The Impact of Myosteatorsis Percentage on Short-Term Mortality in Patients with Septic Shock

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Research

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Abstract

Background: The impact of myosteatosi s on septic patients has not been fully revealed. This study aimed to evaluate the impact of myosteatosi s area and percentage on the 28-day mortality in patients with septic shock.

Methods: We conducted a single-center, retrospective study with prospectively collected data from a registry of adult patients with septic shock who presented to the emergency department and performed abdominal computed tomography (CT) from May 2016 to May 2020. Myosteatosi s area defined as the sum of the low-attenuation muscle area and intramuscular adipose tissue at the level of the third lumbar vertebra was measured by CT. Myosteatosi s percentages were calculated by dividing the myosteatosi s area by the total abdominal muscle area. Odds ratios (ORs) and 95% confidence intervals (CIs) for 28-day mortality were estimated using a multivariate logistic regression model.

Results: Of the 896 patients, the 28-day mortality was 16.3% and the abnormal myosteatosi s areas were commonly detected (81.7%). Among variables of body compositions, non-survivors had relatively lower normal-attenuation muscle area, higher low-attenuation muscle area, higher myosteatosi s area, and higher myosteatosi s percentage than survivors. Trends in myosteatosi s according to age groups were different between the male and female groups. In subgroup analysis with male patients, the multivariate model showed that the myosteatosi s percentage (adjusted OR 1.02 [95% CI 1.01–1.03]) was an independent risk factor for 28-day mortality. However, this association was not evident in the female group.

Conclusions: Myosteatosi s was common and a high myosteatosi s percentage was associated with short-term mortality in patients with septic shock. Our results implied that abnormal fatty disposition in the muscle could lead to increased mortality, especially in male patients.

Introduction

Sepsis and septic shock are still the leading cause of in-hospital death worldwide, even though early recognition and aggressive treatment had been applied since a few decades ago [1]. Because of its heterogeneity, identifying which patients with septic shock are at high risk of poor outcomes is needed for personalized management. The third international consensus definitions for sepsis and septic shock proposed to use the sequential organ failure assessment (SOFA) score for screening and prognostication [2]. However, assessing only organ dysfunction could not predict poor outcomes effectively, and intensive research efforts had tried to find out risk factors for septic shock. In this context, the body composition, which is composed of subcutaneous fat, visceral fat, and skeletal muscle, was focused as a potential biomarker to predict the clinical outcomes of patients with various diseases [3–5]. Lately, this concept has gained more interest because the concept of fat and muscle as secretory organs has been proposed. Body composition measurements could be done using computed tomography (CT) performed as a routine clinical practice [6]. The measured body composition by CT scan at the third lumbar vertebra

could be a representative value of the whole-body muscle mass [7–9]. To find out the source of infection and pre-intervention workup, abdominal CT evaluation in patients with septic shock is prevalent. Therefore, measuring body compositions for screening muscle depletion and abnormal fatty disposition can be applied in this group of patients.

We previously reported that a decreased skeletal muscle index was associated with poor outcomes in cancer patients with septic shock [10]. However, the skeletal muscle index only reflects muscle quantity and not function or strength; hence, it is limited [10]. Recent studies demonstrated that muscle quality and strength are associated with the degree of fatty infiltration or fatty degeneration called myosteatorsis [11, 12]. Myosteatorsis, once referred to as age-related excessive fatty disposition, is now considered to be a pathological phenomenon and can be estimated by the attenuation of skeletal muscle Hounsfield Units (HU) on CT scan [13, 14]. Although the impact of myosteatorsis in patients with malignancy, liver cirrhosis, and inflammatory bowel disease had been reported, little is known about its impact on the outcome of patients with septic shock [15–18]. Recent studies with critically ill patients proved that abnormal fat disposition could be associated with poor prognosis due to an overactivated inflammatory response [19–21]. However, their sample sizes were relatively small and their definitions of myosteatorsis were different. Furthermore, the mean muscle attenuation for the entire muscle area could be inaccurate for detecting the exact amount of myosteatorsis because the proportion of myosteatorsis might be markedly dependent on the entire muscle area [22]. Therefore, we hypothesized that the myosteatorsis percentage, which is the myosteatorsis area divided by total abdominal muscle area (MA), would be a better predictor of outcomes in patients with septic shock than the myosteatorsis area alone.

This study aimed to determine the prognostic significance of the myosteatorsis area and percentage in patients with septic shock treated with protocolized bundle therapy in the emergency department (ED).

Materials And Methods

Study design and population

This single-center, observational prospectively collected registry-based study was performed at the ED of a tertiary, university-affiliated hospital in Seoul, Korea, with an annual record of approximately 120,000 visits between May 2016 and May 2020. The ED of the study facility enrolled all adult (≥ 18 years old) patients with suspected or confirmed septic shock in the registry to monitor and improve outcomes [23]. Refractory shock was defined as persistent hypotension (systolic blood pressure < 90 mmHg, or a mean arterial pressure < 65 mmHg) [24]. Hypoperfusion was defined as a serum lactate level ≥ 4 mmol/L [25]. Patients were excluded in the registry if they were transferred from another hospital after initial resuscitation, were transferred to other hospitals, had “do-not-resuscitate” orders, refused management, developed septic shock 6 or more hours after ED arrival or did not require vasopressors after fluid loading.

All enrolled patients equally underwent protocol-driven resuscitation following the current guidelines and bundles of the Surviving Sepsis Campaign [24]. In brief, the administration of sufficient crystalloids with

the evaluation of volume status, acquisition of blood for both laboratory workup and blood cultures, and administration of broad-spectrum antibiotics were immediately performed for every patient.

This study included registry-enrolled patients who underwent abdominal CT examination, which had been taken for diagnostic purposes, at ED presentation. The institutional review board of the study facility approved this study (IRB number: 2021 – 0392) and waived the requirement for informed consent because of the retrospective characteristics.

Data Collection And Definition Of Variables

Demographic data, focus of infection, SOFA score, acute physiology and chronic health evaluation (APACHE) II score, and initial lactate level were extracted from the registry. The SOFA and APACHE II scores were calculated using the worst variables during the initial 24 hours after ED presentation. The primary outcome was 28-day mortality.

Electronic medical records were used to collect additional data to assess body morphometry, such as body weight, height, and the presence of an abdominal CT scan. The body mass index (BMI) was computed as the weight in kilograms divided by the height squared in meters (kg/m^2). The body composition and quality, including the subcutaneous fat area (SFA), visceral fat area (VFA), skeletal muscle area (SMA), normal-attenuation MA, intramuscular adipose tissue area, and low-attenuation MA, were assessed at the third lumbar (L3) vertebral level of abdominal CT scan performed at ED presentation using a previously developed web-based iAID toolkit [26]. Briefly, this algorithm selected a single axial image at the inferior endplate level of the L3 vertebra at the portal venous phase and segmented the abdominal body compartments into three areas (i.e., total abdominal MA, SFA, and VFA). Moreover, total abdominal MA was divided into three muscle components using the pixel-wise measurement of CT density with the following range of HU for each component: normal-attenuation MA with + 30 HU to + 150 HU, low-attenuation MA with = 29 HU to + 29 HU, and intramuscular adipose tissue area with – 190 HU to – 30 HU [13, 27]. The accuracy of the generated muscle quality map composed of normal-attenuation MA, low-attenuation MA, and intramuscular adipose tissue area was confirmed by a board-certified abdominal radiologist by comparing the original CT image and the muscle quality map image (Fig. 1).

The skeletal muscle index was calculated as the SMA which was defined as the sum of normal-attenuation MA and low-attenuation MA in cm^2 divided by the height (in meters) squared (cm^2/m^2) [28]. Abnormal SMI was diagnosed based on the low muscle mass and impaired function and was defined using sex-specific SMIs [29]. Myosteatorsis was defined as the sum of the low-attenuation MA and intramuscular adipose tissue area. Furthermore, the myosteatorsis percentage was calculated as the myosteatorsis area divided by the total abdominal MA to adjust the effect of the total muscle amount.

Statistical analysis

Descriptive statistics were stratified by 28-day all-cause mortality (i.e., survivor and non-survivor). Baseline demographics, clinical characteristics, laboratory results, and variables relating to body composition are presented as the frequency and percentage for categorical and median with interquartile range (IQR) for continuous variables. The Kolmogorov-Smirnov test was used to determine the normality of the distribution. Categorical variables were analyzed using Chi-squared or Fisher's exact tests. We also evaluated the association between the skeletal muscle index, myosteatos percentage and 28-day mortality separately according to gender. Univariate logistic regression tests were conducted with potential risk factors, which showed differences between survivors and non-survivors. Multivariate logistic regression was conducted with the variables that were statistically significant upon univariate logistic regression analysis. The absence of multicollinearity was checked by using regression analysis with calculations of the variance inflation factor values. We considered *P* values less than 0.05 as statistically significant. Analyses were performed using SPSS Statistics for Mac, version 26 (IBM Corp., Armonk, NY, USA) and R version 3.5.0 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Out of the 1160 patients with septic shock in the registry, 896 (77.2%) who underwent an abdominal CT at ED were included. The rate of 28-day mortality was 16.3% (*n* = 146) (Fig. 2).

The baseline characteristics of the study population are presented in Table 1. The median age was 67.0 (58.0–75.0) years with male predominance (58.8%). Non-survivors had higher proportions of chronic pulmonary disease (8.9% vs. 4.5%), malignancy (50.7% vs. 40.4%), hematologic disorder (11.6% vs. 5.5%), and liver cirrhosis (21.2% vs. 14.4%) than survivors. Except for unknown foci and the bloodstream, most sites of infection differed significantly between groups. Non-survivors showed more frequent pulmonary (24.0% vs. 14.9%) and intra-abdominal sources (22.6% vs. 14.4%), but less in the urinary tract (9.6% vs. 16.9%), hepato-biliary-pancreas sources (32.2% vs. 41.5%) than survivors. Also, the non-survivor group had significantly higher lactate levels, SOFA scores, and APACHE scores than the survivor group. Based on diagnosing with current cut-off values, low SMI (63.3%) and myosteatos (81.7%) were common in the study population; however, there were no significant differences between the two groups. Separate demographics and clinical characteristics of each gender are presented in the supplementary tables (Supplementary Table S1, Supplementary Table S2).

Table 1
Baseline characteristics of septic shock according to 28-day mortality

Characteristics	Total (n = 896)	Survivor (n = 750)	Non-survivor (n = 146)	P-value
Age	67.0 (58.0–75.0)	69.0 (60.0–76.0)	63.5 (53.8–69.0)	0.11
Male	527 (58.8)	433 (57.7)	94 (64.4)	0.14
Past illness				
HTN	299 (33.4)	253 (33.7)	46 (31.5)	0.60
DM	230 (25.7)	195 (26.0)	35 (24.0)	0.61
CAD	77 (8.6)	69 (9.2)	8 (5.5)	0.14
Chronic pulmonary disease	47 (5.2)	34 (4.5)	13 (8.9)	0.03
Malignancy	377 (42.1)	303 (40.4)	74 (50.7)	0.02
Hematologic disorder	58 (6.5)	41 (5.5)	17 (11.6)	< 0.01
CKD	51 (5.7)	45 (6.0)	6 (4.1)	0.37
LC	139 (15.5)	108 (14.4)	31 (21.2)	0.04
Site of infection				
Unknown	82 (9.2)	67 (8.9)	15 (10.3)	0.61
Lung	147 (16.4)	112 (14.9)	35 (24.0)	< 0.01
Urinary tract	141 (15.7)	127 (16.9)	14 (9.6)	0.03
Intra-abdomen	141 (15.7)	108 (14.4)	33 (22.6)	0.01
Hepato-biliary-pancreas	358 (40.0)	311 (41.5)	47 (32.2)	0.04
Blood stream	66 (7.4)	51 (6.8)	15 (10.3)	0.20
Lactate level	3.6 (1.9–5.8)	3.2 (1.7–5.4)	5.4 (2.6–9.2)	< 0.01
SOFA score	7.0 (5.0–10.0)	7.0 (5.0–9.0)	10.0 (6.0–13.0)	< 0.01
APACHE score	15.0 (11.0–20.0)	13.0 (11.0–23.0)	17.0 (11.0–23.0)	< 0.01
Low SMI	567 (63.3)	474 (63.2)	93 (63.7)	0.91
Myosteatorsis	732 (81.7)	607 (80.9)	125 (85.6)	0.19
Data are presented as n (%) or median (interquartile range).				
Abbreviations: HTN, hypertension; DM, diabetes mellitus; CAD, coronary artery disease; CKD, chronic kidney disease; LC, liver cirrhosis; SOFA, sequential organ failure assessment; APACHE, acute physiology and chronic health evaluation; SMI, skeletal muscle index.				

The baseline characteristics and body composition of the study population according to the presence of abnormal myosteatorsis are summarized in Supplementary Table S3. Patients with abnormal myosteatorsis were older (68.0 vs. 61.0 years), had fewer males (57.2% vs. 65.9%), more frequent hypertension (37.6% vs. 14.6%), diabetes mellitus (27.0% vs. 19.5%), coronary artery disease (9.6% vs. 4.3%), urinary tract infection (17.1% vs. 9.8%), higher lactate level (4.0 vs. 2.6 mmol/L), SOFA score (7.0 vs. 6.0), APACHE score (16.0% vs. 13.0), BMI (23.0 vs. 19.3 kg/m²), SFA (119.0 vs. 57.9 cm²), VFA (117.8 vs. 33.9 cm²), intramuscular adipose tissue area (18.3 vs. 6.1 cm²), low-attenuation MA (53.5 vs. 28.0 cm²), total abdominal MA (126.5 vs. 110.6 cm²), myosteatorsis area (72.8 vs. 35.0 cm²), and myosteatorsis percentage (58.1% vs. 29.2%). Normal-attenuation MA (51.4 vs. 80.4 cm²) was significantly lower in the abnormal myosteatorsis patient group.

Figure 3 illustrates the median myosteatorsis area and percentage according to age groups for male and female patients. Trends in myosteatorsis area and percentage according to age groups showed differed significantly between males and females. The detailed body morphometry in all patients and by sex is presented in Table 2. Compared with females, the body compositions of males tended to differ significantly between the survivor and non-survivor groups. Male non-survivors had smaller SMA (114.4 vs. 120.3 cm²), smaller normal-attenuation MA (60.3 vs. 73.3 cm²), smaller total abdominal MA (128.8 vs. 138.4 cm²), larger low-attenuation MA (53.8 vs. 49.0 cm²), and larger myosteatorsis percentage (51.8% vs. 46.1%). However, these differences were not observed in female patients, except low-attenuation MA (54.3 vs. 46.5 cm²) and myosteatorsis percentage (69.1% vs. 60.9%).

Table 2
Body composition of the study population

Body composition	Total (n = 896)	Survivors (n = 750)	Non-survivors (n = 146)	P value
Total				
BMI, kg/m ²	22.2 (19.7–24.6)	22.3 (19.7–24.6)	21.9 (19.7–24.9)	0.64
SFA, cm ²	107.3 (65.7–157.0)	110.0 (66.6–157.2)	94.9 (56.6–150.5)	0.07
VFA, cm ²	101.0 (57.7–158.9)	102.3 (57.4–160.4)	90.9 (59.0–147.7)	0.20
SMA, cm ²	106.2 (90.6–125.6)	106.1 (89.8–126.7)	106.7 (93.8–119.6)	0.76
□SMI, cm ² /m ²	40.6 (36.3–46.0)	40.6 (36.3–46.4)	41.0 (36.0–44.6)	0.67
Normal-attenuation MA, cm ²	56.8 (37.8–78.4)	57.4 (39.6–79.7)	52.8 (32.8–69.6)	< 0.01
Intramuscular adipose tissue area, cm ²	16.0 (9.6–23.2)	16.3 (9.7–23.3)	14.9 (9.2–22.6)	0.42
Low-attenuation MA, cm ²	49.2 (36.8–60.9)	47.6 (36.0–59.5)	54.1 (42.7–66.4)	< 0.01
□Total abdominal MA, cm ²	123.5 (109.2–142.1)	123.2 (109.0–143.3)	124.9 (109.9–136.2)	0.59
□□Myosteatorsis area, cm ²	66.6 (47.5–84.1)	65.9 (46.6–83.3)	70.7 (55.2–90.5)	0.03
□□□Myosteatorsis percentage, %	0.53 (0.40–0.67)	0.53 (0.39–0.66)	0.57 (0.44–0.71)	< 0.01
Male				

□Total abdominal MA was derived by adding the Normal-attenuation MA, Intramuscular adipose tissue area, and Low-attenuation MA.

□□Myosteatorsis area was derived by adding the Low-attenuation MA and Intramuscular adipose tissue area.

□□□Myosteatorsis proportion was defined as myostatorsis divided by Total abdominal MA.

Data are presented as median (interquartile range).

Abbreviations: BMI, body mass index; SFA, subcutaneous fat area; VFA, visceral fat area; SMA, skeletal muscle area; SMI, skeletal muscle area index; MA, muscle area.

Body composition	Total (n = 896)	Survivors (n = 750)	Non-survivors (n = 146)	P value
BMI, kg/m ²	22.0 (19.7–24.4)	22.1 (19.7–24.4)	21.6 (20.0–24.4)	0.63
SFA, cm ²	87.7 (52.6–131.1)	88.8 (55.8–131.3)	83.9 (49.6–123.8)	0.26
VFA, cm ²	110.1 (60.4–170.2)	113.1 (59.0–171.7)	97.2 (65.4–158.0)	0.30
SMA, cm ²	118.9 (105.3–137.2)	120.3 (106.2–138.3)	114.4 (101.0–125.9)	< 0.01
□ SMI, cm ² /m ²	42.7 (38.5–49.3)	42.8 (38.6–49.6)	42.1 (37.4–46.0)	0.07
Normal-attenuation MA, cm ²	70.2 (52.0–89.3)	73.3 (54.3–92.2)	60.3 (45.5–73.0)	< 0.01
Intramuscular adipose tissue area, cm ²	14.9 (8.6–21.1)	14.9 (8.7–21.1)	14.0 (7.5–21.7)	0.57
Low-attenuation MA, cm ²	50.0 (36.6–62.8)	49.0 (35.3–62.6)	53.8 (44.8–65.0)	0.02
□ Total abdominal MA, cm ²	135.2 (120.4–152.6)	138.4 (121.3–154.6)	128.8 (115.1–144.7)	< 0.01
□□ Myosteatorsis area, cm ²	65.9 (46.3–84.1)	65.5 (45.7–83.5)	67.0 (55.2–86.4)	0.13
□□□ Myosteatorsis percentage, %	47.7 (35.1–60.2)	46.1 (33.7–59.4)	51.8 (40.5–66.2)	< 0.01
Female				
BMI, kg/m ²	22.6 (19.7–24.9)	22.6 (19.7–24.8)	22.4 (19.6–25.8)	0.96

□ Total abdominal MA was derived by adding the Normal-attenuation MA, Intramuscular adipose tissue area, and Low-attenuation MA.

□□ Myosteatorsis area was derived by adding the Low-attenuation MA and Intramuscular adipose tissue area.

□□□ Myosteatorsis proportion was defined as myostatorsis divided by Total abdominal MA.

Data are presented as median (interquartile range).

Abbreviations: BMI, body mass index; SFA, subcutaneous fat area; VFA, visceral fat area; SMA, skeletal muscle area; SMI, skeletal muscle area index; MA, muscle area.

Body composition	Total (n = 896)	Survivors (n = 750)	Non-survivors (n = 146)	P value
SFA, cm ²	137.8 (93.8–181.4)	138.4 (95.6–181.4)	124.9 (81.0–186.6)	0.53
VFA, cm ²	91.1 (53.8–133.0)	91.7 (55.6–136.4)	85.4 (33.3–130.1)	0.27
SMA, cm ²	90.6 (80.0–100.8)	90.9 (80.3–100.4)	89.3 (79.1–104.0)	0.51
□ SMI, cm ² /m ²	37.9 (34.1–41.7)	37.8 (33.9–41.5)	37.9 (34.1–43.6)	0.60
Normal-attenuation AMA, cm ²	41.0 (28.2–55.9)	42.4 (28.6–56.0)	33.7 (23.5–53.3)	0.08
Intramuscular adipose tissue area, cm ²	17.9 (12.0–25.7)	18.0 (11.9–25.5)	16.8 (12.6–27.0)	0.71
Low-attenuation MA, cm ²	48.0 (36.9–58.7)	46.5 (36.6–57.8)	54.3 (40.6–66.6)	< 0.01
□ Total abdominal MA, cm ²	109.8 (98.8–121.7)	109.3 (98.7–120.9)	114.8 (99.1–127.7)	0.29
□□ Myosteatorsis area, cm ²	67.3 (49.4–84.3)	66.8 (48.7–83.0)	75.2 (54.0–95.2)	0.13
□□□ Myosteatorsis percentage, %	61.5 (47.8–75.1)	60.9 (47.3–74.6)	69.1 (53.1–77.7)	0.05
□ Total abdominal MA was derived by adding the Normal-attenuation MA, Intramuscular adipose tissue area, and Low-attenuation MA.				
□□ Myosteatorsis area was derived by adding the Low-attenuation MA and Intramuscular adipose tissue area.				
□□□ Myosteatorsis proportion was defined as myostatorsis divided by Total abdominal MA.				
Data are presented as median (interquartile range).				
Abbreviations: BMI, body mass index; SFA, subcutaneous fat area; VFA, visceral fat area; SMA, skeletal muscle area; SMI, skeletal muscle area index; MA, muscle area.				

Table 3
Multivariate analysis of septic shock patients for its association with 28-day mortality

Variables	Univariate analysis			Multivariate analysis		
	OR	95% CI	P value	Adjusted OR	95% CI	P value
Male						
CAD	0.44	0.16–1.26	0.13	0.44	0.16–1.25	0.12
Hematologic disorder	1.09	0.44–2.73	0.85			
CKD	0.24	0.05–1.20	0.08	0.22	0.04–1.06	0.06
Chronic liver disease	1.45	0.76–2.78	0.26			
Urinary tract infection	0.40	0.13–1.28	0.12	0.33	0.11–0.99	0.05
Intra-abdominal infection	1.39	0.69–2.81	0.36			
Hepato-biliary-pancreas infection	0.52	0.28–0.97	0.04	0.45	0.26–0.77	< 0.01
Blood stream infection	2.46	0.77–7.88	0.13			
Lactate	1.18	1.09–1.28	< 0.01	1.19	1.10–1.29	< 0.01
SOFA	1.11	1.02–1.21	0.02	1.13	1.05–1.21	< 0.01
APACHE	1.01	0.97–1.05	0.68			
SMI	0.97	0.94–1.00	0.07	0.97	0.94–0.99	0.05
Myosteatosi s percentage	1.02	1.01–1.03	0.04	1.02	1.01–1.03	0.04
Female						
Hematologic disorder	0.65	0.13–3.34	0.61			
Malignancy	2.59	1.25–5.37	0.01	2.77	1.35–5.67	< 0.01
Lung infection	2.00	0.82–4.88	0.13			
Blood stream infection	3.32	0.87–12.63	0.08	2.97	0.87–10.11	0.08
Lactate	1.07	0.96–1.19	0.22			
SOFA	1.15	1.01–1.31	0.04	1.19	1.05–1.34	< 0.01
APACHE	1.08	1.01–1.14	0.02	1.08	1.02–1.14	0.01

Abbreviations: OR, odds ratio; CI, confidence interval; CAD, coronary artery disease; CKD, chronic kidney disease; SOFA, sequential organ failure assessment; APACHE, acute physiology and chronic health evaluation.

Variables	Univariate analysis			Multivariate analysis		
	OR	95% CI	<i>P</i> value	Adjusted OR	95% CI	<i>P</i> value
Myosteatosi s percentage	1.01	0.11–8.98	0.99			
Abbreviations: OR, odds ratio; CI, confidence interval; CAD, coronary artery disease; CKD, chronic kidney disease; SOFA, sequential organ failure assessment; APACHE, acute physiology and chronic health evaluation.						

In the univariate analysis, the following covariates were associated with 28-day mortality: coronary artery disease, hematologic disorder, chronic kidney disease, chronic liver disease, urinary tract infection, intra-abdominal infection, hepato-biliary-pancreas infection, bloodstream infection, initial lactate level, SOFA, APACHE, SMI, and myosteatosi s percentage for males; hematologic disorders, malignancy, lung infection, bloodstream infection, initial lactate level, SOFA, APACHE, and myosteatosi s percentage for females (Supplementary Table 1 and Supplementary Table 2). Multivariable logistic regression analyses for male patients showed that the lower SMI (adjusted OR 0.97; 95% CI 0.94–0.99; $P = 0.05$) and higher myosteatosi s percentage (adjusted OR 1.02; 95% CI 1.01–1.03; $P = 0.04$) were independently associated with a lower 28-day mortality. Meanwhile, neither SMI nor myosteatosi s percentage was significantly associated with 28-day mortality in females.

Discussion

In this study of body composition involving patients with septic shock, in which SMI was included as independent parameter, the myosteatosi s percentage was the parameter that was associated with short-term survivors. Our results implied that abnormal fat disposition in the muscle could negatively impact clinical outcomes by weakening the immune response to pathogens or reducing tolerability to treatment, with the effect being more prominent in males than in females.

Myosteatosi s is an abnormal fat depot that increases with age and is known to negatively correlate with muscle strength and mobility and also to impede metabolism [30]. Our results show that myosteatosi s is predominant in patients with septic shock. A recent review reported that the overall prevalence of myosteatosi s in critically ill patients ranged from 25–40% [17, 31]. This relatively low prevalence was attributed to the difference in the definition of myosteatosi s between their study and ours. Traditionally, quantifying myosteatosi s was defined by using the mean muscle density of total abdominal muscle [22]. This definition could be inaccurate in detecting the extent of myosteatosi s and might under- or over-estimate the proportion of the ectopic fat deposit. Moreover, most studies set single cut-off values (e.g., below 40 HU) for detecting myosteatosi s [22]. However, previous studies with healthy study populations showed that the degree of myosteatosi s was differed according to age and sex. In this manner, we measured the direct area of normal-attenuation MA and intramuscular adipose tissue and diagnosed myosteatosi s based on previously reported cut-off values according to age and sex [26]. Interestingly, this method revealed that a surprising portion of patients with septic shock had myosteatosi s and the

differences were largely due to normal-attenuation MA than intramuscular adipose tissue in both males and females.

We identified statistical differences in myosteatosi s percentages among 28-day survivors and non-survivors in both males and females. This scaling has a definite physiological basis that the myosteatosi s area was largely affected by total abdominal MA. Although causality can be inferred only from randomized controlled trials, we found that myosteatosi s could be a surrogate marker for short-term survival among patients with septic shock. This result is in line with those of previous studies which report that the progression of myosteatosi s contributed to the development of sepsis [32]. Furthermore, a recent longitudinal laboratory study carried out on mice reported that the amount of myosteatosi s had a positive correlation with the severity of inflammation with non-alcoholic fatty liver disease [33]. Although the exact pathologic mechanism has not been completely revealed, it seems to be the result of a complex cascade involving dysregulation of the inflammatory response by excess adipose tissue [34]. A recent pre-clinical study also announced that a worse muscle quality was associated with abnormally higher levels of expression of inflammatory markers, suggesting the existence of abnormal responses to pathogens [35]. Our results also supported this assumption that patients with myosteatosi s had more chronic illnesses (such as hypertension, diabetes, and coronary artery disease) and tended to suffer more frequently from severe septic shock (i.e., higher lactate level, SOFA, and APACHE score) (Supplementary Table 3).

Although the myosteatosi s percentages differed between survivors and non-survivors, only the male group presented this variable as an independent risk factor for 28-day mortality. Sex-specific differences have been largely reported for fat distribution, properties, secretory function, and fatty acid handling in healthy participants and pre-clinical models [36]. The exact mechanism of this dimorphism is not yet elucidated; however, one possibility is the different proportions of sex hormones because sex steroids seem to act as endogenous modulators of development and function, and also influence the distribution of fat [37, 38].

Limitations

Our study has several limitations. First, because of the single-center retrospective design in South Korea, it might be hard to generalize the results of this study to other populations. Race-ethnic differences in body composition have been widely announced [39]. Because there were no definite cut-off values for myosteatosi s area or percentage, we diagnosed myosteatosi s based on previous reports and this could over- or under-estimate the prevalence of the condition [26]. However, our study results added data on body composition in the population of Asians who developed septic shock. Second, we analyzed only patients with septic shock who clinically performed CT; given that the utility of CT is limited by its high cost, radiocontrast, and high-dose radiation exposure, the baseline characteristics of the study population showed a relatively low proportion of lung infection and a high proportion of abdominal infection. Finally, the septic shock registry of the study facility excludes patients who refused admission or who signed a “do-not-attempt-resuscitation” order; all these could lead to selection bias.

Conclusion

In conclusion, most patients with septic shock had myosteatorsis, which was independently associated with 28-day mortality. Even though this association was evident in male patients, myosteatorsis could be a modifiable risk factor for short-term outcomes; therefore, it could be the target of future therapeutic modalities.

List Of Abbreviations

APACHE, acute physiology and chronic health evaluation

BMI, body mass index

CT, computed tomography

ED, emergency department

MA, myosteatorsis area

HU, hounsfield units

IQR, interquartile range

SMA, skeletal muscle area

SMI, skeletal muscle index

SFA, subcutaneous fat area

SOFA, sequential organ failure assessment

VFA, visceral fat area

Declarations

Acknowledgments:

Author's contributions: W.Y.K. designed the study and supervised the writing of the paper. J.S.K. contributed to the literature search, figures, study design, data analysis, interpretation and writing, and revisions. J.Y.H. contributed to the figures, data analysis, and revisions. Y.J.K. contributed to the revisions and validation of the study. Y.S.K., T.P., and K.W.K contributed to the study design and data collection.

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Figures

Figure 1

Example of body composition measurements. Muscle quality map generation using a web-based toolkit. After dividing the body composition into three parts (i.e., subcutaneous fat, visceral fat, and skeletal muscle), skeletal muscle was classified into three areas according to certain attenuations (i.e., NAMA, LAMA, and IMAT). The myosteatosi s area was defined as the sum of LAMA and IMAT. Abbreviations: IMAT, inter/intramuscular adipose tissue area, LAMA, low-attenuation muscle area, NAMA, normal-attenuation muscle area, SMA, skeletal muscle area, TAMA, total abdominal muscle area

Figure 2

Flowchart of patient enrollment and allocation in the study. Abbreviations: DNR, do-not-resuscitation; CT, computed tomography.

Figure 3

Distribution of myosteatosi areas and percentage according to the age groups in male and female patients

Supplementary Files

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