muscle index (panel A) and myosteatosis (panel B) stratified by tertiles over 90-day follow-up with a Kaplan-Meier survival curve. Log-rank test on population tertiles was significant for both parameters (p = 0.019 and p < 0.001, respectively). This finding was confirmed at the 1-year follow-up for both skeletal muscle index and myosteatosis (Log-rank p-value = 0.045 and < 0.001, respectively, see eFigure 1, Supplementary Material).

Besides the significant and independent predictive ability of some well-recognized risk factors (SAPS II and CCI) on 90-day mortality, the association of low skeletal muscle index and myosteatosis remained significant after adjusting for covariates (Table 3, and Supplementary Material - eTable 1 for univariate analysis of association between covariates and 90-day mortality). The Harrel's C-Index of this model was 77.8%, higher than alternate Cox models which included only one of the 2 indexes (76.8% with only SMI and 76.8% with only MS, see Supplementary Material eTables 2 and 3).

Table 3
Multivariate analysis of predictors of 90-day mortality. SAPS II, simplified acute physiology score; CCI, Charlson Comorbidity Index.

Variable	HR	95% CI	p
SAPS II score	1.05	1.03−1.07	< 0.001
CCI > 4	2.41	1.36−4.28	0.003
Skeletal muscle index	0.45	0.24−0.83	0.011
● Middle versus lowest tertile	0.42	0.21−0.82	0.011
● Highest versus lowest tertile			
Myosteatosis	0.92	0.31−2.03	0.828
● Middle versus lowest tertile	2.11	1.10−4.02	0.024
● Highest versus lowest tertile			

The independent association of low SMI and high myosteatosis with the primary outcome was further confirmed by the analysis of combination of high or low SMI with high or low myosteatosis (i.e. 4 groups) with 90-day mortality and survival. The group with low SMI and high myosteatosis showed the highest rate of mortality (eFigure 2, Supplementary Material). This finding was confirmed by the Kaplan-Meier survival curves over 90-day follow-up (eFigure 3, Supplementary Material).

An overall description of the role of composite body composition indexes on ICU, in-hospital and 1-year outcome was adjusted for confounders and described in Table 4.

Table 4
Multivariate analyses for mortality. Data are expressed as OR (95%CI) with p-value (two-tailed).

Variable	ICU mortality	In-hospital mortality	1-year mortality
Age	1.07 (1.02−1.12); p = 0.004	-	-
SOFA	1.34 (1.18−1.51); p < 0.001	-	-
SAPS II	-	1.08 (1.05−1.11); p < 0.001	1.06 (1.03−1.08); p < 0.001
CCI > 4	-	2.47 (1.17−5.19); p = 0.017	4.35 (2.19−8.66); p < 0.001
Skeletal muscle index Middle versus lowest tertile Highest versus lowest tertile	0.98 (0.38−2.53); p = 0.963 0.21 (0.06−0.74); p = 0.016	0.50 (0.21−1.15); p = 0.104 0.28 (0.11−0.71); p = 0.008	0.52 (0.24−1.15), p = 0.108 0.36 (0.16−0.84), p = 0.018

Myosteatosis was independently associated with prolonged mechanical ventilation (Table 5) and ICU length of stay (Table 6).

Table 5
Multivariate analysis of predictors of mechanical ventilation days.

Variable	Beta	95% CI	p
Age	-0.17	-0.25 - -0.08	< 0.001
SOFA	0.75	0.45−1.05	< 0.001
Myosteatosis	1.63	-1.30−4.56	0.274
● Middle versus lowest tertile	4.20	1.21−7.19	0.006
● Highest versus lowest tertile			

Table 6
Multivariate analysis of predictors of ICU length of stay.

Variable	Beta	95% CI	p
Age	-0.21	-0.31 - -0.12	< 0.001
SOFA	0.77	0.45–1.09	< 0.001
Myosteatosis	1.83	-1.28–4.95	0.248
● Middle versus lowest tertile	4.49	1.31–7.67	0.006
● Highest versus lowest tertile			

Discussion

In the present study, we assessed the impact of body composition indexes on outcome of critically ill surgical patients admitted to ICU after urgent procedures. We found that low skeletal muscle index and high myosteatosis were independently associated with 90-day mortality. The prognostic value of these parameters was independent from other well-known risk indicators such as SAPS II score, SOFA score and pre-existing comorbid burden [23]. Moreover, myosteatosis was significantly associated with prolonged mechanical ventilation and increased ICU length of stay

Improving the prognostic performance of predictors in critically ill surgical patients may help to enhance the value of care, as the above scores can help the clinicians to choose the right treatment for the right patient. Several outcome scoring systems [8] have been developed in critical care medicine. Most of the current outcome predictors (such as SAPS) rely on age, comorbidities, derangement of clinical parameters and laboratory tests. Other scores focus on the severity of the disease by assessing the number and degree of sequential organ failure (e.g. SOFA). None of these scores evaluate patient physical status and/or performance, as these can hardly be standardized. However, when evaluating a critical patient for possible ICU care, clinicians routinely assess patient frailty and resilience and include these variables into prognostication.

Unfavorable outcomes often occur in patients lacking the physiological reserve to survive major emergency procedures or postoperative complications, even when treated with best available care [24, 25].

In surgical oncology, the assessment of preoperative body composition obtained by the morphologic analysis of CT scans has shown that low skeletal muscle index and other specific indexes (i.e. SO and MS) are associated with unfavorable short- and long-term outcomes [1, 2, 20, 26, 27]. CT imaging is easily available because it is performed routinely before any scheduled major abdominal operation and before most urgent cases. Furthermore, due to its accuracy and reproducibility, CT is the reference technique [18] to appraise quantity and quality of body compartments.

Data showing a relationship between radiologically determined low skeletal muscle mass and short- and long-term mortality [28–30] in mixed ICU populations are not new. Several authors reported that low muscle mass may predict adverse outcomes in critically ill patients with blunt trauma [10, 11], septic shock [12–14] or severe injury [31]. Less evidence is available for more specific ICU cohorts, namely critically ill surgical patients. Rangel et al. [15] described an association between low skeletal muscle mass and mortality in elderly patients undergoing emergency abdominal surgery. Recently, reports from Eastern countries confirmed the association of low skeletal muscle mass with ICU mortality [18], difficult weaning from mechanical ventilation [32], and extubation failure in surgical patients with long-term mechanical ventilation [33]. Our findings are consistent with the above results, and confirm low SMI as a key determinant for ICU, in-hospital, and 1-year survival, even though they are collected in a Western population, with documented differences in body architecture and component distribution,

The originality of the present study lies in reporting the different impact of specific body composition indexes on outcomes. Indeed, our data suggest that muscle degenerative morphologic features, such as myosteatosis, are significant determinants of 90-day mortality. We did not collect any parameter of physical performance or functional capacity tests, but the association of fat infiltration of the muscle and need for prolonged ventilation support suggests that CT-assessed muscle quality is a reliable surrogate of muscle function. The presence of adipose tissue in the muscle may induce the release of pro-inflammatory cytokines driving decreased protein synthesis, increased proteolysis, oxidative stress and other mitochondrial dysfunction eventually leading to impaired respiratory muscle performance [34]. Notably, while low SMI performed as an independent predictor of mortality at all time points, myosteatosis turned out to be a predictor of increased ICU length of stay and extended need for mechanical ventilation. Based on this finding, we might speculate that while the overall degree of muscle depletion (i.e. a low SMI) implies a reduction of muscle strength with an impact on patient outcome, the proportion of intramuscular fat (myosteatosis) drives an impairment of muscle endurance, as reflected by a prolonged duration of mechanical ventilation.

Our findings do not support recent results of Ji et al. [14] who reported that sarcopenic obesity was the only determinant of short-term mortality in patients with abdominal sepsis. The relative proportion of muscle mass and visceral fat may represent a different risk factor according to ethnicity.

Another peculiarity of this study is that ICU, in-hospital, and 1-year mortality were associated with different risk variables. Specifically, while low skeletal muscle index had a significant impact across all time-related mortality, age and SOFA were risk factors for ICU mortality, whereas SAPS and comorbidity burden for in-hospital and 1-year mortality. This implies that a multiparametric assessment of the risk is required to intercept different time-related outcome measures.

Last, our analysis showed that the including both skeletal muscle index and myosteatosis in the of the multivariate Cox model improved its discrimination performance on the primary end-point (i.e. 90 days mortality), highlighting the importance of these two indexes as predictors.

This study has some limitations. First, it is a single-center retrospective study, and the observed associations will need to be validated in prospective observational trials. Second, in some patients the preoperative CT scan was used for elective patients who experienced a complication, preceding ICU admission up to 30 days. We assumed that body composition in elective patients went through non-significant changes during that period of time. However, this assumption cannot be confirmed, and thus represent a limitation of the present study. Third, being a retrospective data collection, some relevant risk factors could have been missed. Due to the retrospective nature of our study and on the smaller sample size – in comparison with the Phase Angle Project Study [17] we could not propose a score that integrated body composition indexes with already validated scores (such as SAPS and SOFA score). This would be an analysis of potential clinical relevance to further optimize the prediction of long-term outcomes in critically ill surgical patients. Fourth, no formal sample size calculation was performed. Fifth, as we measured body composition indexes with CT-scan, longitudinal changes in body parameters during the clinical course were not described. Currently, novel, alternative, non-invasive, and repeatable methods are emerging to estimate muscle mass easily, allowing to evaluate the extent of changes of muscle breakdown and turnover over time. Among those, muscle ultrasound [35], bioelectric impedance analysis [36] and urinary creatinine extraction [37] have been shown to be reliable tools to estimate skeletal muscle mass. These techniques may also allow to measure the effect of interventions on the management and prevention of sarcopenia in critically ill patients [38]. Last, our study was not designed to assess superiority of any body composition index over another.

In conclusion, the present results support the inclusion of specific body composition indexes in the evaluation of surgical critically ill patients. The routine measurement of these parameters whenever a CT is performed before or after ICU admission may help to predict the risk of unfavorable outcome at ICU admission. Future prospective observational studies may help to better define the exact predictive value of the different body composition indexes on outcomes.

Abbreviations

BMI, body mass index; CCI, Charlson Comorbidity Index; CT, computed tomography; ICU, intensive care unit; ECMO, extracorporeal membrane oxygenation; IMFA, intramuscular fat area; HU, Hounsfield units; MS, Myosteatosis; RRT, renal replacement therapy; SAPS II, simplified acute physiology score; SFA, subcutaneous fat area; SMI, Skeletal Muscle Index; SO, Sarcopenic Obesity; SOFA, sequential organ failure assessment; TFA, total fat area; TMA, total muscle area; VFA, visceral fat area.

Declarations

Ethics approval and consent to participate

The study protocol was reviewed by the institutional review board (Comitato Etico ASST Monza) and informed consent was waived.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request, after local Institutional Review Board (Comitato Etico ASST Monza) approval.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

AGi, MG and LG conceived the study, participated in its design and wrote the manuscript. AGr, AB and SF performed the data collection and contributed to the body composition indexes calculation. LR, MP performed the CT scan analysis. ER performed the statistical analysis and contributed to the writing of the manuscript. MB, GB, DI and GF participated in the trial design and coordinated the study. All authors revised the manuscript and approved the final version.

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Figures

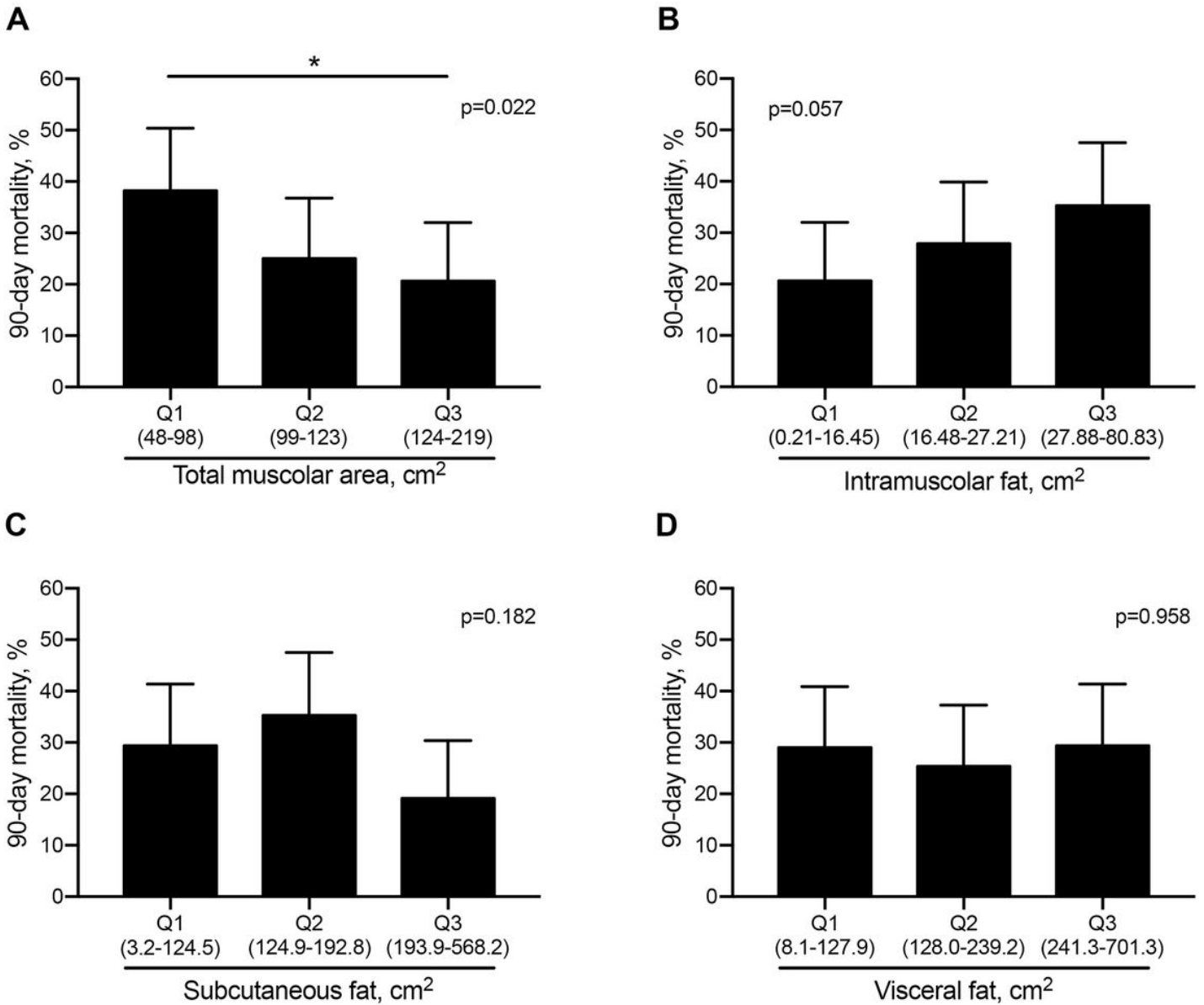



Figure 1

shows the association of single body composition indexes (stratified by tertiles) and 90-day mortality. A lower total muscular area (panel A) was associated with a higher 90-day mortality.

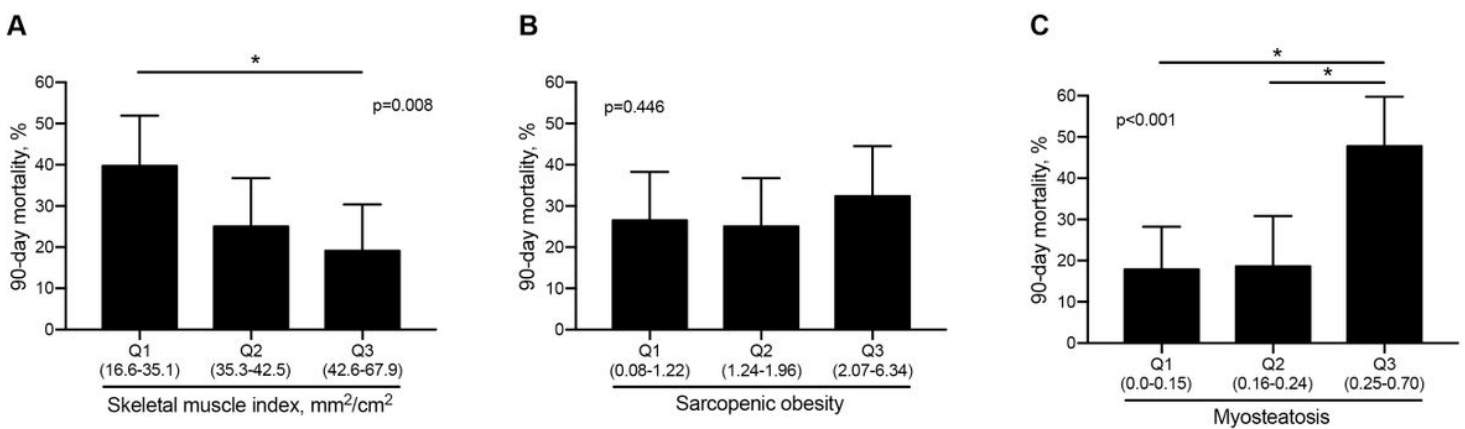
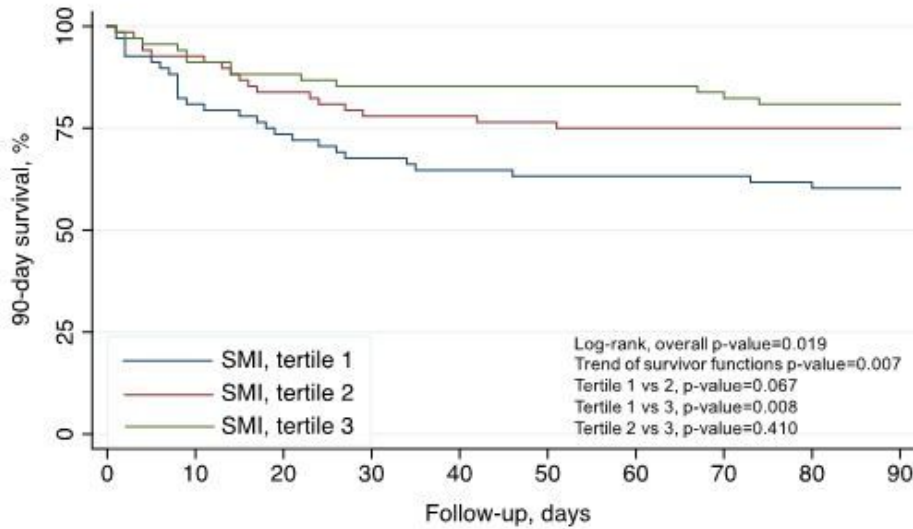



Figure 2

shows the association of composite body composition indexes and 90-day mortality. A low skeletal muscle index (SMI, Panel A) and a higher degree of myosteatosis (MS, Panel C) were associated with a higher 90-day mortality.

A

# patients											
	Q1	68	56	51	47	45	44	44	44	42	41
	Q2	68	64	58	54	54	53	52	52	52	51
	Q3	68	64	62	59	59	59	59	57	56	55

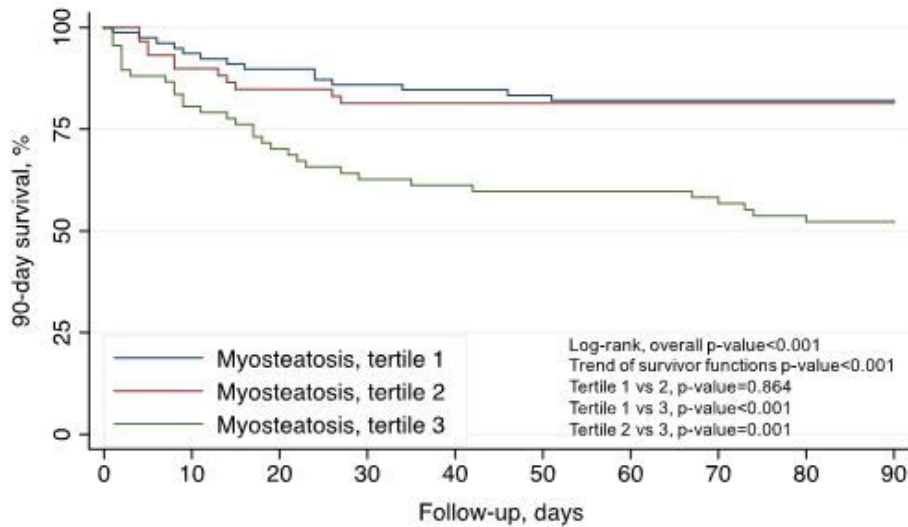
B

# patients											
	Q1	78	74	71	68	67	66	65	65	65	64
	Q2	59	55	51	49	49	49	49	49	49	48
	Q3	67	56	48	43	42	41	41	39	36	35

Figure 3

displays the impact of skeletal muscle index (panel A) and myosteatosis (panel B) stratified by tertiles over 90-day follow-up with a Kaplan-Meier survival curve. Log-rank test on population tertiles was significant for both parameters (p=0.019 and p<0.001, respectively). This finding was confirmed at the 1-year follow-up for both skeletal muscle index and myosteatosis (Log-rank p-value =0.045 and <0.001, respectively, see eFigure 1, Supplementary Material).