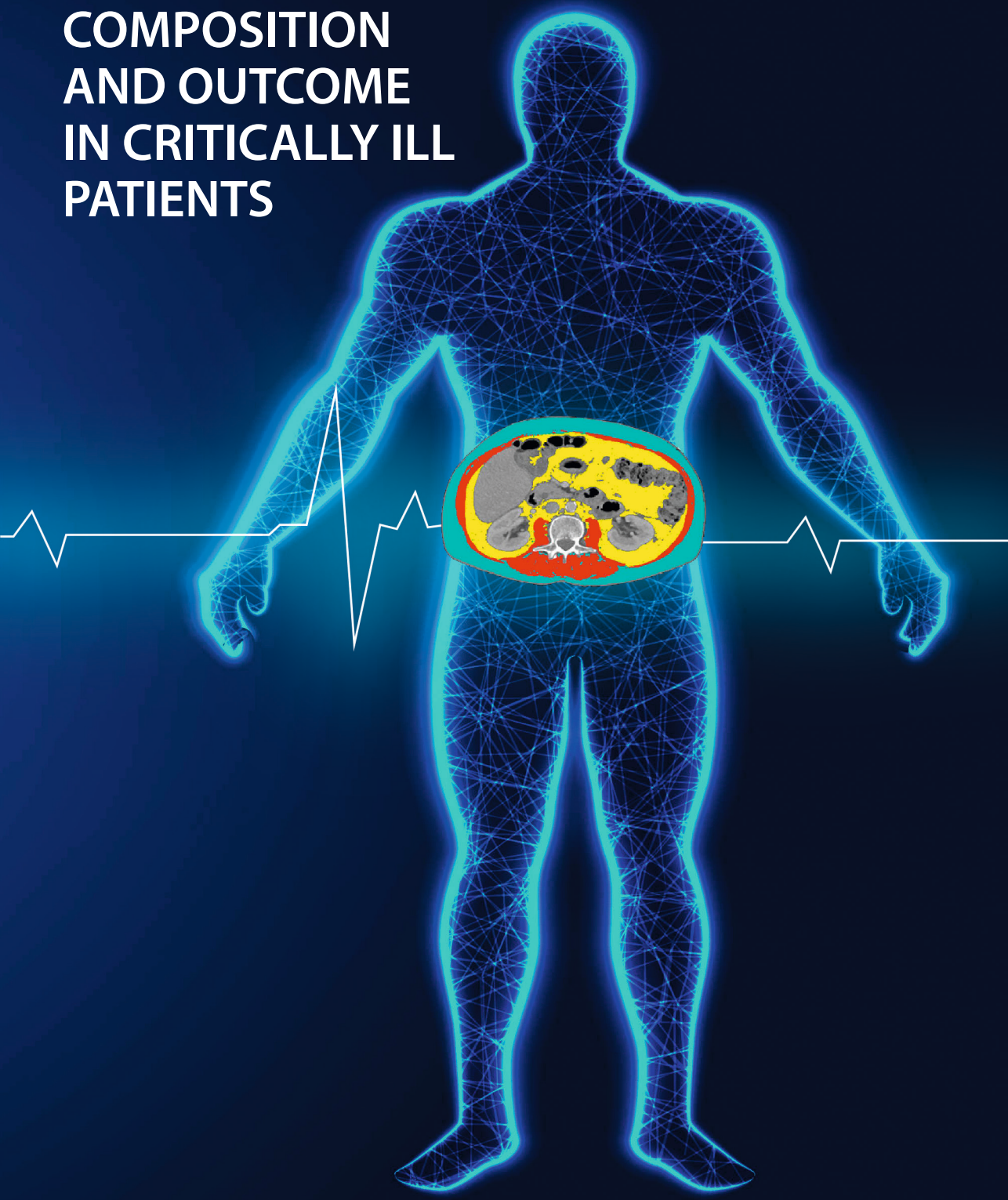
The measurement of body composition and outcome in critically ill patients

THE MEASUREMENT OF BODY COMPOSITION AND OUTCOME IN CRITICALLY ILL PATIENTS



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The measurement of body composition and outcome in critically ill patients

PROEFSCHRIFT

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The burden of critical illness

Critical illness is the impairment of one or more vital organ systems causing a life-threatening deterioration in the patient's condition and requiring pharmacological and/or mechanical support of these vital organ functions [1]. This support is generally provided in Intensive Care Units (ICU's). The primary goal of an Intensive Care admission is to prevent further deterioration in physiological function and to sustain life while any underlying disease is treated [1, 2]. The survival rate of critically ill patients has increased over the past decades [3, 4]. Every year, approximately 76.000 patients are admitted to Dutch ICU's. Of those patients, 13% do not survive to hospital discharge. More than one third of the admissions consider elective surgical patients that are routinely admitted to the ICU for postoperative care. These patients have a rather low mortality rate of 2.5% and should clearly be distinguished from patients with an unplanned ICU admission. In patients with an unplanned ICU admission, e.g. due to community acquired pneumonia (≈3.400 admissions per year) or sepsis (≈5.000 per year) mortality rates rapidly increase. The hospital mortality for all ICU patients admitted for community acquired pneumonia or sepsis is over 20% and over 27% respectively [5].

An ICU admission is most often burdening for patients as well as for their relatives [6]. ICU admission can cause delirium, mood disorders and anxiety. Following ICU discharge sequelae such as depression and Post Traumatic Stress Disorder (PTSD) can persist for a long period of time [7]. The impairment in physical function, cognition and mental health that is encountered by ICU survivors is referred to as the Post-Intensive Care Syndrome (PICS) and occurs in up to 25% of the ICU survivors and is associated with a reduced quality of life [8]. Up to 30% of the relatives of patients experience stress, anxiety, depression and complicated grief following ICU admission of their loved one, predominately caused by the uncertainty of the prognosis of the patient [7] and probably by the impotence to influence the outcome.

Apart from the personal impact of ICU admission on patients and relatives, the societal impact of Intensive Care Medicine is vast. With an average cost of at least 2500 euro per day [9], the total annual costs of Intensive Care treatment in the Netherlands exceed 200 million euros. Due to the ageing of the population and a growing prevalence of chronic diseases the expectation is that healthcare costs will further increase in the future [4]. Concerns about the sustainability of this development are growing. Increasing the efficiency of healthcare utilization by improving quality of care or by better stratification of patients who may or may not benefit from certain (expensive) treatments may contribute to the control of healthcare costs.

Outcome prediction

Adequate outcome prediction may be valuable to better inform patients, family members and healthcare professionals about the prognosis of survival and disability of critically ill patients. Traditional outcome predictors for critical illness rely on "hard data", particularly on organ function or physiological condition (e.g. APACHE [10] or SOFA score [11]). As an alternative to such scores, the Clinical Frailty Score that assesses fitness and dependency in daily activities of patients (Figure 1) is increasingly used to predict ICU outcome, for example in the Dutch triage guideline for the COVID19 pandemic [12]. It can be argued that The Clinical Frailty Score offers a more holistic alternative to traditional risk scores [13], however, it is a rather subjective instrument.

Clinical frailty is associated with changes in body composition such as low muscle mass, which led to the notion that muscle mass, quality and function affects clinical outcome after ICU admission. Indeed, in the last decade, numerous studies have indicated that low muscle mass is associated with poor outcome in critically ill patients [14, 15]. Apart from being a potential (bio-)marker in critical illness, muscle mass and particularly muscle loss can also be a modifiable target for therapy or prevention.

Figure 1. The Clinical Frailty Scale [16]

Body Composition

Body composition can be analyzed using Computed Tomography (CT) scans according to the method of Mourtzakis et al [17]. The density of tissues on a CT-image is in proportion to the attenuation of the x-rays passing through, therefore different organs and tissues have a specific grey-tone and can easily be distinguished on CT-images. The cross-sectional area of particularly skeletal muscle, visceral and subcutaneous adipose tissue at the level of the third lumbar vertebra is representative for total body composition [17]. The greytone of a region of interest on a CT-image can be quantified in Hounsfield Units (HU). Every tissue has a broad physiological range of Hounsfield Units (e.g. skeletal muscle area (-29 to 150 HU) and visceral adipose tissue (-150 to -50 HU), which is determined by the water and lipid content of the tissue of interest.

Body composition is increasingly used as a predictor of outcome in various diseases such as cancer or COPD [17-19]. In addition, it is gaining interest in the context of targeting modifiable adverse body composition phenotypes, for example to improve muscle mass and/or function by prehabilitation prior to oncological surgery [20, 21].

Muscle Mass

Previous research shows that low muscle mass, or sarcopenia, at ICU admission is associated with a higher mortality, increased length of mechanical ventilation and increased length of ICU stay [14, 15]. The concept that low muscle mass is a predictor for outcome seems logic and appealing, however, research has predominantly been done in heterogenous mixed ICU populations without correction for comorbidities and presenting disease. Such heterogenous cohorts are susceptible for bias. For example, the outcome of young trauma patients is likely better than that of older patients suffering from COPD, not because they have a higher muscle mass but because their underlying disease has a better prognosis in itself. Moreover, there is a high prevalence of low muscle mass in conditions that are associated with poor outcome after ICU admission [18, 22-25]. It is not well addressed whether low muscle mass is an independent risk factor for mortality or mere a marker for chronic disease. Moreover, no uniform quantitative definition for "low muscle mass" or sarcopenia have been applied in available literature and in many instances, such as studies in body composition research apply cut-off values for low muscle mass that are relative to the cohort under study [14, 26-28]. Particularly in cohorts with a skewed distribution of muscle mass this induces the risk of incorrect grouping and confounding.

Muscle loss

Muscle mass on ICU admission should be clearly distinguished from muscle loss during ICU admission. Patients with multiple organ failure can lose up to 25% of their muscle mass during ICU admission [29]. ICU acquired weakness is one of the most important patient reported outcome measures in ICU survivors since it can affect functional ability up to five years after ICU admission [30-32]. To gain more insight in the possible pathophysiology behind profound muscle loss on the ICU and in potential remedies, it is important to quantify this muscle loss in individual patients. Some advocate the use of muscle ultrasonography to this end [33], but its routine implementation is still limited and longitudinal studies on changes in muscle mass in critical illness are scarce [29, 34]. Additionally, since ultrasonography of muscle mass is hitherto no part of routine critical care, the broad execution of retrospective cohort studies is not possible.

In critically ill patients CT-scans are often made for clinical purposes, in many cases on multiple sequential occasions. This opens the potential opportunity for the design of retrospective cohort studies on changes in body composition. However, a few caveats, such as variations in position between various scans may threaten the reliability of the application of sequential CT-scans in body composition analysis in critically ill patients. Moreover, the acute phase of critical illness, particularly sepsis is characterized by systemic inflammation and high capillary leakage, resulting in distributive shock. Patients often receive extensive amounts of fluids to maintain adequate blood pressure [35]. This can lead to edema in various organs and tissues including the muscle, which may affect body composition measurements and jeopardize the reliability of the assessment of changes in muscle mass during critical illness.

Adipose Tissue

In addition to the well-established association between muscle mass and outcome in several disease states, the insight in the role of adipose tissue, particularly visceral adipose tissue, as a mediator of outcome of disease is growing [36, 37]. An excess of visceral adipose tissue is also referred to as visceral obesity. It leads, amongst others, to immune cell activation and chronic inflammation, increased lipid uptake by macrophages, matrix remodeling and increased angiogenesis [38]. Visceral obesity is associated with the metabolic syndrome and a three times higher risk for cardiovascular disease and a five times higher risk for diabetes mellitus [36, 39-42].

Several literature data suggest that in sepsis, patients with overweight, defined by body mass index have a better survival than patients with a normal body weight. This remarkable observation is referred to as “the obesity paradox” [43]. It is not known whether this obesity

paradox actually is true and, if so, whether it is caused by factors associated with obesity [44] or by a protective effect of adipose tissue itself. Given the metabolic activity of visceral adipose tissue, it may be conceived that in particular visceral obesity could play a role in the obesity paradox. Since there can be quite a disparity between total body mass and visceral fat mass [45] it may be important to assess the association between visceral adipose tissue and clinical outcome in addition to the association between BMI and clinical outcome in critically ill patients. There is no gold standard or cut-off value to define visceral obesity in the literature. Ideally, this cut-off value should indicate the threshold of the amount of visceral adipose tissue that is associated with an increased for risk for metabolic complications and the metabolic syndrome.

Aim

The overall aim of this thesis is to increase insight in the association between body composition and clinical outcome in critically ill patients. To this end both the association of (changes in) muscle mass and visceral adipose tissue will be described. The resulting knowledge may particularly become valuable in the prognostication of patients considered for ICU admission and in the development of treatments aimed at ameliorating muscle loss during ICU admission. Improving prognostication may help patients, relatives and physicians to make informed decisions and to manage expectations with respect to the outcome of an imminent ICU admission. Improving risk stratification and quality of care may ultimately reduce the personal and societal burden of (futile) ICU utilization.

Outline of the thesis

There is a clear association between sarcopenia and outcome in critical illness, however also chronic diseases and increasing age are associated with poor outcome in the same condition. It is not clear whether the association between sarcopenia and outcome is independent or whether it is confounded by the high prevalence of sarcopenia in chronic diseases and the elderly per se, that are in itself associated with poor ICU survival. Therefore, in chapter 2 we investigated if sarcopenia is an independent risk factor for hospital mortality in critical illness, or whether this relation is confounded by co-morbidities or age that are characterized by sarcopenia.

Sequential CT scans can possibly be used to assess muscle loss during ICU admission. However, during the acute phase of critical illness, patients receive extensive amounts of fluids. In chapter 3 we aimed to study changes in muscle mass and quality in critical illness using repeated

computed tomography scans with special emphasis on the influence of edema on this assessment.

For the outcome of ICU patients not only muscle mass but also visceral adipose tissue may be important. To investigate this association properly, a reliable definition of visceral adiposity is warranted. However, reference values for the Caucasian population are lacking. In chapter 4 we describe the association between the amount of visceral adipose tissue and metabolic risk factors and propose gender specific cut-off values for visceral obesity in a Caucasian population that can be used as external reference values in studies on visceral obesity. These gender specific cut-off values were applied in chapter 5 to a large cohort of mixed ICU patients to assess the association between visceral obesity and outcome.

The thesis is concluded with a general summary and discussion and with an overview of the societal and scientific impact of its results.

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Muscle wasting associated co-morbidities, rather than sarcopenia are risk factors for hospital mortality in critical illness

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Abstract

Background

Low skeletal muscle mass on intensive care unit admission is related to increased mortality. It is however unknown whether this association is influenced by co-morbidities that are associated with skeletal muscle loss. The aim of this study was to investigate whether sarcopenia is an independent risk factor for hospital mortality in critical illness in the presence of co-morbidities associated with muscle wasting.

Methods

Data of 155 patients with abdominal sepsis were retrospectively analyzed. Skeletal muscle area was assessed using CT-scans at the level of vertebra L3. Demographic and clinical data were retrieved from electronic patient files. Sarcopenia was defined as a muscle area index below the 5th percentile of the general population. Uni- and multivariable analyses were performed to assess the association between sarcopenia and hospital mortality, correcting for age and comorbidities.

Results

The prevalence of sarcopenia was higher in patients that did not survive until hospital discharge. However, it appeared that this relation was confounded by the presence of chronic renal insufficiency and cancer. These were independent risk factors for hospital mortality, whereas sarcopenia was not.

Conclusion

In critically ill patients with abdominal sepsis, muscle wasting associated co-morbidities rather than sarcopenia were risk factors for hospital mortality.

Introduction

There is increasing interest in the relationship between body composition and outcome in critically ill patients. Several studies showed a relationship between low skeletal muscle mass on Intensive Care Unit (ICU) admission and mortality [1-6].

A clear definition of low skeletal muscle mass is lacking and terminology such as low muscle mass and sarcopenia are often used interchangeably. Formally, sarcopenia is defined as the (age related) loss of skeletal muscle mass and function [7]. Since skeletal muscle function is difficult to assess in large groups, it has been proposed to use the 5th percentile of the skeletal muscle area index of a healthy reference population to define sarcopenia [8].

The ICU population is very heterogeneous. Of the patients with sepsis, a large proportion is of advanced age [4] and suffering from chronic comorbidities, for example cardiovascular failure, renal failure or cancer. These comorbidities are associated with a decline of skeletal muscle mass, potentially leading to sarcopenia [9-11]. Moreover, they are all known to be negatively associated with ICU survival.

It is unclear whether the relationship between sarcopenia and mortality in critically illness is associated with sarcopenia itself, or by comorbidities that are associated with skeletal muscle wasting. There are no studies at hand to assess whether sarcopenia is an independent risk factor for mortality.

An established method for the assessment of body composition and skeletal muscle mass is to measure the total skeletal muscle area at the level of the third lumbar vertebra (L3) on an abdominal CT-scan [12]. This method was used to assess the skeletal muscle area of patients with abdominal sepsis. This patient category was chosen since it provides a relatively homogeneous cohort of critically ill patients with a high prevalence of chronic co-morbidities as well as a large proportion of these patients undergo abdominal CT-scanning.

The aim of this study was to investigate whether sarcopenia is an independent risk factor for hospital mortality in critical illness in the presence of skeletal muscle wasting associated co-morbidities.

Methods

Patients

Data of all adult patients consecutively admitted with abdominal sepsis to the 33-bed Intensive Care Unit of the Maastricht University Medical Centre between July 2013 and August 2017 were retrospectively analyzed. Patients with abdominal sepsis were retrieved from a prospective database containing all patients admitted with sepsis of any origin at our department. Sepsis was defined as infection and at least one organ dysfunction according to the sepsis-3 criteria [13]. Subsequently, patients were selected in which an abdominal CT-scan was performed between 6 days before and 2 days after ICU admission.

Demographic data and data on disease severity (APACHE-II), co-morbidities, ICU mortality, and hospital mortality were retrieved from the Patient Data Management System (IntelliVue Clinical Information Portfolio (ICIP), Philips Medical Systems, Best, the Netherlands).

CT-scan analysis

CT-scan analysis of skeletal muscle area was performed using the method of Mourtzakis *et al* [12]. Briefly, a single slice of each patient's CT scan was selected at the level of the 3rd lumbar vertebra. Muscles included into the analysis were the m. obliquus internus and externus abdominis, m. transversus abdominis, m. rectus abdominis, m. psoas, m. quadratus lumborum, and m. erector spinae. All CT-scans were reviewed for applicability of skeletal muscle area analysis. CT-scans with movement artifacts, radiation artifacts, CT-scans with low contrast or low quality hampering sharp delineation of the skeletal muscle area or CT-scans were the abdominal muscle was partially cut off were deemed to be of insufficient quality for muscle area analysis.

Using predefined Hounsfield Unit (HU) ranges, the total cross-sectional area (cm^2) of skeletal muscle area (SMA) (–29 to 150 HU), visceral adipose tissue (VAT) (-150 to -50 HU) and subcutaneous adipose tissue (SAT) (-190 to -30 HU) were determined. The total area of SMA, VAT and SAT were estimated by assessing the total tissue area at vertebra L3 and dividing it by height squared resulting in the L3-skeletal muscle index (SMI) in cm^2/m^2. In addition, the Visceral Adipose Tissue Index (VATI) and Subcutaneous Adipose Tissue Index (SATI) were determined [12]. CT scans were analyzed using sliceOmatic 5.0 (TomoVision, Magog, Canada) software for Microsoft Windows®.

Evaluation of skeletal muscle area index and definition of sarcopenia

Skeletal muscle mass is gender dependent [14]. To facilitate gender independent analysis of the impact of sarcopenia on hospital mortality, gender specific cut-off values were used. Sarcopenia was defined as a skeletal muscle area index below the gender specific 5th percentile of a healthy Caucasian population (41.6 cm^2/m^2 and 32.0 cm^2/m^2 for males and females, respectively) [8].

Evaluation of skeletal muscle quality

Skeletal muscle quality, also known as skeletal muscle density, was assessed using the radiation attenuation of skeletal muscle tissue. The radiation attenuation was calculated by the mean Hounsfield Unit (HU) value of the total skeletal muscle tissue area within the predefined HU ranges of muscle tissue [12, 15, 16]. Because the use of contrast agents may influence the radiation attenuation of muscle tissue, only unenhanced CT scans were included in the analysis. [17]

Statistics

Univariable analyses, i.e. chi-square and Fisher's exact tests for categorical variables and independent-samples t-tests for numerical variables, were performed to assess the association with hospital mortality (yes/no). Normality was checked for numerical variables using histograms.

A multivariable logistic regression analysis was performed to assess the effect of sarcopenia on hospital mortality, corrected for variables known to be related to skeletal muscle loss, such as chronic renal insufficiency, chronic cardiovascular disease, COPD, cancer, and age. Collinearity was checked using the variance inflation factor (VIF ≥ 10 indicates (multi)collinearity) and linearity assumption for age was assessed by testing whether a centered quadratic term adds significantly to the model. A sensitivity analysis was performed by replicating both uni- and multivariable analysis using the gender specific quartiles for skeletal muscle mass index of the current cohort. Analyses were performed using IBM SPSS Statistics for Windows (version 25, IBM Corp., Armonk, NY) and Prism version 8.0.0 (GraphPad Software, San Diego, CA). The statistical analyses were supervised by a statistician (BW). A two-sided p-value ≤ 0.05 was considered statistically significant.

Ethics

The study protocol was reviewed and approved by the Institutional Review Board of the Maastricht University Medical Centre (METC 2018-0803). Since data were coded, informed

consent was waived for this retrospective analysis, which is in agreement with the European General Data Protection Regulation.

Results

Patients

During the inclusion period 263 adult patients with abdominal sepsis were admitted to the ICU. In 75 patients, no abdominal CT-scan was made between day 6 before and day 2 after ICU admission. In 33 cases the abdominal CT-scans were of insufficient quality for reliable analysis. This resulted in a total number of 155 patients eligible for analysis (58.9%), of whom 93 males (60%) and 62 females (40%). Figure 1 shows the flow diagram of patient selection.

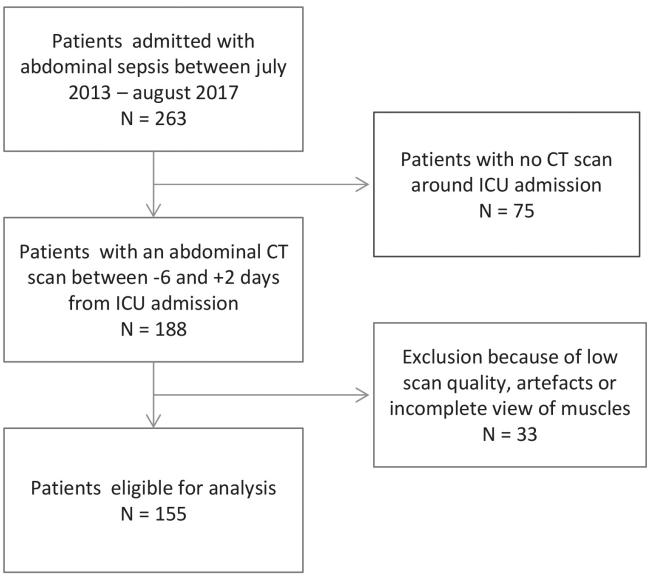

Figure 1. Flowchart of the inclusion and exclusion

Mean (±SD) age was 66.0 (±13.6) years and mean (±SD) APACHE II score was 84.3 (±27.4). Of the 155 patients, 15 (9.7%) suffered from chronic renal insufficiency, 7 (4.5%) from chronic cardiovascular insufficiency, 12 (7.7%) from COPD, and 28 (18.1%) from cancer. Sixty-one patients (39.4%) underwent emergency surgery before ICU admission. Most patients were referred by the department of surgery (71.6%), followed by internal medicine (16.1%), gastroenterology (5.8%), urology (3.2%), and other (3.2%).

The median (IQR) ICU stay was 5 (1-14) days and the median (IQR) hospital stay following ICU admission was 21 (11-38) days. Mean (±SD) time between ICU admission and CT-scanning was -0.8 (±1.3) days. ICU mortality was 45 out of 155 patients (29.0%) and hospital mortality was 59 out of 155 patients (38.1%). All patient characteristics are presented in Table 1. The body composition at baseline for men and women separately and per age group is given in table 2. In a large number of the CT scans, subcutaneous adipose tissue (SAT) off the flanks was cut-off from the image by the radiologist, creating unreliable values. Therefore, only skeletal muscle area index (SMI) and visceral adipose tissue index (VATI) were reported.

Table 1. Patient characteristics (N=155)

		Mean (SD), number (%) or median (IQR)
Demographics and body composition	Male	93 (60%)
	Age (years)	66.0 (± 13.6)
	BMI (kg/m^2)	26.9 (± 6.4)
	Sarcopenia*	48 (31.0%)
	Time between ICU admission and CT scan (days)	-0.8 (± 1.3)
Disease severity	APACHE II score	84.3 (± 27.4)
Referring specialism	Internal medicine	25 (16.1%)
	Gastroentology	9 (5.8%)
	Surgery	111 (71.6%)
	Urology	5 (3.2%)
	Other	5 (3.2%)
	Emergency surgery before admission	61 (39.4%)
Chronic co-morbidities	Chronic renal insufficiency	15 (9.7%)
	Chronic cardiovasculair insufficiency	7 (4.5%)
	COPD	12 (7.7%)
	Cancer	28 (18.1%)
Outcomes	ICU stay (days)	5 (1-14)
	Hospital stay following ICU admission (days)	21 (11-38)
	ICU Mortality	45 (29.0%)
	Hospital Mortality	59 (38.1%)

*Data are presented as mean (± SD), median (IQR) or as absolute number (%) * Muscle area index (cm^2/m^2) < 5th percentile of the population [8]*

Table 2. Body composition

Sex	Age (years)	n (%)	L3-index (cm^2/m^2)	
			SMI	VATI
Male	<60	19 (12%)	48.3 ± 11.8	51.6 ± 36.9
	60-70	31 (20%)	47.0 ± 8.7	57.5 ± 31.1
	>70	43 (28%)	43.5 ± 8.3	66.2 ± 39.2
Female	<60	25 (16%)	41.6 ± 10.7	35.6 ± 48.0
	60-70	14 (9%)	42.5 ± 13.9	49.7 ± 16.9
	>70	23 (15%)	39.2 ± 6.4	48.2 ± 29.9

Sex- and age-specific body composition parameters were assessed using computed tomography at the level of vertebra L3 and were corrected for height resulting in a L3-index given in cm^2/m^2. Data are presented as mean (± SD). Abbreviations: SMI: Skeletal Muscle Index, VATI: Visceral Adipose Tissue Index.

Univariable association of sarcopenia with hospital mortality

Sarcopenia, defined as a skeletal muscle area index below the 5th percentile of the reference population, was observed in 15 of 62 women (24.2%) and in 33 of 93 men (35.5%), yielding a total prevalence of 31.0%. In a univariable analysis, hospital mortality was significantly higher in patients with sarcopenia compared with patients without sarcopenia (50.0% *vs.* 32.7%, P = 0.040, Figure 2).

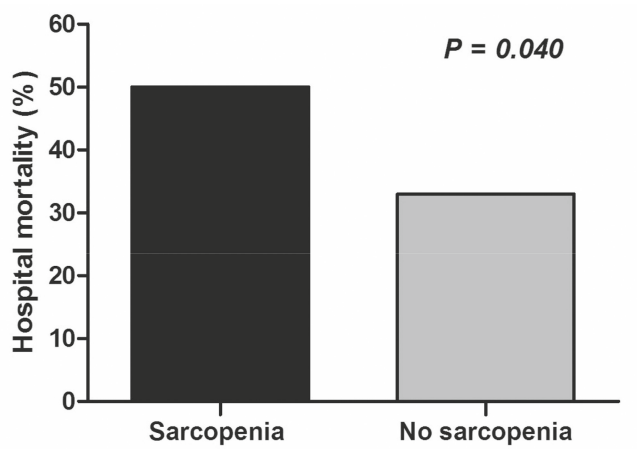

Figure 2. Relationship between sarcopenia and hospital mortality in patients with abdominal sepsis. *Sarcopenia is defined as a muscle area index below the 5th percentile of a general Caucasian population. Using this definition, a significant relation between hospital mortality and sarcopenia is found (P = 0.040).*

Univariable association of age and co-morbidities with hospital mortality

Associations between hospital mortality and co-morbidities that were known to be related to skeletal muscle wasting are presented in Table 3. Of the co-morbidities that were studied, chronic renal insufficiency (P = 0.003), chronic cardiovascular disease (P = 0.001), and cancer (P = 0.022) were significantly more prevalent in non-survivors than in survivors. The prevalence of COPD was not significantly different between non-survivors and survivors (P = 0.375). The age of survivors and non-survivors was significantly different (P = 0.010).

Table 3. Univariable analysis of age and chronic co-morbidities and hospital mortality

	Alive (N = 96)	Dead (N = 59)	P-value
Sarcopenia*	24 (25.0%)	24 (40.7%)	0.040[1)]
Chronic renal insufficiency	4 (4.2%)	11 (18.6%)	0.003[1)]
Chronic cardiovascular insufficiency	0 (0.0%)	7 (11.9%)	0.001[2)]
COPD	6 (6.3%)	6 (10.2%)	0.375[1)]
Cancer	12 (12.5%)	16 (27.1%)	0.022[1)]
Age (years)	63.8 (± 14.0)	69.5 (± 12.4)	0.010[3)]

*Analysis of sarcopenia, muscle wasting associated co-morbidities and age. Numerical data are presented as mean (±SD), categorical data are presented as number of patients (%). Statistical tests that were used were: 1) chi-square test, 2) Fisher's exact test, and 3) independent-samples t-test. * Sarcopenia was defined as a gender specific muscle area index (cm^2/m^2) < 5^{th} percentile of normal population [8].*

Univariable association of skeletal muscle quality with hospital mortality

Skeletal muscle quality assessed in a subgroup of 84 patients with unenhanced CT scans tended to be lower in non-survivors than in survivors. However this trend failed to reach statistical significance (P = 0.379, Table 4).

Table 4. Univariable analysis of muscle quality and hospital mortality

	Alive (N = 53)	Dead (N = 31)	P-value
Low muscle quality *	29 (54.7%)	20 (64.5%)	0.379

*Analysis of muscle quality. * Low muscle quality was defined as a mean skeletal muscle radiation attenuation (HU) of < 5^{th} percentile of the general population: 29.3 HU and 22.0 HU for men and women respectively. [8]. Because the radiation attenuation is influenced by the use of contrast agents, only unenhanced CT scans were included in the analysis (N=84). The data is presented as number of patients (%). The statistical test that was used was the chi-square test.*

Multivariable analysis of the effect of sarcopenia, age and co-morbidities on hospital mortality

The multivariable analysis revealed that sarcopenia was not an independent risk factor for hospital mortality in critical illness (OR 1.6, 95% CI: 0.734 – 3.328, P = 0.247) when co-morbidities

that are associated with skeletal muscle wasting were included in the multivariable regression (Table 5).

Table 5. Multivariable analysis, assessing the effects of sarcopenia, muscle wasting associated co-morbidities, and age on hospital mortality.

	OR	95% CI	P-value
Sarcopenia*	1.6	0.734 – 3.328	0.247
Chronic renal insufficiency	6.8	1.914 – 24.010	0.003
Cardiovasculair insufficiency**	**	**	**
COPD	2.1	0.596 – 7.289	0.251
Cancer	3.0	1.231 – 7.243	0.016
Age (years)	1.0	0.999 – 1.057	0.060

*Multivariable analysis of sarcopenia, muscle wasting associated co-morbidities and age was performed using logistic regression. Data are presented as Odds Ratio (OR), 95% Confidence Interval (CI), and p-value. Collinearity was checked and was not applicable since the variance inflation factor for all variables was < 1.2. * Sarcopenia was defined as a gender specific muscle area index (cm^2/m^2) < 5^{th} percentile of normal population [8]. ** Odds ratio (OR) could not be estimated because there were no survivors.*

Logistic regression analysis revealed that cancer (OR 3.0, 95% CI: 1.231 – 7.243, P = 0.016) and chronic renal insufficiency (OR 6.8, 95% CI: 1.914 – 24.010, P = 0.003) were independent risk factors for hospital mortality.

All seven patients with chronic cardiovascular insufficiency within the current cohort did not survive until hospital discharge which indicates that this is a possible confounder for mortality. However, because all patients died, the odds ratio and 95% confidence interval could not be estimated. In the presented data (Table 5) cardiovascular insufficiency was not added in the multivariable analysis. Including the comorbidity chronic cardiovascular insufficiency into multivariable analysis did not significantly change the results. In this cohort, COPD and age were not a risk factor for hospital mortality (OR 2.1, 95% CI: 0.596 – 7.289, P = 0.251 and OR 1.0, 95% CI: 0.999 – 1.057, P = 0.060 respectively). Collinearity was checked and was not applicable since the variance inflation factor for all variables was < 1.2.

Sensitivity analysis of muscle mass defined by quartiles of the current investigated population

A sensitivity analysis revealed that when low muscle mass was defined by cohort-specific reference values there was no relation between low muscle mass and hospital mortality, both in a uni- and multivariable analysis (Table 6).

Table 6. Sensitivity analysis of muscle mass defined by quartiles of the current investigated population

Univariable analysis				Multivariable analysis*	
Cut-off value	Mortality below cut-off value	Mortality above cut-off value	P-value [a]	OR (95% CI)	P-value*
P25	16/38 (42.1%)	43/117 (36.8%)	0.555	1.0 (0.447 - 2.318)	0.965
P50	33/77 (42.9%)	26/78 (33.3%)	0.222	1.2 (0.574 – 2.385)	0.666

*Quartiles of the current investigated population were used as cut-off values. * In the multivariable analysis the effect of low muscle mass was corrected for chronic renal insufficiency, chronic cardiovascular insufficiency, COPD, cancer and age. a) Chi square test*

Discussion

The aim of this study was to investigate whether sarcopenia is an independent risk factor for hospital mortality in critical illness in the presence of skeletal muscle wasting associated co-morbidities.

We found that despite the fact that sarcopenia was significantly more prevalent in patients that deceased during the hospital admission, chronic co-morbidities that are associated with muscle wasting such as chronic renal insufficiency and cancer, rather than sarcopenia itself, were independent risk factors for hospital mortality in critical illness.

The odds ratio of chronic cardiovascular disease could not be estimated since no patient from the investigated cohort that was affected by chronic cardiovascular disease survived until hospital discharge. However, this observation suggests that chronic cardiovascular failure is also a risk factor for hospital mortality in critical illness. In the current study, COPD was not a significant risk factor for hospital mortality in patients with abdominal sepsis. COPD is known to be associated with muscle loss [18]. However, the amount of muscle loss in COPD is among other things depending on disease stage and muscle loss within COPD patients has therefore a prevalence ranging from 15-40% [18]. For the COPD patients in this study disease stage was unknown. Therefore it is possible that the patients with COPD in this study have a less severe disease stage.

In the studied population consisting of patients with abdominal sepsis admitted to the ICU, 31% of the patients fulfilled the criteria for sarcopenia: a skeletal muscle area index below the 5th percentile of the healthy Caucasian population[8]. The prevalence of sarcopenia was therefore substantially higher than in the general population but in line with the prevalence that might be expected in a population with high age and a high prevalence of chronic co-morbidities.

In previous studies, no uniform definition for low skeletal muscle mass or sarcopenia was used. Some investigators determined cut-off values for low skeletal muscle mass relative to their own populations using either ROC analyses [4, 5] or by calculating population medians [1, 19]. Others used cut-off values derived from published reference data [2]. The first approach allows to assess the linear effect of declining skeletal muscle mass throughout the investigated population, whereas the latter approach clearly distinguishes patients meeting externally validated criteria for sarcopenia. Several publications have reported "normal values" for skeletal muscle area index at the level of vertebra L3 and have provided thresholds to define sarcopenia [8, 12, 20]. Since some ethnical variation may exist and to increase the external validity of the current study, reference values derived from a population from our own country are chosen. In this population, a skeletal muscle area index of smaller than 41.6 cm^2/m^2 for men and of smaller than 32.0 cm^2/m^2 for women defined sarcopenia [8]. The cut-off values for sarcopenia in this healthy reference cohort are considerably lower than those reported elsewhere in the literature [2, 21].

Several studies have described the relation between low skeletal muscle mass and mortality in critical illness [1-6]. All of these performed multivariable and subgroup analyses that identified low skeletal muscle mass or sarcopenia as an independent risk factor for mortality. Potential confounders that have been studied include age, gender, and BMI [1, 2, 4, 5]. In addition, acute disease severity scores such as SAPS-2 [22], APACHE [23] and SOFA [24] have been used in multivariable analyses. To our knowledge the present study is the first that addresses the specific effect of chronic co-morbidities that are associated with skeletal muscle wasting on the relation between sarcopenia and outcome in critical illness.

Although the current study does not show that sarcopenia is an independent risk factor for mortality the impact of skeletal muscle loss and sarcopenia on the outcome of acute and chronic diseases should not be simply disregarded. Sarcopenia is an important factor that is strongly associated with the outcome of chronic diseases including various forms of solid malignant tumors [19, 25], chronic kidney disease [26], and chronic cardiovascular disease [27]. As such it is very well conceivable that sarcopenia may play a pathophysiological role in the adverse outcome of critically ill patients with chronic co-morbidities.

Not only skeletal muscle mass on ICU admission is important for the outcome in critically ill, but critical illness is also associated with acute and rapid skeletal muscle wasting. The rate of this skeletal muscle loss is dependent on disease severity and number of organ failures and can amount to a cumulative loss of 10-26% of total skeletal muscle mass during the first 10

days of critical illness [28]. This loss of muscle mass has been associated with worse long-term outcomes after ICU admission [29-31], although the relationship between ICU-associated skeletal muscle loss and long-term outcome is still unclear.

The effect of skeletal muscle mass at the time of ICU admission and skeletal muscle loss during ICU admission are frequently used interchangeably in the literature. It is important to clearly distinguish between these two entities. Limiting skeletal muscle loss and preservation of muscle mass during critical illness is widely regarded as a means to improve short-term, and in particular long-term outcome, whereas chronic sarcopenia is very challenging to reverse [29-31].

The present study has several strengths and weaknesses. Due to the retrospective nature of this study, data had to be retrieved from the medical files, which may have caused variation in the results. For example in some cases length and weight of patients were patient reported or were estimated by the ICU staff rather than actually measured. In addition, since different iv contrast phases were used among the CT scans of patients we did not have sufficient power to assess radiation attenuation, which is a marker of muscle quality as was described previously. [16, 17, 32] Although we did observe a clear trend towards an association between low muscle quality and mortality, it remains to be seen to what extent this association is also dependent on muscle wasting co-morbidities [16]. Also, the skeletal muscle area measurements on CT scans of patients with abdominal sepsis might be influenced by the existence of edema. Strong points are the relative homogeneity of the cohort and the high prevalence of pathophysiological relevant co-morbidities which enhanced the reliability of the multivariable analysis. Using a cut-off value from a healthy reference population for sarcopenia that is not dependent on the study population increases the external validity.

Conclusion

The effect of sarcopenia on mortality, in a relatively homogenous group of critically ill patients with abdominal sepsis, was confounded by comorbidities that are associated with skeletal muscle wasting. Without correction, hospital mortality was significantly higher in patients with sarcopenia than in patients without sarcopenia. However, in a multivariable analysis cancer and chronic renal insufficiency appeared to be independent risk factors for hospital mortality, whereas sarcopenia was not.

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Edema in critically ill patients leads to overestimation of skeletal muscle mass measurements using Computed Tomography scans

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Abstract

Background

Changes in muscle mass and quality are important targets for nutritional intervention in critical illness. Effects of such interventions may be assessed using sequential Computed Tomography(CT) scans. However, fluid and lipid infiltration potentially affects muscle area measurements. We aimed to study changes in muscle mass and quality in critical illness with special emphasis on the influence of edema on this assessment.

Methods

Changes in Skeletal Muscle area Index(SMI) and Radiation Attenuation(RA) at the level of vertebra L3 were analyzed using sequential CT scans of 77 patients with abdominal sepsis. Additionally, the relation between these changes and disease severity using the maximum Sequential Organ Failure Assessment(SOFA) score and change in edema were studied.

Results

Skeletal Muscle area Index(SMI) declined on average 0.35%(±1.22%) per day(p=0.013). However, in 41.6% of the study population SMI increased. Increasing edema formation was significantly associated with increased SMI and with a higher SOFA score. Muscle Radiation Attenuation decreased during critical illness, but was not significantly associated with changes in SMI or changes in edema.

Conclusion

In critically ill patients, edema affects skeletal muscle area measurements which leads to an overestimation of skeletal muscle area. A higher SOFA score was associated with edema formation. Since both edema and fat infiltration may affect muscle radiation attenuation, the separate effects of these on muscle quality are difficult to distinguish. When using abdominal CT scans to changes in muscle mass and quality in critically ill patients, researchers must be aware and careful with the interpretation of the results.

Introduction

Skeletal muscle mass at the time of Intensive Care Unit (ICU) admission is an important determinant for short term and long term outcomes in ICU patients. It is associated with the length of mechanical ventilation, the length of ICU stay, and mortality [1, 2]. Not only muscle mass at the time of ICU admission is important for the outcome of patients, but also the amount of muscle loss during ICU admission. During the first 10 days of ICU admission, patients with single organ failure and multi organ failure lose up to 10% and 26% of their muscle mass respectively [3]. Muscle loss during ICU admission is associated with the development of ICU acquired weakness which results in functional disability that can last up to 2-5 years after ICU admission. As such, it is one of the key factors affecting long term quality of life of former ICU-patients [4-7].

Not only low skeletal muscle mass, but also low muscle quality at the time of ICU admission is associated with higher mortality [8, 9]. Both muscle mass and muscle quality can be measured using Computed Tomography (CT) scans [8, 10]. Each tissue or compound has a specific physical density which affects its Radiation Attenuation (RA) on a CT scan. Muscle tissue consists of proteins, lipids, water and other compounds. The content of all these compounds within a muscle determines its mean Radiation Attenuation which is expressed in Hounsfield Units (HU) [8-10]. Healthy muscle tissue has an average Radiation Attenuation of around 40 HU [11, 12]. A decreased muscle Radiation Attenuation, can be the result of lipid or fluid infiltration and is associated with lower muscle quality and decreased muscle function and strength[8].

Research on the relationship between skeletal muscle mass, muscle quality and clinical outcome in critical illness using body composition analysis on Computed Tomography (CT) imaging mainly uses CT-scans that are made for clinical purposes [1, 2, 9, 13-17]. The main advantage of this approach is that large cohorts can be analyzed retrospectively. In contrast, prospective research on skeletal muscle loss in critical illness is mostly assessed using sequential ultrasonography (US) assessments of the leg musculature [3]. As this examination is not part of routine clinical care, it is not available in large retrospective cohorts. Therefore, the measurement of skeletal muscle mass and quality using sequential CT scans would be an interesting method to assess the influence of nutrition, for example protein intake, on muscle wasting and muscle quality in large cohorts. Also it would be interesting to phenotype patients with a higher and lower amount of muscle wasting. This in order to find possibilities to attenuate muscle breakdown in critically ill patients.

Up to now, there are a few studies that assessed changes in muscle mass during ICU admission using sequential CT scans in a small heterogenous group of critically ill patients [18, 26, 29]. During the acute phase of critical illness, patients receive extensive amounts of intravenous fluids, especially in the case of sepsis. This leads to edema in tissues among which the muscle tissue. This may affect the skeletal muscle area and skeletal muscle radiation attenuation measurements on CT scans. There are studies that mention that edema affects body composition analysis using CT scans, but the effect on the reliability of repeated measurements is unknown [18, 19].

Therefore, our aim is to study the influence of edema on the reliability of skeletal muscle area measurements and assessment of muscle quality using sequential CT scans in ICU patients with abdominal sepsis. This patient category was chosen since it provides a relatively homogeneous cohort of critically ill patients and a large proportion of these patients undergo repeated abdominal CT-scanning.

Methods

Patient selection

All patients with abdominal sepsis admitted to the Intensive Care Unit of the Maastricht University Medical Centre between August 2012 and July 2017 were retrospectively analyzed. Patients with abdominal sepsis were retrieved from a database with all patients who were admitted to the ICU with sepsis. Sepsis was defined according to the sepsis-3 criteria [20]. All patients with an available baseline abdominal CT scan between 8 days before and 2 days after ICU admission, and sequential CT scanning 8-20 days from ICU admission were selected. CT-scans with movement artifacts, radiation artifacts, CT-scans with low quality and CT-scans with missing parts of the abdominal musculature were excluded [10]. Demographic data and disease severity scores (Acute Physiology And Chronic Health Evaluation II; APACHE-II score [21] and the Sequential Organ Failure Assessment; SOFA score [22] were retrieved from the Patient Data Management System (IntelliVue Clinical Information Portfolio (ICIP), Philips Medical Systems, Best, the Netherlands).

Body composition analysis using Computed Tomography

CT-scan analysis of skeletal muscle area was performed using the method of Mourtzakis *et al* [10]. A single slice of each patient's CT scan was selected at the level of the 3rd lumbar vertebra. Using predefined Hounsfield Unit (HU) ranges, the total cross-sectional area (cm^2) of skeletal muscle tissue (–29 to 150 HU) visceral adipose tissue (-150 to -50 HU) and subcutaneous

adipose tissue (-190 to -30 HU) were determined. Muscles included into the analysis were the m. obliquus internus and externus abdominis, m. transversus abdominis, m. rectus abdominis, m. psoas, m. quadratus lumborum, and m. erector spinae. The total amount of skeletal muscle mass was estimated by assessing the tissue area at the level of vertebra L3 and dividing it by height in meters squared resulting in the L3-muscle index in cm^2/m^2 [10]. CT scans were analyzed using SliceOmatic 5.0 (TomoVision, Magog, Canada) software for Microsoft Windows®.

Edema classification

As described by Mourtzakis *et al*, body composition analysis using CT scans is based on tissue specific Radiation Attenuation which is expressed in Hounsfield units (HU) [10]. Healthy skeletal muscle tissue has an average Radiation Attenuation of around 40 HU and water (edema) has a Radiation Attenuation of 0 HU, which lies within the Hounsfield Unit range for skeletal muscle tissue (–29 to 150 HU) [11, 12]. This is in contrast to subcutaneous and visceral adipose tissue, where the Hounsfield Unit of edema lies outside the predefined Hounsfield Unit ranges. Therefore edema can be seen as opafications in the colored adipose tissue, and edema can easily be discriminated from adipose tissue. Using this knowledge, the amount of edema on all CT scans was assessed semi-quantitatively by two researchers (MB and DvD) and rated as: None/low (1), Moderate (2) or Severe (3). Examples of CT scans with different edema classifications are shown in Figure 1. Patients were stratified in 5 groups according to the difference in edema classification between the two scans, ranging from -2 (substantial decrease), through -1 (moderate decrease), 0 (no change) and +1 (moderate increase), to +2 (substantial increase).

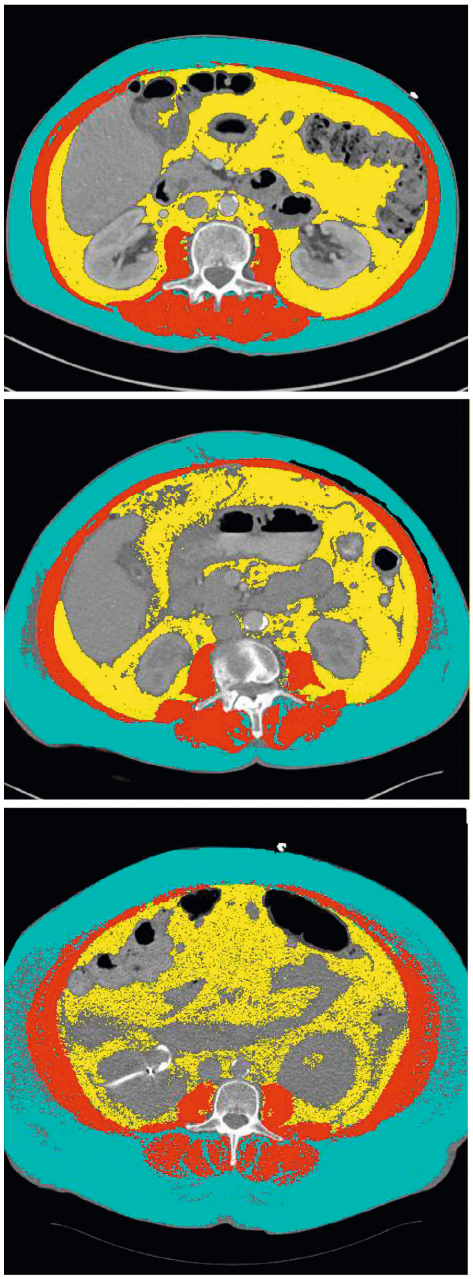

Figure 1. The classification of edema

Representative images of various classifications of edema. All CT scans were scored by two researchers as 1: no/low edema, 2: moderate edema and 3: severe edema, based on the opafications in the colored tissue. The tissue were colored according established methods using predefined Hounsfield Unit (HU) ranges of skeletal muscle tissue (red) (–29 to 150 HU), visceral adipose tissue (yellow) (-150 to -50 HU) and subcutaneous adipose tissue (blue) (-190 to -30 HU)

Skeletal muscle Radiation Attenuation

The Radiation Attenuation (RA) of skeletal muscle tissue was expressed as the mean Hounsfield Unit (HU) value of the total skeletal muscle tissue area within the predefined HU ranges for muscle tissue (–29 to 150 HU) [8].

Since contrast agents may influence skeletal muscle Radiation Attenuation [11], changes in Radiation Attenuation were only analyzed for patients with sequential CT scans with identical contrast phases at both time points (e.g. 2x Portal Venous Phase or 2x unenhanced CT scan).

Disease severity

To evaluate disease severity in critically ill patients during ICU admission, the Sequential Organ Failure Assessment (SOFA) score is widely used [22]. A higher SOFA score indicates more severe organ failure. Especially in the acute phase of critical illness, patients may receive extensive fluid resuscitation, therefore in this study the maximum SOFA score during ICU admission is used to evaluate disease severity.

Statistical Analysis

Normality was checked visually using histograms. The loss of skeletal muscle area index was calculated as percentage loss per day from baseline and tested with a one sample t-test to see whether there was a change from baseline. The differences in skeletal muscle area index, Radiation Attenuation and edema classification between the first and second CT scan were tested with a paired t-test. In cases where the first CT scan was made before ICU admission, the ICU admission date was used as baseline to prevent bias in the results by the calculation of muscle loss per day.

The correlation between changes in skeletal muscle area index, Radiation Attenuation, the maximum SOFA score during ICU admission and the change in edema classification between sequential CT scans were tested with Pearson (r) or Spearman (r_s) test for correlations where appropriate.

Analyses were performed using IBM SPSS for Windows version 25.0 (Armonk, NY: IBM Corp.) and Prism version 8.0.0 (GraphPad Software, San Diego, CA). A two-sided p-value ≤0.05 was considered statistically significant.

Ethics

The study protocol was reviewed and approved by the Institutional Review Board of the Maastricht University Medical Center (METC 2018-0803). Informed consent was waived for this retrospective analysis. The data were coded and kept in agreement with the European General Data Protection Regulation.

Results

Patients

Between August 2012 and July 2017 327 patients with abdominal sepsis were admitted to the ICU of the Maastricht University Medical Centre. Of these patients, 90 patients received at least two sequential CT scans. From this group, the abdominal CT scans of 13 patients were of insufficient quality for reliable analysis. This resulted in 77 abdominal sepsis patients who were included in the analysis. Figure 2 shows a flow diagram of the patient selection.

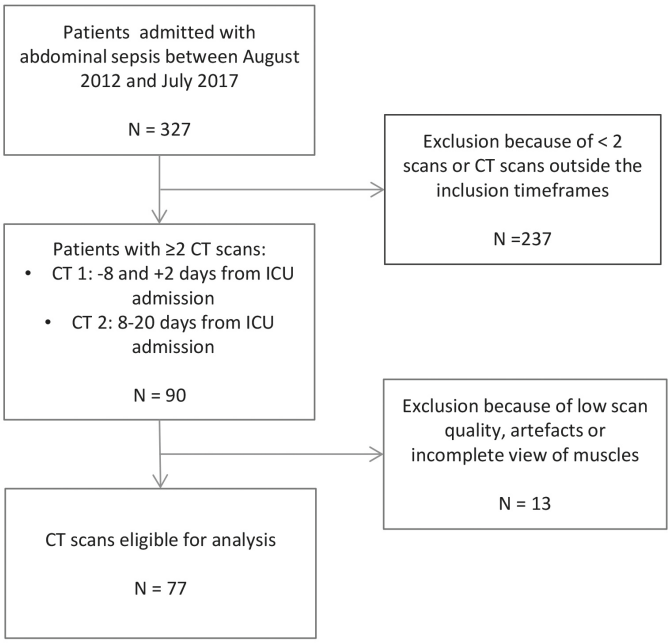

Figure 2. Flowchart of the inclusion and exclusion

Normality was checked visually using histograms. The mean (±SD) age was 65 (± 14) years, 47% (41 patients) was male, the mean (±SD) length was 1.72(± 0.1) meter and the mean (±SD) BMI was 27 (± 6) kg/m^2. The mean (±SD) APACHE II score was 22 (± 7) and ICU mortality was 17% (13 patients). The median (IQR) time between ICU admission and the first CT scan was 0 (-1.0 – 0.0) days. The median (IQR) time between ICU admission and the second CT scan was 11 (8.5 – 14.0) days. More patient characteristics are presented in Table 1. The skeletal muscle area index at baseline is shown in Table 2. Since body composition and muscle mass are gender dependent, Skeletal Muscle Index is given per gender separately [23]. Skeletal muscle Radiation Attenuation at baseline is shown in Table 3. The muscle Radiation Attenuation is given per type of CT scan, since the use of contrast agents during computed tomography imaging influences the Radiation Attenuation [11].

Table 1. Patient characteristics

		Number (%), mean (±SD) or median (IQR)	
Demographics	Male	41 [a]	47%
	Female	36 [a]	53%
	Age (years)	65 [b]	± 14
	Lenght (m)	1.72 [b]	± 0.1
	BMI (kg/m^2)	27 [b]	± 6
Timepoint scans	Time between ICU admission and 1st CT scan (days)	0 [c]	(-1.0* – 0.0)
	Time between ICU admission and 2nd CT scan (days)	11 [c]	(8.5 – 14.0)
Disease severity	APACHE II score	22 [b]	± 7
	ICU mortality	13 [a]	17%
	Mechanical ventilation	63 [a]	82%
	Duration of mechanical ventilation (days)	8 [c]	4-11
	Use of vasopressors/inotropics	64 [a]	83%
	Net fluid balance at the time of the 2nd CT scan (Liter)	0.75 [b]	± 1.01
	Enteral nutrition during ICU admission	56 [a]	73%
	Parenteral nutrition during ICU admission	51 [a]	66%
	Maximum C-Reactive Protein (CRP) during ICU admission	347 [b]	± 103

*Data are presented as [a] absolute number (%), [b] mean (± SD),or [c] median (IQR). * A negative timepoint of the CT scan means that the CT scan is made before the ICU admission date.*

Table 2. Skeletal Muscle area Index at baseline per gender

Gender	Skeletal Muscle area Index (SMI) in (cm^2/m^2)
Male (N=41)	43.5 (±8.7)
Female (N=36)	39.8 (±9.9)

Skeletal muscle area index (SMI) at the level of vertebra L3 at baseline is given per gender since body composition is gender dependent [23]. The values were corrected for height resulting in a L3-index given in cm^2/m^2. Data are presented as mean (± SD).

Table 3. Skeletal Muscle Radiation Attenuation at baseline per type of CT scan

Type of CT scan	Radiation Attenuation of Skeletal Muscle (HU)
Unenhanced (N=49)	24.4 (±7.7)
Portal Venous Phase (PVP) (N=28)	28.3 (±10.1)

Skeletal muscle radiation attenuation expressed as the mean Hounsfield Unit (HU). Skeletal muscle Radiation Attenuation (RA) at baseline is given per type of Computed Tomography (CT) scan since contrast agents influence Radiation Attenuation[11]. Data are presented as mean (± SD).

Association between change in edema classification with change in Skeletal Muscle area Index, skeletal muscle Radiation Attenuation and with disease severity

Overall, a mean decline of -0.35% (±1.22%) per day in skeletal muscle area index was observed between the two CT scans ($p = 0.013$) (Figure 3). However, in 41.6% of the study population an increase in skeletal muscle area index was found (Figure 3).

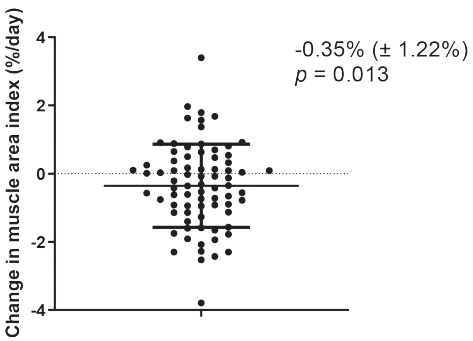

Figure 3. The change in skeletal muscle area index during ICU admission.
The mean (±SD) change in skeletal muscle area index (cm^2/m^2) was calculated as the difference between the second CT scan and the first (baseline) CT scan of the measured skeletal muscle area index and was calculated in percentage per day. The difference from baseline was tested using a one sample t-test.

The mean (±SD) edema classification was 1.9 (±0.9) on the first CT scan and increased to 2.5 (±0.8) on the second CT scan (mean increase = 0.6, 95%CI: 0.3-0.9, $p < 0.001$). In 57 patients with identical contrast phases at both time points, mean (±SD) skeletal muscle radiation attenuation was decreased between the two CT scans from 25.7 HU (±8.9) to 22.2 HU (±8.2) (mean difference = 3.5, 95%CI: 1.78 – 5.2, $p<0.001$).

There was a significant correlation between the change in edema classification and the change in skeletal muscle area index, where an increase in edema formation was associated with an increase in skeletal muscle area index (N= 77 patients, $r_s = 0.486$, $p <0.001$) (Figure 4).

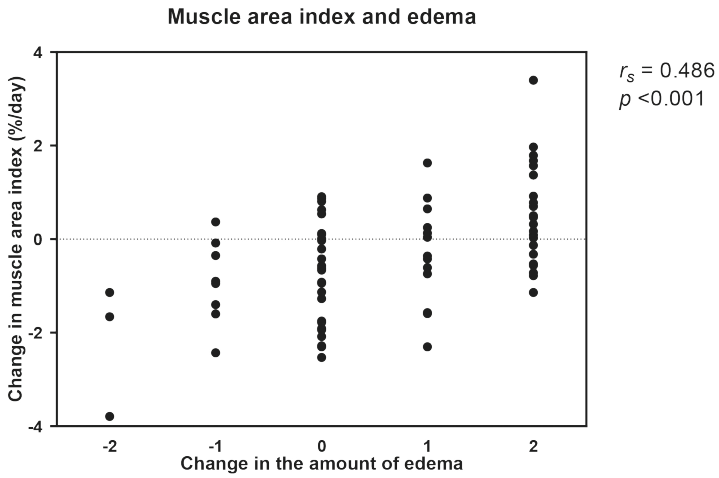

Figure 4. The correlation between the change in skeletal muscle area index and the change in edema classification.

The change in skeletal muscle area index (cm^2/m^2) was calculated as the difference between the first and second CT scan of the measured muscle area index and was calculated in percentage per day. The change in edema classification was calculated as the difference in edema classification between the first and second CT scan (1: no/low edema, 2: moderate edema, 3: severe edema). The change in edema classification was defined from -2 (substantial decrease), through -1 (moderate decrease), 0 (no change) and +1 (moderate increase), to +2 (substantial increase). The correlation was tested using a Spearmans test for correlation.

Also, there was a significant correlation between the change in edema classification and disease severity using the maximum SOFA score, where an increase in edema formation was associated with a higher maximum SOFA score during ICU admission (N=77 patients, r_s =0.239, $p = 0.04$) (Figure 5).

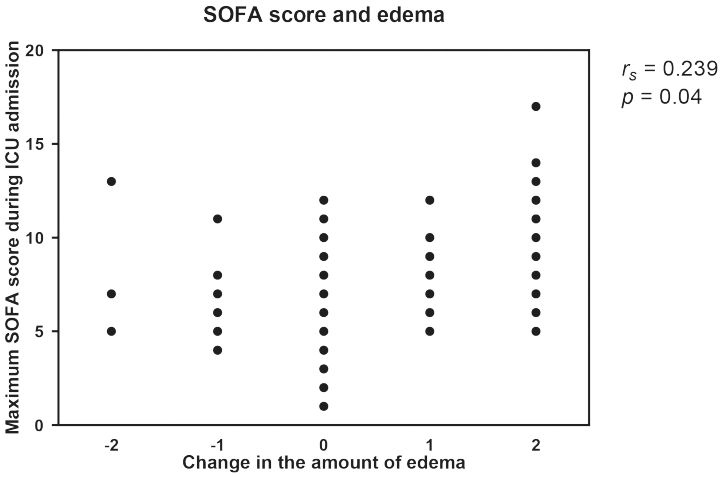

Figure 5. The correlation between the SOFA score and the change in edema classification.
The change in edema classification was calculated as the difference in edema classification between the first and second CT scan (1: no/low edema, 2: moderate edema, 3: severe edema). The change in edema classification was defined from -2 (substantial decrease), through -1 (moderate decrease), 0 (no change) and +1 (moderate increase), to +2 (substantial increase).The maximum SOFA score was measured as the highest SOFA score during ICU admission. The correlation was tested using a Spearmans test for correlation.

There was also a significant correlation between the change in skeletal muscle radiation attenuation per day and the disease severity using the maximum SOFA score during ICU admission, where an increase in the SOFA score was associated with a decrease in skeletal muscle radiation attenuation (N = 57 patients, r_s = -0.285, p = 0.032, Figure 6).

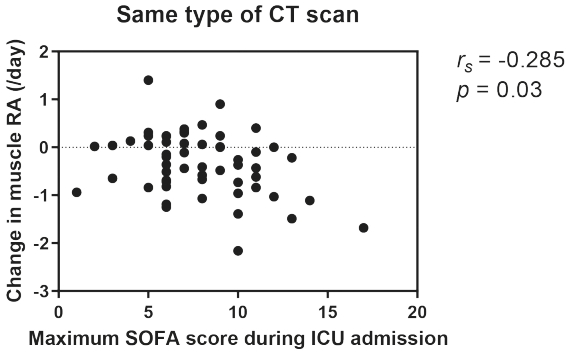

Figure 6. Correlation between the maximum SOFA score and the change in muscle radiation attenuation
The change in skeletal muscle radiation attenuation was calculated as the mean difference in Hounsfield Units between the first and second CT scan and was calculated per day. The maximum Sequential Organ Failure Assessment (SOFA) score was calculated as the maximum SOFA score of a patient during ICU admission. Since the use of contrast agents influence Radiation Attenuation, only patients with the same type of CT scan on both time points were analyzed (2x unenhanced or 2x porto venous phase). The correlation was tested using a Spearmans test for correlation. Abbreviations: RA = Radiation Attenuation.

There was no significant correlation between changes in edema classification and changes in skeletal muscle radiation attenuation (N= 57 patients, r_s = -0.227, p = 0.089, Figure 7).

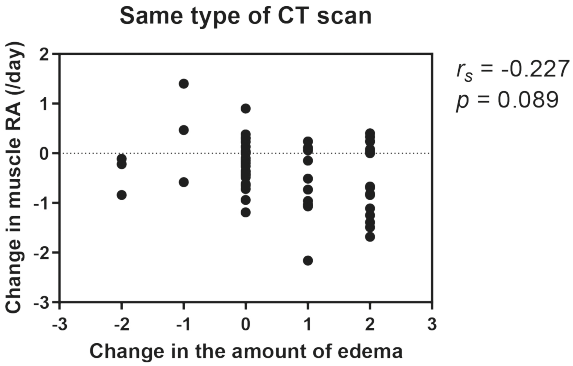

Figure 7. Correlation between the change in muscle radiation attenuation and the change in edema classification
The change in skeletal muscle radiation attenuation was calculated as the mean difference in Hounsfield Units between the first and second CT scan and was calculated per day. The change in edema classification was calculated as the difference in edema classification between the first and second CT scan (1: no/low edema, 2: moderate edema, 3: severe edema). The change in edema classification was defined from -2 (substantial decrease), through -1 (limited decrease), 0 (no change) and +1 (limited increase), to +2 (substantial increase). Since the use of contrast agents influence Radiation Attenuation, only patients with the same type of CT scan on both time points were analyzed (2x unenhanced or 2x porto venous phase). The correlation was tested using a Spearmans test for correlation. Abbreviations: RA = Radiation Attenuation.

Discussion

The aim of this study was to investigate whether sequential CT scans, made for clinical purposes, can be used to quantify muscle loss and changes in muscle quality in a retrospective cohort of critically ill patients with abdominal sepsis. Sequential assessment of skeletal muscle using CT scans appears to be a useful tool to study the influence of nutrition on muscle wasting. We found however that the analysis of changes in skeletal muscle mass and skeletal muscle quality in critically ill is severely hampered, in particular by the formation of edema. Edema was significantly correlated with the change in skeletal muscle area index, even resulting in a substantial increase of measured skeletal muscle area in the most severely ill patients. Our data show that the assessment of muscle loss in ICU patients that is based on repeated CT-scans should be cautiously interpretated, as edema can cause an overestimation of muscle area measurements.

Apart from changes in muscle mass, the composition of the muscle may undergo changes due to infiltration of fluid and lipids as a consequence of extensive fluid resuscitation or due to factors directly affecting the muscle such as inflammation, oxidative stress, inactivity and mitochondrial damage [8, 24, 25]. Indeed, we observed a decreasing radiation attenuation in our cohort of critically ill patients. The correlation between edema formation and increasing muscle area was statistically significant, whereas the correlation between edema formation and changes in muscle RA was not. This indicates that other factors than fluid infiltration, such as lipid infiltration affects muscle RA and thus muscle quality. However, since the eventual radiation attenuation of muscle is affected by both processes it is very difficult to distinguish them quantitatively.

Both muscle mass on ICU admission and the loss of skeletal muscle mass during ICU admission are associated with worse short and long term outcome [1, 2, 5-7]. Therefore the measurement of skeletal muscle mass and the loss of muscle mass is important in ICU patients. Especially to assess the influence of nutrition, for example protein intake, on muscle wasting in large cohorts. This to find possibilities to attenuate muscle breakdown in critically ill patients. Single CT-scans are widely used to study relations between body composition and clinical outcome [1, 2, 14-16]. Whether repeated CT-scans can be reliably applied to quantify changes in body composition has remained unaddressed.

There are only a few studies that assessed changes in muscle mass during ICU admission using computed tomography. Dusseaux *et al.* found no significant decrease in skeletal muscle

mass between the first CT scan made within 48 hours of ICU admission and second a CT scan made 7-14 days later in a heterogeneous patient group (-2.09 (±6.96) cm^2/m^2, $p = 0.183$) [18]. Braunschweig *et al.* found a significant overall decline in skeletal muscle mass of -0.49% per day (not indexed to height) in patients with respiratory failure with a mean (±SD) number of 9.97 (±4.7) days between the two scans and a comparative APACHE score as the present study [26]. There are some studies that mention that edema causes difficulty in body composition measurements, but they did not assess the influence of edema on muscle area measurements [18, 19, 27, 28]. Haines *et al.* showed in a cohort of trauma patients an overall decline of muscle mass, however a close look to the data showed that when the second CT scan was made within 10 days of ICU admission it showed an increase in muscle area in contrast to patients where the second CT scan was made more than 10 days after ICU admission [29]. Dusseaux *et al.* found no decrease in skeletal muscle mass in critically ill patients, but found a decrease in skeletal muscle radiation attenuation, possible due to lipid or fluid infiltration [18].

In the present study, during the first median 11 days of ICU admission, a statistically significant decline of a skeletal muscle area index of -0.35% per day was observed. Moreover, we observed an increase in muscle area in 41.6% of the patients. It is highly unlikely that this observation represents a true increase in muscle mass as the acute phase of critical illness is characterized by profound muscle protein breakdown [30]. Muscle loss in the present study is substantially lower than data from the study of Puthucheary *et al.* who report a total muscle loss of 10 to 26% during the first 10 days of an ICU admission in respectively single organ failure and multi organ failure using muscle mass measurements using ultrasonography [3]. The current study also shows that in critically ill patients with abdominal sepsis, the measurement of skeletal muscle area using sequential CT scans is significantly influenced by the amount of edema, which leads to overestimation of skeletal muscle area measurements. There was a significant correlation between an increase in edema and an increase in muscle area index during ICU admission, further supporting our hypothesis. There was also a significant correlation between a higher maximum Sequential Organ Failure Assessment (SOFA) score during ICU admission with increased edema formation and lower muscle radiation attenuation.

When using body composition measurements in critically ill patients, researchers must therefore be aware of the influence of edema on skeletal muscle mass measurements. Edema leads to overestimation of skeletal muscle area measurements. Previous literature reports on this difficulty but up to now, there is no tool to correct for the formation of edema in muscle area and muscle quality measurements using CT scans. In the present study skeletal muscle radiation attenuation was analyzed in order to find a way to correct for edema. Unfortunately skeletal

muscle radiation attenuation is also influenced by the amount of lipid infiltration and could therefore not be used to correct for edema formation. Consequently repeated ultrasonography is the only tool that is claimed to be for the assessment of skeletal muscle loss during ICU admission [3, 27]. However a close interpretation of published data indicates that the issue we encountered using CT-scans also affects repeated ultrasonography [3, 27].

The method of using abdominal CT scans at the level of vertebra L3 for body composition analysis is validated with generally a good intra- and interobserver agreement [10, 31]. This method is used in various field, especially in the field of oncology [32]. Perthen *et al.* showed a variation coefficient of 2% in single measurements [31]. This variation coefficient of 2% may possibly cause a higher variability when not the absolute muscle mass, but the difference in muscle mass between two CT scans is assessed. Therefore this method may be suited better for assessing effects in a population rather than comparing individual measurements.

The present study has several strengths and weaknesses. This study assesses changes in muscle mass using CT scans during ICU admission in a larger cohort of critically ill patients than described before [18, 26]. Besides, this is the first study assessing the influence of edema on sequential muscle area measurements on abdominal CT scans. Since the fluid balance in ICU patients is often unreliable [33], edema classification on the CT scans was scored independently by two researchers, which optimized its objective quantification. To optimize comparability of repeated CT scans it is crucial to follow standardized protocols regarding patient positioning and contrast agent use, which is usually not feasible in critically ill patients. Some of the drawbacks encountered in the current ICU population may not be applicable in other patient populations which may somewhat limit the external validity of our results for non-ICU populations.

Conclusion

In critically ill patients with abdominal sepsis, the measurement of skeletal muscle area using sequential CT scans is significantly influenced by the amount of edema, which leads to overestimation of skeletal muscle area measurements. Increased edema formation and decreased muscle quality were associated with a higher maximum Sequential Organ Failure Assessment (SOFA) score during ICU admission. Edema formation and muscle radiation attenuation were not associated.

Muscle quality is determined by the influx of fluid and lipids into the muscle. Since these processes occur simultaneously the separate effects of fluid and fat infiltration on muscle mass and muscle quality are difficult to distinguish. Therefore, the radiation attenuation alone cannot be used to assess changes in muscle water content during critical illness. When using abdominal CT scans for the assessment of skeletal muscle loss in critically ill patients, researchers must be aware and careful with the interpretation of the results due to the influence of edema on the measurement of muscle area and muscle quality.

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Computed Tomography reference values for visceral obesity and increased metabolic risk in a Caucasian cohort

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Abstract

Background

Visceral obesity is associated with the metabolic syndrome. The metabolic risk differs per ethnicity, but reference values for visceral obesity for body composition analyses using Computed Tomography(CT) scans in the Caucasian population are lacking. Therefore, the aim of this study was to define gender specific reference values for visceral obesity in a Caucasian cohort based upon the association between the amount of visceral adipose tissue(VAT) and markers of increased metabolic risk.

Methods

Visceral Adipose Tissue Area Index (VATI cm^2/m^2) at the level of vertebra L3 was analyzed using CT scans of 416 healthy living kidney donor candidates. The use of antihypertensive drugs and/or statins was used as an indicator for increased metabolic risk. Gender specific cut-off values for VATI with a sensitivity ≥80% were calculated using receiver operating characteristic (ROC) curves.

Results

In both men and women who used antihypertensive drugs, statins or both, VATI was higher than in those who did not use these drugs($p \leq 0.013$). In males and females respectively, a value of VATI of ≥38.7 cm^2/m^2 and ≥24.9 cm^2/m^2 was associated with increased metabolic risk with a sensitivity of 80%. ROC analysis showed that VATI was a better predictor of increased metabolic risk than BMI (area under ROC curve (AUC)=0.702 vs AUC=0.556 in males and AUC=0.757 vs AUC=0.630 in females).

Conclusion

Gender and ethnicity specific cut-off values for visceral obesity are important in body composition research, although further validation is needed. This study also showed that quantification of VATI is a better predictor for metabolic risk than BMI.

Introduction

Obesity is an increasing global healthcare problem. It is the number one risk factor for morbidity and mortality in high income countries [1, 2]. The estimation is that the number of people with obesity will increase and that in 2030 20% of the worldwide adult population will be obese and another 38% of the population will have overweight [3].

The most dangerous is a high amount of Visceral Adipose Tissue (VAT), also known as abdominal obesity or visceral obesity [1, 4]. Visceral obesity is associated with a three times higher risk for developing cardiovascular disease and a five times higher risk for developing diabetes [5-8]. In contrast to subcutaneous adipose tissue, VAT is metabolic active tissue and associated with dyslipidaemia, insulin resistance and hypertension [5, 9, 10]. Visceral adipose tissue is associated with the development of the metabolic syndrome that consists of a cluster of symptoms that include hypertension, impaired glucose metabolism with insulin resistance and dyslipidaemia in the presence of obesity [5, 6, 11, 12].

VAT can be measured using Computed Tomography (CT) scans. On CT scans every tissue has its own tissue specific shade of grey, which is measured in Hounsfield Units (HU). Using predefined HU ranges, visceral adipose tissue can be distinguished from other tissues [13]. This method of body composition analysis is a reliable method and increasing in popularity.

Body composition is both gender and ethnicity dependent [14-16]. There are several Asian publications that have reported cut-off values to indicate when VAT becomes a metabolic risk factor [17-22]. However, it is also known that with the same BMI Asians have a higher morbidity and mortality risk compared to Caucasians [16, 23]. Therefore these cut-off values may not be applicable for a Caucasian cohort. Hence, there is need for reference values in a Caucasian population that identifies a pathological threshold beyond which the amount of visceral adipose tissue becomes associated with metabolic complications.

In body composition research it is important to use general applicable reference values. This is recently shown in a cohort of Intensive Care patients where sarcopenia, defined by reference values obtained from a representative, otherwise healthy cohort, was able to point out patients at risk for dying in the hospital [24]. Likewise, when studying the effect of body composition on disease related outcomes in specific populations, it may be crucial to use cut-off values for pathological visceral obesity within these specific populations.

Therefore, the aim of this study was to assess the association between visceral adipose tissue and metabolic risk in a Caucasian cohort and to define gender specific reference values for visceral obesity based upon this association.

Methods

Study population

The study cohort consisted of individuals that were screened for potential living kidney donation in the Amsterdam University Medical Center between 2006 and 2014. Individuals were included in this study if they were medically approved as a living kidney donor candidate [25], had a Caucasian background, and a non-contrast CT-scan available to perform body composition analysis.

Data from this cohort were published before by van der Werf et al. [25]. As described in this previous publication, demographics and data regarding the use of medication and comorbidities were retrieved from the medical record of the individuals as part of the kidney donor screening. The weight of individuals were measured as part of the screening and the height was reported by the individuals. BMI was calculated as the weight in kilogram divided by the height in meter squared and was given in kg/m^2.

Measurement of Visceral Adipose Tissue Index (VATI)

CT-scan analysis of body composition was performed according to an established method as described by Mourtzakis *et al* [13]. The CT scans that were used in the Amsterdam University Medical Center were in location VUmc the Sensation 64 (Siemens, Forchheim, Germany) and in location AMC the CT Brilliance 64 (Philips, Eindhoven, Netherlands). The rotation time was 0.5 s and pitch value was 0.8 (VUmc) and 0.992 (AMC), colimitation 64 × 0.6 mm; effective mAs 70 (VUmc) or 125 (AMC). The reconstruction algorithms were similar for all scans (kernel B30f (VUmc) and filter B (AMC). Every 3 months the CT scans were calibrated using air-water phantoms (tolerance ± 4.0 HU) [25]. The non-contrast CT with the largest slice thickness (3-5 mm) was selected and if not available, the 1.5 mm reconstruction was selected. Thereafter, a single slice of each individual CT scan was selected at the level of the 3rd lumbar vertebra where both processus transversus were the best visible.

CT scans were reviewed for sufficient quality for analysis, including no artifacts and clear differentiation between visceral adipose tissue and the surrounding tissues. Using tissue specific Hounsfield Unit (HU) ranges, the total cross-sectional area (cm^2) of visceral adipose tissue (VAT)

(-150 to -50 HU) was determined. The total area of VAT is estimated by assessing the total tissue area in cm^2 at the level of vertebra L3 and dividing it by height in meter squared. This results in the L3 Visceral Adipose Tissue Index (VATI) given in cm^2/m^2 [13]. Previous research shows that a single slice on the level of vertebra L3 is representative for whole body composition and also for total visceral adipose tissue [4,13, 40]. CT scans were analyzed using SliceOmatic V5.0 (TomoVision, Magog, Canada) software for Microsoft Windows®.

Assessment of metabolic risk

The metabolic syndrome is defined as: central obesity measured as ethnic specific waist circumference, plus any of two of the following: triglycerides > 1.7 mmol/L or on specific treatment, high-density lipoprotein cholesterol < 1.03 mmol/L in males and < 1.29 mmol/L in females or on specific treatment, blood pressure ≥ 130/85 mmHg or on anti-hypertensive treatment and/or fasting plasma glucose ≥5.6 mmol/L or previously diagnosed with type 2 diabetes [14].

In the present study, as an indicator of complications that may be associated with the metabolic syndrome, the use of antihypertensive drugs and/or statins was used as an indicator for increased metabolic risk.

In this cohort of living kidney donor candidates, individuals with diabetes were excluded as kidney donor and could therefore not be included in the analysis [25].

Reference values for visceral obesity

To establish reference values for visceral obesity, receiver operating characteristic (ROC) analysis were performed using the presence or absence of increased metabolic risk (yes/no) based on medication use as outcome and VATI as discrimination threshold. A cut-off value of VATI with a sensitivity of at least 80% was considered to be relevant.

To compare the applicability of VATI with Body Mass Index (BMI), additional ROC analysis were performed using BMI as discrimination threshold. The area under the curve of the ROC analysis (AUC) was used as measure for overall prediction quality. A p-value ≤0.05 was considered statistically significant.

Statistical Analysis

Categorical variables are presented as number of patients (%), where mean ± standard deviation (SD) are used for numerical variables. Numerical variables were checked for normality using histograms.

Independent-samples t-tests were used to assess the relationship between VATI and the use of statins and/or antihypertensive medication. Mann-Whitney U-tests were used as sensitivity analyses.

Since body composition is gender dependent, statistical analysis for VATI for men and women was performed separately [15].

Analyses were performed using IBM SPSS Statistics for Windows version 25 (Armonk, NY, USA; IBM Corp.) and Prism version 8.0.0 (GraphPad Software, San Diego, CA, USA). A p-value ≤0.05 was considered statistically significant. The statistical analyses were supervised by a statistician (BW).

Ethics

The study protocol was reviewed and approved by the Medical Ethics Committee of the VUmc. The Medical Research Involving Human Subjects Act does not apply to the study and the study was conducted in accordance with the Declaration of Helsinki.

Results

Study population

Between 2006 and 2014, 692 individuals were selected as potential living kidney donor candidate of whom 639 were eligible as kidney donor. Of these 639 individuals, 223 individuals were excluded from this study because there was no CT scan available or the CT scan was of insufficient quality. This resulted in 416 individuals (173 men (42%) and 243 women (58%)) eligible for analysis. The flowchart of the inclusion and exclusion of individuals is presented in Figure 1.

Mean (±SD) age of the subjects was 52.5 (± 11.8) years. Mean (±SD) BMI was 25.8 (± 3.5) kg/m^2, 48 persons (12%; 21 males, 27 females) of the studied cohort used antihypertensive drugs, and 21 persons (5%; 6 males, 15 females) used statins. The characteristics of the study cohort are presented in Table 1. The Visceral Adipose Tissue Index per BMI group (<24.9, 25.0-29.9 and > 30) and per gender is given in Table 2.

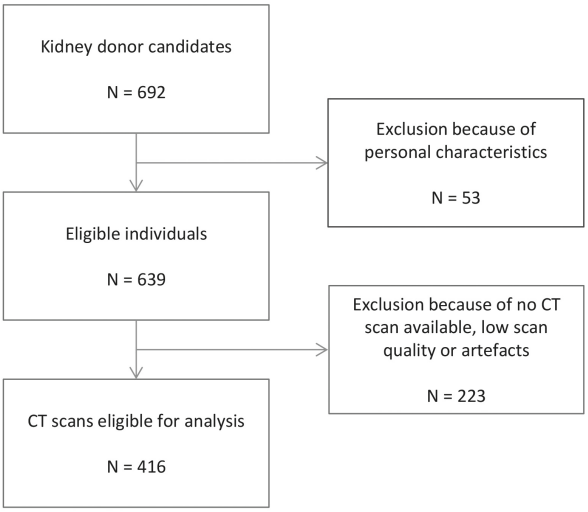

Figure 1. Flowchart of the inclusion and exclusion

Table 1. Characteristics of the study cohort

Mean or number		Male (N=173)		Female (N=243)	
		SD or %	Mean or number	SD or %	
Demographics	Age (years)	51.0	± 12.4	53.5	± 11.3
Body composition	Weight (kg)	86.0	± 12.2	72.0	± 11.1
	Height (cm)	181.5	± 7.7	168.1	± 6.4
	BMI (kg/m^2)	26.1	± 3.3	25.5	± 3.7
Medication use	Antihypertensive drugs[1]	21	12.1%	27	11.1%
	Statins[1]	6	3.5%	15	6.2%

Data are presented as absolute number (%) or mean ± SD
[1] Medication use is retrieved from the medical records of individuals.

Table 2. Gender specific Visceral Adipose Tissue Index per BMI group

Visceral Adipose Tissue Index (cm^2/m^2)				
	BMI < 24.9	BMI 25.0 – 29.9	BMI > 30.0	Total
Male	30.8 ± 17.2 (N=64)	49.7 ± 20.4 (N=86)	72.2 ± 22.4 (N=23)	45.7 ± 23.7 (N=173)
Female	16.2 ± 12.0 (N=118)	33.1 ± 16.3 (N=95)	51.6 ± 23.1 (N=28)	26.9 ± 19.4 (N=241*)
Total	21.3 ± 15.6 (N=182)	41.0 ± 20.1 (N=181)	60.9 ± 24.9 (N=51)	34.7 ± 23.2 (N=414*)

*Visceral Adipose Tissue Index parameters at baseline measured on a Computed Tomography scan at the level of vertebra L3. The values were corrected for the height of individuals resulting in a L3-index given in cm^2/m^2. Values were given per gender and per Body Mass Index (BMI) measured in kg/m^2. Data are presented as mean (± SD). *For two females BMI was missing.*

The association between VATI and metabolic risk

Mean VATI was significantly higher in males and females who use antihypertensive drugs compared to individuals who did not use antihypertensive drugs (Table 3). Mean VATI was also significantly higher in individuals who were using statins compared to individuals who did not use statins (Table 3). In keeping, mean VATI was significantly higher in subjects with an increased metabolic risk, defined as the use of either statins and/or antihypertensive medication, compared to subjects who did not use medication for hypertension and/or hypercholesterolemia. (Figure 2, Table 3).

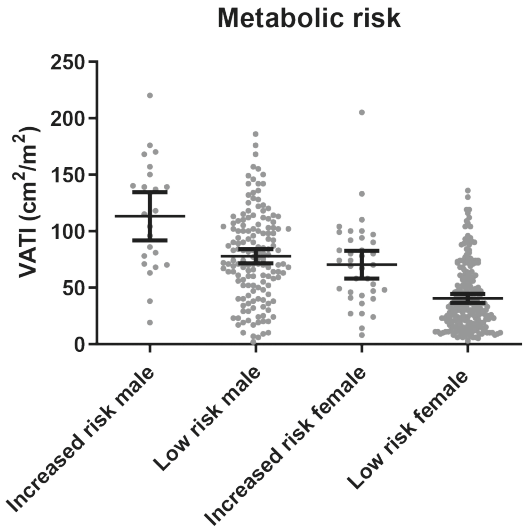

Figure 2. Mean Visceral Adipose Tissue Index and metabolic risk per gender

Increased metabolic risk is defined as: the use of antihypertensive drugs and/or statins. Low metabolic risk is defined as: no use of antihypertensive drugs or statins. Data are presented with mean (95% confidence interval). Visceral Adipose Tissue Index (VATI) measured at the level of L3 on an abdominal CT-scan and indexed for height and is given in cm^2/m^2.

Table 3 . Visceral Adipose Tissue Index and indicators for metabolic risk

Visceral Adipose Tissue Index (cm^2/m^2)									
	Antihypertensive drugs +	Antihypertensive drugs -	P -value	Statins +	Statins -	P -value	Antihypertensive drugs + and/or statins +	Antihypertensive drugs and statins -	P -value
Male	43.1 ±21.8 (N=21)	64.2 ±28.9 (N=152)	0.004	69.1 ±26.0 (N=6)	44.8 ±23.2 (N=167)	0.013	62.8 ±28.1 (N= 23)	43.1 ±21.9 (N=150)	<0.001
Female	24.8 ±17.6 (N=27)	43.9 ±24.4 (N=216)	<0.001	41.0 ±15.9 (N=15)	26.0 ±19.3 (N=228)	0.003	42.4 ±22.4 (N=37)	24.1 ±17.4 (N=206)	<0.001

Indicators of metabolic risk (the use of antihypertensive drugs and/or statins) and Visceral Adipose Tissue Index parameters at baseline measured on a Computed Tomography scan at the level of vertebra L3. The Visceral Adipose Tissue area was corrected for height resulting in a L3-index given in cm^2/m^2. Values were given per gender as mean (±SD). Mann-Whitney U-tests were used as sensitivity analyses and showed similar p-values yielding the same conclusions.

Reference values for visceral obesity

There were 23 males who used medication for hypertension and/or statins. For males the area under the ROC curve (AUC) was 0.702 with a 95% confidence interval (CI) of 0.580- 0.823 (p=0.002). To determine a cut-off value for visceral adipose tissue, the best VATI value was chosen, i.e. the one yielding the highest specificity for a sensitivity value of at least 80%. In males this resulted in a sensitivity of 82.6% (with a CI of 61-95% and a specificity of 42.7%) and the value of VATI that indicated an increased risk was 38.71 cm^2/m^2.

There were 37 females who used medication for hypertension and/or statins. In this group, the area under the curve (AUC) was 0.757 with a 95% confidence interval (CI) of 0.676- 0.838 (p<0.001). In females, the best VATI value (highest specificity) where a sensitivity of at least 80% was reached yielded a sensitivity of 81.1% (with a CI of 65-92% and a specificity of 61.2%) and the value of VATI that indicated an increased risk was 24.94 cm^2/m^2.

VATI was a better predictor for the increased metabolic risk (AUC) than BMI for both males and females as shown in Figure 3. In males, the AUC was 0.556 (95% CI 0.418 - 0.695, p=0.385) and in females the AUC was 0.630 (95% CI 0.531- 0.729, p=0.012) for BMI.

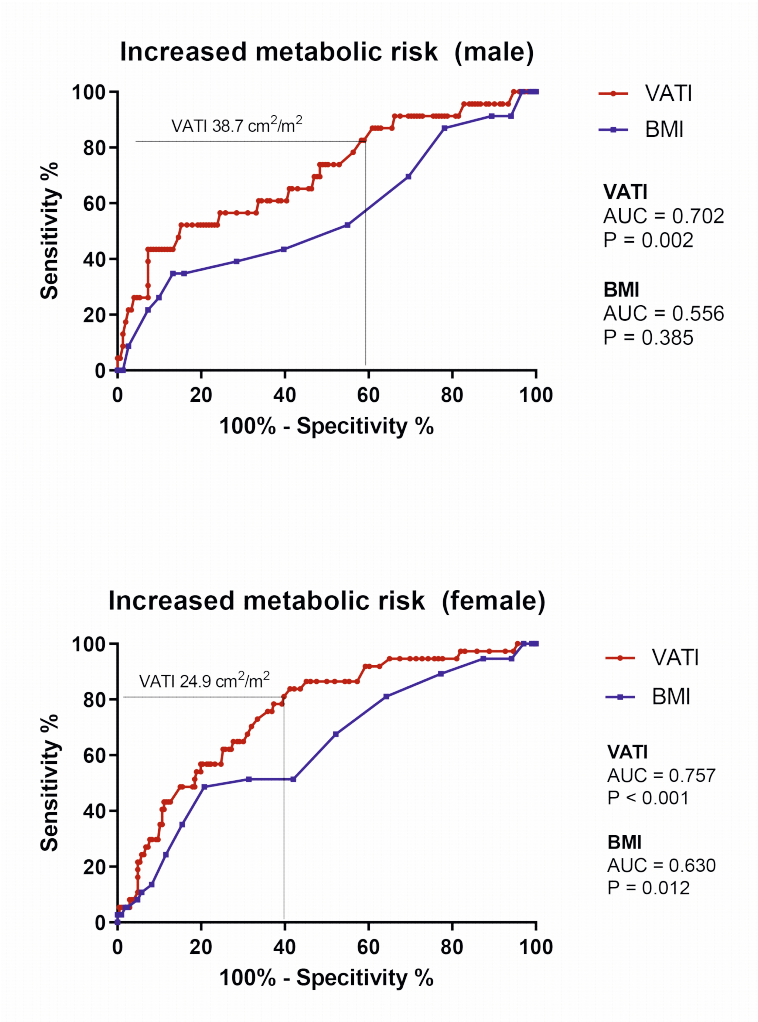

Figure 3. Reference values for visceral obesity per gender

Increased metabolic risk is defined as: the use of antihypertensive drugs and/or statins. The risk is given per gender using Receiver Operating Characteristic (ROC) analysis. Visceral Adipose Tissue Index (VATI) measured at the level of vertebra L3 on an abdominal CT-scan is given in cm^2/m^2. Body Mass Index (BMI) is given in kg/m^2. The value with a sensitivity of at least 80% is used as a cut-off value for visceral obesity indicating increased metabolic risk. VATI showed to be a predictor with a higher sensitivity and specificity for metabolic risk than BMI.

Discussion

This study was designed to assess the association between the amount of visceral adipose tissue and indicators of metabolic risk and to define gender specific reference values for visceral

obesity upon this association in a Caucasian cohort. The use of antihypertensive drugs and/or statins was used as an indicator for increased metabolic risk. In an otherwise healthy Caucasian cohort, a value of VATI of ≥38.7 cm^2/m^2 for males and ≥24.9 cm^2/m^2 for females was associated with an increased metabolic risk with a sensitivity >80%. Also, VATI showed to be a better predictor for metabolic risk than BMI for both genders.

Given the growing prevalence of obesity and the metabolic syndrome and the increasing scientific attention for these problems reference values for visceral obesity are needed. The importance of generally applicable reference values in body composition research is recently shown in previous research [24, 25]. Several studies have been performed addressing the association between the amount of VATI and clinical outcome. In all of these studies, cut-off values were based upon the investigated study cohort or upon disease outcome [4, 26-31]. When studying the effect of visceral obesity on disease related outcomes in specific cohorts it may be crucial to define pathological visceral obesity using externally validated reference values [24]. To define a reference value for visceral obesity for body composition analysis using CT scans it is important to identify those patients for whom the amount of visceral adipose tissue actually becomes a health risk.

To our knowledge, this is the first study providing reference values for visceral obesity for body composition analysis using Computed Tomography scans in a relatively homogenous Caucasian cohort. In the Asian population, several publications have reported cut-off values to indicate when visceral obesity becomes a risk factor [17-22]. However, body composition is ethnicity dependent and with the same BMI Asians have a higher morbidity and mortality compared to Caucasians [14, 16, 23]. Therefore these reference values may not be applicable in the Caucasian population.

In Asian studies, cut-off values on Computed Tomography of VAT that are associated with the metabolic syndrome approximate 133-136 cm^2 in men and 91-95 cm^2 in women [20, 32, 33]. Commonly, tissue areas measured at a single CT slice are normalized to height, but unfortunately no normalized ratios are reported in the Asian literature. Accounting for an average height of 1.53 and 1.74 meter for Japanese and Korean males respectively and 1.53 and 1.61 meter for Japanese and Korean females respectively, it can be estimated that the cut-off value form visceral obesity based on normalized VATI based on Asian data approximates 44-58 cm^2/m^2 for males and 35-41 cm^2/m^2 for females. These reference values are higher than the reference values found in the current study. However, the present study consists of a cohort of relatively healthy living kidney donor candidates and in the Asian studies also patients from

obesity clinics were included [34]. Besides, some studies used CT slices from the umbilical level with wider Hounsfield Unit ranges for adipose tissues (HU -250 to -50) [20, 32].

Body composition and also the amount of visceral adipose tissue is different between men and women [15]. Therefore gender specific reference values were created. In the present study, it appears that even when the amount of VAT is corrected for height, the relative amount of VATI that is associated with health problems is much lower in women than in men. The average normalized VATI in women with an increased metabolic risk was the same as in men without increased metabolic risk (Figure 2). This may suggest that women with a masculine fat distribution with more VAT around the waist run a higher risk of developing the metabolic syndrome.

Using ROC analysis the current study also showed that the amount of visceral adipose tissue on Computed Tomography seemed to be a better predictor for metabolic risk than BMI. This is in agreement with previous studies, where the amount of visceral adipose tissue was a better predictor for the development of the metabolic syndrome compared to BMI [1, 4, 20, 33, 35]. Previous research also showed that the amount of VAT is a better indicator for the risk on the metabolic syndrome than waist circumference [20, 33]. Both BMI and waist circumference contain both subcutaneous adipose tissue and visceral adipose tissue. However, it is the amount of visceral adipose tissue that causes the highest risk on the metabolic syndrome and associated health problems since visceral adipose tissue is metabolically active [5, 10].

This study has several strengths and weaknesses. Strong point of the study is that a large and relatively homogenous cohort of healthy kidney donor candidates was used. Body composition measurements using Computed Tomography is an accurate and widely used method with a good reproducibility [13, 36]. For the measurement of visceral adipose tissue and therefore visceral obesity, CT and MRI are the gold standards since visceral adipose tissue can be easily distinguished from other tissues [4, 32, 37-39]. However, the visibility of VAT is also dependent of the anatomy of the intra-abdominal organs. The movement of soft tissues, bowel movement and the variable filling of the intestine can cause variability in the measurements [4]. However, VAT measurements on a single slice at 5 centimetre superior to the L4-L5 level showed a high correlation with total adipose tissue [4, 40].

In the present study two CT scanners are used which may cause variation between CT scans produced by different scanners. For the current research question concerning measurements of the VAT no significant differences are expected since on both CT scanners VAT could be

discriminated equally well from adjacent tissues and structures. The variation due to different machines more prominently affects measurement of radiological density than quantification of area.

A limitation of the study is that we only could use prescribed medication as readout of increased metabolic risk instead of measured values. In addition, apart from hypertension and dyslipidaemia, hyperglycaemia and diabetes are characteristics of the metabolic syndrome. Since diabetes and hyperglycaemia are contra-indications for kidney donation subjects with these conditions were not present in our cohort. The reference values we propose have a high sensitivity but relatively poor specificity, this is obviously due to the multifactorial pathogenesis of hypertension and dyslipidaemia.

Another limitation is the single-center nature of the study which still warrants external validation in other (international and Caucasian) cohorts, since apart from differences in genetic background also socio-economic status and cultural differences may play a role. Computer tomography is a resource-consuming diagnostic procedure. Currently there is no solid basis to justify its primary use in body composition assessment. However many patients that have CT performed for clinical grounds may very well benefit from a body composition analysis of the CT images. Examples of those patients include patients that are assessed for major surgery or critically ill patients.

Conclusion

In conclusion, VATI value of ≥ 38.7 cm^2/m^2 for males and ≥ 24.9 cm^2/m^2 for females can be used as reference value for visceral obesity on computed tomography scans in a Caucasian population. These values of visceral adipose tissue are associated with increased metabolic risk, but further validation is needed. This study also showed that visceral adipose tissue is a better predictor for metabolic risk than BMI for both genders.

Since the amount of visceral adipose tissue and increased metabolic risk is different between men and women, and different from other populations, it is important to use gender and ethnicity specific reference values to define pathological visceral obesity in body composition research to increase the comparability and reproducibility.

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Supplemental materials

Supplemental table 1. Sensitivity analysis: univariable and multivariable Cox regression analysis of visceral obesity and 90-day mortality

	Univariable analysis (N=514)			Multivariable analysis (N=514)		
	HR	95% CI	P-value	HR	95% CI	P-value
Visceral obesity	1.161	0.837 – 1.612	0.371	0.744	0.522 – 1.060	0.102
Sex (male vs female)	-	-	-	0.974	0.677 – 1.402	0.889
Age (years)	-	-	-	1.020	1.008 – 1.033	0.001
APACHE II score*	-	-	-	1.056	1.035 – 1.077	<0.001
Sarcopenia	-	-	-	1.493	0.997 – 2.238	0.052
Muscle quality	-	-	-	0.987	0.969 – 1.006	0.180

*Multivariable analysis using Cox regression analysis with 90 day mortality as outcome. Data are presented as Hazard Ratio (HR), 95% Confidence Interval (CI) and p-value. Visceral obesity is defined as a VAT value of ≥ 38.7 cm^2/m^2 for males and ≥ 24.9 cm^2/m^2 for females [1]. Disease severity is defined using the APACHE II score (Acute Physiology and Chronic Health Evaluation) [2]. Sarcopenia is defined as a SMI for males of 41.6 cm^2/m^2 and a SMI for females of 32.0 cm^2/m^2 [3]. Muscle quality, assessed by Computed Tomography derived muscle density, is given as the mean Radiation Attenuation (RA), expressed in Hounsfield Units (HU) of the total skeletal muscle tissue area [4, 5]. * Of 2 surviving ICU patients APACHE II score is missing.*

Supplemental table 2. Sensitivity analysis: univariable and multivariable Cox regression analysis of BMI categories and 90-day mortality

	Univariable analysis (N=540)			Multivariable analysis (N=540)		
	HR	95% CI	P-value	HR	95% CI	P-value
BMI*						
Normal weight (reference)			0.659			0.168
Underweight	1.244	0.455 – 3.397	0.671	1.110	0.399 – 3.092	0.841
Overweight	0.883	0.615 – 1.268	0.501	0.762	0.521 – 1.115	0.162
Obesity	0.717	0.381 – 1.347	0.301	0.501	0.257 – 0.977	0.042
Sex	-	-	-	1.043	0.718 – 1.516	0.825
Age (years)	-	-	-	1.016	1.004 – 1.029	0.012
APACHE II score*	-	-	-	1.057	1.035 – 1.078	<0.001
Sarcopenia	-	-	-	1.331	0.863 – 2.054	0.196
Muscle quality				0.981	0.962 – 1.001	0.058

*Multivariable analysis using Cox regression analysis with 90 day mortality as outcome. Data are presented as Hazard Ratio (HR), 95% Confidence Interval (CI) and p-value. Underweight is defined as a BMI ≤18.5 kg/m^2, normal weight is defined as a BMI of 18.5-24.9 kg/m^2, overweight is defined as a BMI of 25.0-29.9 kg/m^2 and obesity is defined as a BMI ≥30.0 kg/m^2according to the WHO [6]. Disease severity is defined using the APACHE II score (Acute Physiology and Chronic Health Evaluation) [2]. Sarcopenia is defined as a SMI for males of 41.6 cm^2/m^2 and a SMI for females 32.0 of cm^2/m^2 [3]. Muscle quality, assessed by Computed Tomography derived muscle density, is given as the mean Radiation Attenuation (RA), expressed in Hounsfield Units (HU) of the total skeletal muscle tissue area [4, 5]. * Of 2 surviving ICU patients APACHE II score is missing and of 12 patients BMI is missing.*

Visceral obesity measured using Computed Tomography scans: no significant association with mortality in critically ill patients

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Abstract

Introduction

The association between obesity and outcome in critical illness is unclear. Since the amount of visceral adipose tissue(VAT) rather than BMI mediates the health effects of obesity we aimed to investigate the association between visceral obesity, BMI and 90-day mortality in critically ill patients.

Method

In 555 critically ill patients (68% male), the VAT Index(VATI) was measured using Computed Tomography scans on the level of vertebra L3. The association between visceral obesity, BMI and 90-day mortality was investigated using univariable and multivariable analyses, correcting for age, sex, APACHE II score, sarcopenia and muscle quality.

Results

Visceral obesity was present in 48.1% of the patients and its prevalence was similar in males and females. Mortality was similar amongst patients with and without visceral obesity (27.7% vs 24.0%, p=0.31). The corrected odds ratio of 90-day mortality for visceral obesity was 0.667 (95%CI 0.424–1.049, p=0.080). Using normal BMI as reference, the corrected odds ratio for overweight was 0.721 (95%CI 0.447–1.164 p=0.181) and for obesity 0.462 (95%CI 0.208–1.027, p=0.058).

Conclusion

No significant association of visceral obesity and BMI with 90-day mortality was observed in critically ill patients, although obesity and visceral obesity tended to be associated with improved 90-day mortality.

Introduction

The association between body composition and outcome in critical illness is increasingly gaining interest. It is known that sarcopenia and low muscle quality are associated with increased mortality in critically ill patients [1, 2]. In contrast, the relation between obesity and outcome in critical illness is less clear.

In the general population, it is known that obesity is associated with increased health risks such as chronic inflammation, a procoagulant state, insulin resistance, type 2 diabetes, dyslipidemia, hypertension, cardiovascular disease, chronic kidney disease and various types of cancer [3-8]. However, in critically ill patients several studies suggest that obesity is associated with better survival [3, 9-14], although this so-called "obesity paradox" is not uniformly reproduced by other studies [3, 15].

The metabolic consequences of obesity are also different between men and women [16-18]. There is increasing recognition that BMI is not the most factor that determines the impact of adiposity on health status, but that the distribution of the adipose tissue and in particular the amount of visceral adipose tissue mediates the metabolic consequences of obesity [19, 20].

To shed further light on the association between obesity and outcome in critical illness it seems important to investigate in particular the association between the amount of visceral adipose tissue and outcome. The aim of the present study was to evaluate the association of visceral obesity and BMI with 90-day mortality in critically ill patients.

Methods

Patients

The study population consisted of patients admitted to the Intensive Care Unit (ICU) of the Amsterdam University Medical Center between September 2003 and February 2016. All patients had an abdominal CT scan suitable for body composition analyses between one day before to four days after admission to the ICU. Patients with an abdominal CT scan of sufficient quality to perform analyses were included in the study. Data on muscle mass and muscle quality originating from the same cohort have been published before [1, 2]. For this analyses, we selected patients with a non-elective ICU admission as showed in Figure 1.

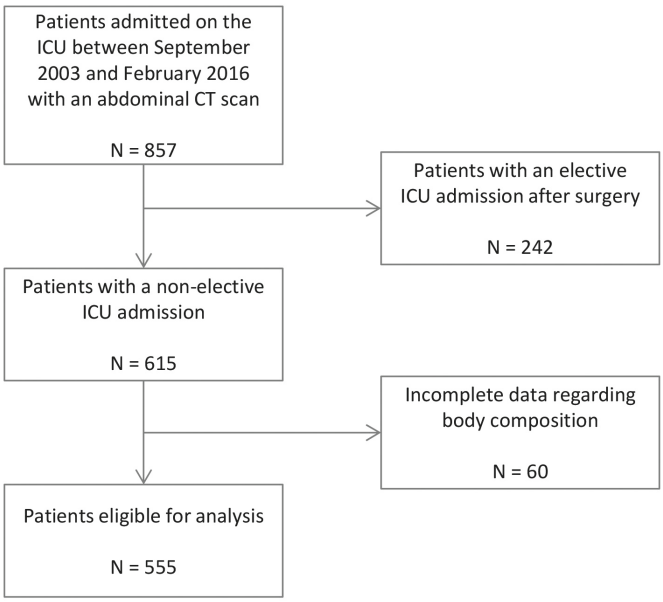

Figure 1. Patient selection

Body composition analysis

CT-scan analysis of body composition was performed as described by Mourtzakis *et al* [21]. Briefly, a single slice of each individual CT scan was selected at the level of the 3rd lumbar vertebra. Using predefined Hounsfield Unit (HU) ranges, visceral adipose tissue (VAT) (–150 to –50 HU) was determined. The total area of VAT was estimated by assessing the total tissue area at vertebra L3 and indexed for height by dividing it by height squared, resulting in the Visceral Adipose Tissue Index (VATI) given in cm^2/m^2. In a large number of CT scans the subcutaneous adipose tissue was cut off, whereby reliable analysis of subcutaneous adipose tissue was not possible. In addition we calculated the Skeletal Muscle area Index (SMI) (-29 to 150 HU). Muscle quality, assessed by Computed Tomography derived muscle density, is given as the mean Radiation Attenuation (RA), expressed in Hounsfield Units (HU) of the total skeletal muscle tissue area [2, 22]. Body composition analyses were performed by 2 trained researchers. Each CT scan was analyzed by a single researcher who had frequent consultation with another trained researcher if there was any doubt about eligibility, landmarking, or analysis. Previous research shows a variability of less than 2% for this method [2, 23]. CT scans were analyzed using SliceOmatic V4.3 and 5.0 (TomoVision, Magog, Canada) software for Microsoft Windows®.

The definition of visceral obesity

Body composition and the Visceral Adipose Tissue Index (VATI) are ethnicity and sex dependent [24, 25]. To define visceral obesity sex specific cut-off values for VATI from a healthy Caucasian population were used [25]. The cut-off value of VATI for visceral obesity in males was ≥ 38.7 cm^2/m^2 and for females ≥ 24.9 cm^2/m^2 [25].

The definition of sarcopenia

To define sarcopenia, a Skeletal Muscle area Index (SMI) below the 5th percentile of a healthy Caucasian population were used. For males, this was a SMI of 41.6 cm^2/m^2. For females, a SMI of 32.0 cm^2/m^2 was used as a cut-off value [26].

BMI categories

BMI was categorized according to the definition of the World Health Organization (WHO): 1) a BMI value of < 18.5 kg/m^2 indicating underweight, 2) BMI 18.5 - 24.9 kg/m^2 indicating a normal weight, 3) BMI 25 - 29.9 kg/m^2 indicating overweight and 4) BMI ≥ 30 kg/m^2 indicating obesity [27].

Statistical Analysis

Categorical variables are presented as number of patients (%), where mean ± standard deviation (SD) or median (interquartile range, IQR) were used for numerical variables.

Differences in categorical and numerical variables between groups (visceral obesity yes/no; died within 90 days yes/no) were assessed using chi-square and independent samples t-tests, respectively. In case of clear non-normality based on histograms, medians and IQRs were reported and a Mann-Whitney U-test was performed instead of a t-test.

Multivariable logistic regression analysis were performed to test the association of visceral obesity and BMI with 90-day mortality, correcting for variables that may influence mortality such as disease severity using the APACHE II score [28], age, sex, the presence of sarcopenia and muscle quality. To assess potential effect-modification of sex, the interaction between sex and BMI, visceral obesity, sarcopenia and muscle quality were tested. In case of significant interaction with sex, the effects were reported separately for men and women. In case of non-significant interaction, the interaction term was removed from the model and the effects were reported for men and women combined. Collinearity was checked using Variation Inflation Factor (VIF). To check the robustness of the results, a Cox regression analysis assessing the time-to-event was included as a sensitivity analysis, where the same variables were included

as in the logistic regression analysis model. Additionally, Kaplan Meier curves (and log-rank test) were used to visualize the association between visceral obesity and 90 day mortality.

Analyses were performed using IBM SPSS Statistics for Windows version 25 (Armonk, NY, USA; IBM Corp.). A p-value ≤ 0.05 was considered statistically significant. The statistical analyses were supervised by a statistician (BW).

Ethics

The study protocol was reviewed and approved by the Medical Ethics Committee of the Amsterdam University Medical Center, location VUmc (IRB00002991, decision 2012/243). The study has also been registered at ClinicalTrials.gov (NCT02817646). The need for informed consent was waived because of the retrospective nature of the study using coded data obtained from standard care. The Medical Research Involving Human Subjects Act does not apply to the study and the study was conducted in accordance with the Declaration of Helsinki.

Results

Study population

A total number of 555 (378 male (68%) and 177 female (32%)) patients were included in the analysis. Mean (±SD) age was 55 (±19) years and mean APACHE II [28] score was 24 (±8). Median (IQR) duration of mechanical ventilation was 10.0 (6.0 – 18.0) days, median ICU stay was 12 (7 - 22) days and median hospital stay was 30 (17 – 52) days. The ICU mortality was 16% and overall mortality within 90 days after admission to the ICU was 26%. ICU and 90 day mortality was not different between sexes (p=0.287 and p=0.261 respectively). ICU mortality in females was 18.1% and 90 day mortality was 28.8%. In males, ICU mortality was 14.6% and 90 day mortality was 24.3%. More patient characteristics and characteristics of patients with visceral obesity and without visceral obesity are presented in Table 1.

Table 1. Characteristics of the study population

		Mean (±SD), median (IQR) or number (%)			P-value
		Overall (N = 555)	Visceral obesity (N = 267)	No visceral obesity (N = 288)	
Demographics and body composition	Sex (%) Male Female	 378 (68.1%) 177 (31.9%)	 183 (68.5%) 84 (31.5%)	 195 (67.7%) 93 (32.3%)	0.834 [1]
	Age (years)	55 (±19)	64 (±14)	47 (±20)	<0.001 [2]
	Weight (kg)	77.5 (±14.8)	82.6 (±14.6)	72.7 (±13.2)	<0.001 [2]
	Height (m)	1.75 (± 0.1)	1.75 (±0.1)	1.75 (±0.1)	0.554 [2]
	BMI (kg/m^2)	25 (±4)	27 (±4)	24 (±3)	<0.001 [2]
	Hospital stay before ICU admission (days)	0 (0 – 1)	0 (0 – 2)	0 (0 – 1)	0.042 [3]
	Time between ICU admission and CT scan (days)	0 (0 – 1)	0 (0 – 1)	0 (0 – 0)	0.610 [3]
Admission diagnosis					<0.001 [1]
	Cardiovascular	34 (6.1%)	24 (9.0%)	10 (3.5%)	
	Metabolic/Renal	21 (3.8%)	16 (6.0%)	5 (1.7%)	
	Neurologic	56 (10.1%)	26 (9.7%)	30 (10.4%)	
	Post resuscitation	44 (7.9%)	26 (9.7%)	18 (6.3%)	
	Respiratory insufficiency	86 (15.5%)	53 (19.9%)	33 (11.5%)	
	Sepsis	61 (11.0%)	32 (12.0%)	29 (10.1%)	
	Trauma	191 (34.4%)	59 (22.1%)	132 (45.8%)	
	Other / unknown	62 (11.1%)	31 (11.6%)	31 (10.8%)	
Disease severity	APACHE II score	24 (±8)	24 (±8)	23 (±8)	0.008 [2]
Outcomes	ICU stay (days)	12 (7 – 22)	13 (8 – 21)	12 (7 – 23)	0.058 [3]
	Hospital stay (days)	30 (17 – 52)	30 (17 – 54)	31 (18 – 50)	0.559 [3]
	Duration of mechanical ventilation (days) *	10.0 (6.0 – 18.0)	9.0 (6.0 – 18.3)	10.0 (6.0 – 18.0)	0.752 [3]
	Mortality within 90 days after admission to the ICU	143 (26%)	74 (27.7%)	69 (24.0%)	0.312 [1]

*Values are presented as mean (±SD), median (IQR) and absolute number (%). Normality was checked using histograms. [1] chi square test [2] independent sample t-test [3] Mann-Whitney U-test. *262 patients with visceral obesity and 287 patients without visceral obesity received mechanical ventilation.*

The prevalence of visceral obesity and BMI categories

Mean (±SD) VATI was 42.2 cm^2/m^2 (± 32.8) for males and 30.3 cm^2/m^2 (± 25.6) for females. Using sex specific cut-off values from an otherwise healthy Caucasian population [25] visceral obesity was present in 183 (48%) males and 84 (47%) females. A comparison of patients with and without visceral obesity and their BMI is presented in Table 2.Twenty-nine percent of the patients with a normal weight according to BMI were classified as having visceral obesity.

Table 2. Comparison of visceral obesity and BMI

	Underweight	Normal weight	Overweight	Obese	Total
Visceral obesity	1 (7.7%)	83 (28.8%)	126 (66.3%)	49 (94.2%)	259 (47.7%)
No visceral obesity	12 (92.3%)	205 (71.2%)	64 (33.7%)	3 (5.8%)	284 (52.3%)
Total	13 (2.4%)	288 (53.0%)	190 (35.0%)	52 (9.6%)	

*Visceral obesity was measured using Computed Tomography scans and defined as a VATI value of ≥ 38.7 cm^2/m^2 for males and ≥ 24.9 cm^2/m^2 for females [25].Underweight is defined as a BMI ≤18.5 kg/m^2, normal weight is defined as a BMI of 18.5-24.9 kg/m^2, overweight is defined as a BMI of 25.0-29.9 kg/m^2 and obesity is defined as a BMI ≥30.0 kg/m^2according to the WHO [27]. * BMI of 12 patients is missing.*

Univariable analysis of 90-day mortality

In total, 143 patients (25.8%) died within 90 days after ICU admission. The presence of visceral obesity was not significantly associated (p = 0.312) with higher mortality (Table 3, Figure 2). Also BMI (p = 0.774) and sex (p = 0.261) were not significantly associated with a higher mortality as shown in Table 3. The age of patients, disease severity using the APACHE II score, the presence of sarcopenia and muscle quality were significantly associated with a higher 90 day mortality following ICU admission (p ≤ 0.001).

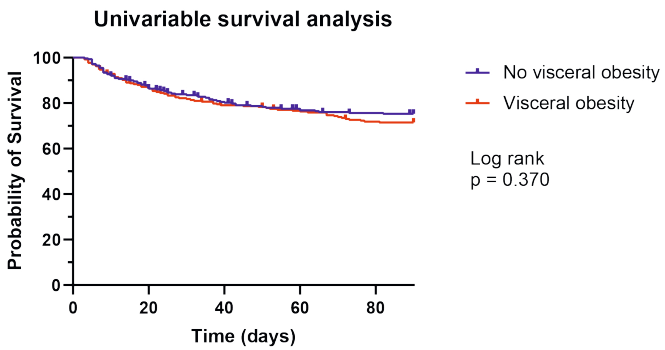

Figure 2. Univariable survival analysis

Univariable survival analysis using Kaplan Meier assessing the association between the presence of visceral obesity with 90-day mortality. Visceral obesity is defined as a Visceral Adipose Tissue Index (VATI) measured using Computed Tomography scans of ≥ 38.7 cm^2/m^2 for males ≥ 24.9 cm^2/m^2 for females [25].

Table 3. Univariable analysis of 90-day mortality

	Alive (N = 412)	Dead (N = 143)	P-value
Age (years)			
N = 555	52.0 (±19.2)	64.1 (±16.6)	<0.001 (1
Sex			0.261 (2
Male N = 378	286 (69.4%)	92 (24.3%)	
Female N = 177	126 (71.2%)	51 (28.8%)	
APACHE II *			<0.001 (1
N = 553	22.0 (±8.0)	27.5 (±7.9)	
Sarcopenia			<0.001 (2
Yes N = 85	47 (55.3%)	38 (44.7%)	
No N = 470	365 (77.7%)	105 (22.3%)	
Muscle quality (HU)			<0.001 (1
N = 555	36.7 (±12.8)	29.0 (±12.0)	
Visceral obesity			0.312 (2
Yes N = 267	193 (72.3%)	74 (27.7%)	
No N = 288	219 (76.0%)	69 (24.0%)	
BMI *			0.774 (2 **
N=543			
Underweight N = 13	9 (69.2%)	4 (30.8%)	
Normal weight N = 288	210 (72.9%)	78 (27.1%)	
Overweight N = 190	143 (75.3%)	47 (24.7%)	
Obesity N = 52	41 (78.8%)	11 (21.2%)	

*Numerical data are presented as mean (±SD), categorical data are presented as number of patients (%). Statistical tests that were used were: (1 independent sample t-test, (2 chi square test. * Of 2 surviving ICU patients APACHE II score is missing and of 12 patients BMI is missing. ** The trend test for BMI categories was not significant (p=0.296). Sarcopenia is defined as a SMI for males of 41.6 cm^2/m^2 and a SMI for females of 32.0 cm^2/m^2 [26]. Muscle quality, assessed by Computed Tomography derived muscle density, is given as the mean Radiation Attenuation (RA), expressed in Hounsfield Units (HU) of the total skeletal muscle tissue area [2, 22].Visceral obesity is defined as a VATI value of ≥ 38.7 cm^2/m^2 for males ≥ 24.9 cm^2/m^2 for females [25]. Underweight is defined as a BMI ≤18.5 kg/m^2, normal weight is defined as a BMI of 18.5-24.9 kg/m^2, overweight is defined as a BMI of 25.0-29.9 kg/m^2 and obesity is defined as a BMI ≥30.0 kg/m^2according to the WHO [27].*

Multivariable analysis of 90 day mortality

The interaction terms between sex and BMI (p=0.469), visceral obesity (p=0.949), sarcopenia (p=0.654 in model with BMI, p=0.537 in model with visceral obesity) and muscle quality (p=0.997 in model with BMI, p=0.837 in model with visceral obesity) were not significant. Therefore, the effects of BMI or visceral obesity on 90-day mortality are presented for men and women combined using logistic regression analysis with correction for age, sex, APACHE II score, sarcopenia and muscle quality.

Visceral obesity was not significantly associated with 90-day mortality, although the 95% confidence interval was largely compatible with a favorable association between visceral obesity and 90-day mortality (OR 0.667 (0.424-1.049, p=0.080) (Table 4). When defined by BMI category, obesity was not significantly associated with 90-day mortality, although also here the 95% confidence interval was largely compatible with a favorable association between obesity and 90-day mortality (Table 5). Of the factors included in the analyses age and APACHE II score were significantly associated with increased mortality ($p \leq 0.001$). Sarcopenia was significant in the model with visceral obesity (p=0.045), but not with BMI (p=0.147). Since there was a collinearity problem with BMI and visceral obesity (VIF values for normal weight and obesity were larger than 10), BMI and visceral obesity could not be analyzed in the same analyses and were therefore analyzed separately.

Table 4. Univariable and multivariable logistic regression analysis of visceral obesity and 90-day mortality

	Univariable analysis (N=553)			Multivariable analysis (N=553)		
	OR	95% CI	P-value	OR	95% CI	P-value
Visceral obesity	1.128	0.832 – 1.783	0.311	0.667	0.424 – 1.049	0.080
Age (years)	-	-	-	1.027	1.012 – 1.043	<0.001
Sex (male vs female)	-	-	-	1.037	0.659 – 1.630	0.877
APACHE II score*	-	-	-	1.067	1.039 – 1.097	<0.001
Sarcopenia	-	-	-	1.751	1.012 – 3.028	0.045
Muscle quality	-	-	-	0.986	0.964 – 1.009	0.231

Multivariable analysis using logistic regression analysis with 90 day mortality as outcome. Data are presented as Odds Ratio (OR), 95% Confidence Interval (CI) and p-value. Visceral obesity is defined as a VATI value of ≥ 38.7 cm^2/m^2 for males and ≥ 24.9 cm^2/m^2 for females [25]. Disease severity is defined using the APACHE II score (Acute Physiology and Chronic Health Evaluation) [28]. Sarcopenia is defined as a SMI for males of 41.6 cm^2/m^2 and a SMI for females of 32.0 cm^2/m^2 [26]. Muscle quality, assessed by Computed Tomography derived muscle density, is given as the mean Radiation Attenuation (RA), expressed in Hounsfield Units (HU) of the total skeletal muscle tissue area [2, 22]. Of 2 surviving ICU patients APACHE II score is missing.*

Sensitivity analysis

To assess a potential difference in time-to-event, we performed a Cox regression analysis as a sensitivity analysis, including the same variables as for logistic regression analysis, namely visceral obesity or BMI category (underweight, normal weight, overweight, obesity), age, sex, APACHE II score, sarcopenia and muscle quality. The results were similar as the results of the logistic regression analysis (see supplemental Tables S1 and S2).

Table 5. Univariable and multivariable logistic regression analysis of BMI categories and 90 day mortality

	Univariable analysis (N=541)			Multivariable analysis (N=541)		
	OR	95% CI	P-value	OR	95% CI	P-value
BMI*						
Normal weight (reference)			0.758			0.234
Underweight	1.185	0.355 – 3.959	0.782	0.884	0.240 – 3.261	0.854
Overweight	0.876	0.576 – 1.334	0.538	0.721	0.447 – 1.164	0.181
Obesity	0.715	0.350 – 1.462	0.358	0.462	0.208 – 1.027	0.058
Age (years)	-	-	-	1.023	1.008 – 1.038	0.003
Sex (male vs female)	-	-	-	1.104	0.691 – 1.762	0.679
APACHE II score*	-	-	-	1.067	1.038 – 1.096	<0.001
Sarcopenia	-	-	-	1.534	0.860 – 2.735	0.147
Muscle quality	-	-	-	0.980	0.957 – 1.004	0.095

*Multivariable analysis using logistic regression analysis with 90 day mortality as outcome. Data are presented as Odds Ratio (OR), 95% Confidence Interval (CI) and p-value. Underweight is defined as a BMI ≤18.5 kg/m^2, normal weight is defined as a BMI of 18.5-24.9 kg/m^2, overweight is defined as a BMI of 25.0-29.9 kg/m^2 and obesity is defined as a BMI ≥30.0 kg/m^{2}according to the WHO [27]. Disease severity is defined using the APACHE II score (Acute Physiology and Chronic Health Evaluation) [28]. Sarcopenia is defined as a SMI for males of 41.6 cm^2/m^2 and a SMI for females 32.0 of cm^2/m^2 [26]. Muscle quality, assessed by Computed Tomography derived muscle density, is given as the mean Radiation Attenuation (RA), expressed in Hounsfield Units (HU) of the total skeletal muscle tissue area [2, 22]. * Of 2 surviving ICU patients APACHE II score is missing and of 12 patients BMI is missing.*

Discussion

The aim of the present study was to investigate the effect of visceral obesity measured using CT scans, on 90-day mortality in critically ill patients, using sex specific cut-off values of a Caucasian cohort to define visceral obesity. This in order to gain more insight in the possible obesity paradox in critical illness. Univariable analysis revealed no significant association between visceral obesity or obesity (based on BMI) and 90-day mortality in critically ill patients with a non-elective ICU admission. After correction for age, sex, sarcopenia, muscle quality and APACHE II score, the association between visceral obesity and 90-day mortality and the association between obesity and 90-day mortality did not reach statistical significance, although the 95% confidence interval of the odds ratios for 90-day for mortality was largely compatible with better survival in patients with visceral obesity as well as in patients with obesity defined by BMI. Of note, the proportion of patients classified as obese based on BMI was considerably smaller than the proportion of patients classified as having visceral obesity.

Previous research regarding the relationship of obesity with ICU outcome is contradictory. In general, obesity is associated with higher mortality [3-8]. In critically ill patients it has been

reported that mild obesity is beneficial compared to normal BMI [3, 9-14]. However, the existence of an obesity paradox in critical illness has been debated by recent studies [15, 29, 30]. In previous studies regarding obesity and outcome, BMI is most frequently used to define obesity. However, to address the relation between obesity and clinical outcomes it seems important to appreciate the pathophysiological processes that may mediate this relation. In particular, visceral adipose tissue is metabolically active and associated with increased health risks and various diseases [3, 19, 20]. This is in contrast to subcutaneous adipose tissue which is not metabolically active and may have benefits such as providing energy and lipid stores during the acute catabolic phase in critical illness [3]. This differentiated distribution of adipose tissue is not reflected when using BMI in the definition of obesity. Moreover, in the BMI the weight of muscle tissue is included and previous research shows that sarcopenia at ICU admission is an important predictor of increased mortality [1]. When using BMI to assess the relation between obesity and outcome, it is not possible to distinguish the separate effects of obesity and sarcopenia on mortality. Since, the distribution of visceral and subcutaneous adipose tissue differs between individuals, and typically between sexes, with males typically having a predominant visceral adipose tissue distribution and females a predominant subcutaneous distribution we used sex specific cut-off values to define visceral obesity [24, 25]. Since body composition differs also per population, we used external reference values from a relatively healthy Caucasian population [25, 31, 32].

An earlier study showed that visceral obesity measured at the third lumbar vertebra using CT scans was a better predictor for metabolic risk than BMI [25]. We have explored whether using visceral adipose tissue area rather than BMI would better describe the obesity paradox, but found that neither BMI nor visceral adiposity was significantly associated with increased mortality risk in our population of critically ill patients with a non-elective ICU admission. In the present study mortality was not significantly associated with BMI or visceral obesity in critically ill patients. However, we observed a trend that was compatible with improved survival in patients with obesity and visceral obesity and therefore based on our current results we cannot definitely reject the obesity paradox.

There is data that suggest that the amount of visceral adipose tissue may protect against muscle weakness [33, 34]. Unfortunately, data on functional outcome regarding muscle strength are not available in this cohort. In the present study muscle quality was not associated with mortality in multivariable in contrast to univariable analysis. An association between mortality and achievement of energy and protein targets has been described in patients from the current

source population [35]. Unfortunately, we were not able to link the currently analyzed data to nutritional data.

Wirtz et al. and Yang et al. addressed the association between VAT and outcome in critically ill patients and COVID-19 patients, respectively, and found an association between the onset and duration of mechanical ventilation and VAT area [36, 37]. They both included a substantial number of patients who did not receive mechanical ventilation which impairs comparability with our data. In addition, the use of cut-off values was different. Wirtz et al used a cut-off value of 241.4 cm^2, which was defined in the investigated population, and Yang et al used a cut-off value of 100 cm^2 for both men and women, which was not indexed for height.

The present study has several strengths and weaknesses. The sample size was quite large in comparison to other body composition studies in critical illness. In addition, by excluding patients that were admitted in the ICU electively after surgery we selected a group of patients with "true critical illness", albeit that considerable heterogeneity persists with respect to admission diagnosis and other baseline characteristics. However, it might be that the observed trends may become statistically significant in larger cohorts or systematic reviews or meta-analyses of multiple cohorts. To increase comparability amongst studies or data pooling of different studies, standardization of methods and definitions are required. Moreover, the study concerns a single center experience over a prolonged period of time. Practice variation among different centers or practice changes over time may have affected the external validity of the results.

In the present study, for the definition of visceral obesity, sex specific cut-off values were used since body composition is sex dependent [38]. We used external reference values which is important since the distribution of body composition in some selected populations may deviate substantially from that of the general population [39]. Also the distribution of adipose tissue and associated health risks is different between populations and therefore we used population specific reference values [31, 32]. This is different from previous studies [36, 37]. Body composition was measured using Computed Tomography (CT) scans which is an established method with a high inter- and intra-observer reliability [21, 23].

Conclusion

In a large heterogenous group of critically ill patients with a non-elective ICU admission, neither visceral obesity nor BMI was significantly associated with an increased or decreased mortality risk. Multivariable analysis showed a trend towards improved 90-day survival in patients with obesity and visceral obesity, therefore the existence of an "obesity paradox" cannot be ruled out based upon the present data.

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Summary and general discussion

Summary and general discussion

Most patients on the Intensive Care Unit (ICU) suffer from life threatening impairment of the function of one or more vital organs [1]. An ICU admission may have a high impact on physical, cognitive and mental status of patients and also on their relatives, both on short and long term [2, 3]. Since the uncertainty about the prognosis causes stress, and futile ICU utilization brings a heavy societal burden [4], there is a need for reliable prognostication of critically ill patients. Traditional risk predictors consider organ function and physiological parameters [5, 6]. During recent years there has been an increasing interest in the relation between body composition and outcome in critical illness [7-9]. Currently, there are predominantly observational data that describe the association between specific body composition phenotypes and outcome in critical illness [10]. However, whether these associations reflect causal relations is largely unknown. So far, little attention is paid to pathophysiological processes that may mediate these associations [11]. Moreover, comparability of studies addressing body composition in critical illness is limited by lack of standardized definitions of deviant body types and by lack of standardized outcome measures [12]. Before body composition can actually become a clinically applicable tool in the assessment of patients being considered for ICU admission or before it can be regarded as a valid therapeutic target, it is important to enhance the understanding of the relation between body composition and outcome in critical illness.

The aim of this thesis was to study epidemiological and methodological aspects of body composition in critically ill patients. Chapter 1 discusses the background of the thesis and the knowledge gaps that were prevalent at the start of this doctoral research. Chapters 2 and 5 provide novel insights in the association between skeletal muscle and clinical outcome (chapter 2) and visceral adipose tissue and clinical outcome (chapter 5) in critically ill patients. Chapters 3 and 4 address methodological aspects of the measurement of muscle loss (chapter 3) and the measurement of visceral obesity (chapter 4).

In chapter 3 we addressed the reliability of computed tomography to quantify muscle loss in critically ill patients. In particular, we investigated the influence of edema formation on muscle area on sequential CT scans in the acute phase of critical illness. In chapter 4, we attempted to contribute to standardization of body composition research by proposing gender specific computed tomography reference values for visceral obesity, based on metabolic risk profiles in the Caucasian population, and in chapter 5 we applied these proposed reference values to study the association between the presence of visceral obesity and hospital mortality in critical illness.

Sarcopenia: a cause or an indicator for higher hospital mortality in critical illness?
Previous research showed that low muscle mass in mixed Intensive Care Unit (ICU) patients is associated with increased mortality [7-9]. The possible causality of this association however is scarcely addressed. Moreover, in general, studies use different definitions of low muscle mass, based on the distribution of muscle mass within the cohorts that were studied.

In chapter 2 we retrospectively analyzed a relatively homogenous group of 155 patients with abdominal sepsis. Skeletal muscle area was assessed using CT scans at the level of vertebra L3. Sarcopenia was defined as a muscle area index below the 5th percentile of the general population [13]. We assessed the association between the presence of sarcopenia and hospital mortality by a univariable analysis, and by multivariable analyses, correcting for age and co-morbidities such as chronic renal insufficiency, chronic cardiovascular insufficiency, COPD and cancer.

Univariable analysis revealed that the prevalence of sarcopenia was higher in patients that did not survive until hospital discharge, which is in line with previous findings [7-9]. However, it appeared that this relationship was confounded by the presence of chronic renal insufficiency and cancer, since these were independent risk factors for hospital mortality in patients with abdominal sepsis, whereas sarcopenia was not. We found no association between muscle quality, assessed by muscle radiation attenuation, and hospital mortality. We concluded that in patients with abdominal sepsis, sarcopenia may be a marker of disease instead of a direct cause for a higher hospital mortality in critical illness.

The findings of this study imply that it is important to take factors that are associated with muscle wasting into account in future research. Such potential confounders may also be present in other fields such as oncology. Sugimoto et al found a significant association between sarcopenia and decreased recurrence free survival and overall survival in patients with pancreatic cancer [14]. Although they corrected for tumor size and extent, it remains not fully elucidated whether the association that they observed reflects a causal relation, or whether sarcopenia is a marker of (microscopically) advanced disease [15].

To assess the robustness of findings from retrospective epidemiological research it is important to validate the results in other (prospective) databases [16]. To enable reproducibility and external validation universally applicable reference values are mandatory. We made use of a cut-off value for sarcopenia, derived from healthy kidney donors [13]. We found that this external reference value was a better predictor of hospital mortality than an internal reference

value of the studied cohort. Although this observation further seems to support the use of external reference values, these findings must be validated in other cohorts.

The reliability of the assessment of muscle loss during critical illness

During the acute phase of critical illness, patients suffer from muscle loss [17]. Theoretically, muscle loss can be quantified by sequential imaging using ultrasound [17, 18] or CT scans [19]. We investigated whether sequential CT scans can be used to assess muscle loss during ICU admission. This is highly relevant since this could provide an opportunity to perform retrospective analyses of large cohorts where sequential CT scans are made for clinical purposes. However, in the acute phase of critical illness, patients develop generalized edema, due to capillary leakage [20], which is a feature of for example sepsis and which is further aggravated by the extensive amount of intravenous fluids that are administered to maintain adequate blood pressure [21]. We hypothesized that the formation of edema in tissues and particularly muscle tissue, could hamper assessment of muscle loss using sequential CT-scans.

In chapter 3 we assessed changes in Skeletal Muscle area Index (SMI) using sequential CT scans at the level of vertebra L3 of 77 patients with abdominal sepsis. The amount of edema was rated by two independent researchers and scored as (1) no/low edema, (2) moderate edema and (3) severe edema. The change in edema was calculated between the sequential CT scans. In addition, we assessed radiation attenuation (RA) of the muscle, which is regarded a readout of muscle quality [22], and that can be decreased by both lipid and fluid infiltration. Finally, we studied the association between changes in SMI and RA, edema and disease severity using the maximum Sequential Organ Failure Assessment (SOFA) score.

This study revealed that SMI declined on average 0.35% per day. However, in 41.6% of the study population we measured an increase of SMI. Physiologically it is not plausible to expect that this observation was due to muscle anabolism during ICU admission, therefore we studied the association between changes in SMI and changes in edema. We found that increased SMI was significantly associated with increased edema formation. Interestingly, the formation of edema was also significantly associated with a higher maximum SOFA score indicating higher disease severity. Muscle RA decreased during critical illness but was not significantly associated with changes in SMI or changes in edema. Since both edema and fat infiltration may affect muscle RA, their separate effects on muscle quality are difficult to distinguish.

In conclusion, we found that the assessment of muscle loss during critical illness using computed tomography scans is hampered by the formation of edema. Edema in critical illness

leads to overestimation of muscle area measured using CT scans and is associated with a higher SOFA score indicating a higher disease severity. This implies that researchers must be aware of this phenomenon and be careful with the interpretation of the results when using abdominal CT scans to assess changes in muscle mass and quality. Although edema formation does not play a role in non-acute settings such as in cancer cachexia, the relative difference in muscle mass between sequential CT scans may be limited, even in patients with cancer cachexia [23]. It may be interesting to establish the margin of error of sequential measurements of muscle mass using CT scans to identify the precision error or least significant change between sequential CT scans. The use of sequential ultrasound studies to quantify muscle loss in critical illness also yields a substantial number of patients with apparent muscle growth [24]. Whether this is due to fluid accumulation or due to the inherent reproducibility of this operator dependent imaging modality remains to be determined.

Reference values for visceral obesity using Computed Tomography

Visceral obesity is associated with the metabolic syndrome and an increased risk for morbidity and mortality [25]. However, in apparent contrast, there is also research that indicates that septic patients with a higher BMI have a better survival than patients with a normal BMI [26]. However, this observation that has been referred to as "the obesity paradox" is not uniformly reproduced in subsequent studies and its existence is subject to debate [27]. It has been argued that some of the discrepant conclusions of studies is due to the use of BMI to define obesity. However, there may be a discrepancy between BMI and visceral fat mass, particularly in men [28]. Given the association between visceral obesity and the metabolic syndrome we hypothesized that visceral obesity rather than BMI affects outcome following critical illness. However, as outlined above, we consider it desirable to use external reference values in body composition research in critically ill patients. At the time of study design, such reference values were not at hand. Therefore, we aimed to develop gender specific cut-off values of visceral adipose tissue that are associated with an increased metabolic risk.

In chapter 4 we describe the development of gender specific reference values for visceral obesity in a Caucasian population. Visceral adipose tissue area indices (VATI) at the level of L3 were analyzed using CT scans of 416 healthy kidney donor candidates. We used the prescription of antihypertensive drugs and/or statins as a readout for increased metabolic risk. Using Receiver Operating Characteristic (ROC) curve, gender specific cut-off values for VATI to identify people with an increased metabolic risk with a sensitivity ≥80% was calculated. To compare the capability of VATI to predict metabolic risk with that of Body Mass Index (BMI),

additional ROC analyses were performed using BMI as discrimination threshold. The area under the curve of the ROC analysis (AUC) was used as measure for overall prediction quality.

This study revealed that a VATI of ≥ 38.7 cm^2/m^2 for males and ≥ 24.9 cm^2/m^2 for females indicated an increased metabolic risk and can be used as a reference value for visceral obesity on computed tomography scans. This study also showed that visceral adipose tissue is a better predictor for metabolic risk than BMI for both genders. However, further validation in other cohorts, for example including patients with diabetes and other (inter)national Caucasian cohorts is needed.

The influence of visceral obesity on hospital mortality in critical illness

As described before, we hypothesized that visceral obesity, rather than BMI is associated with clinical outcome in critical illness. Therefore, in chapter 5 we investigated the association of both visceral obesity and BMI with 90 day mortality. In a cohort of 555 mixed critically ill patients, we measured visceral adipose tissue using Computed Tomography scans on the level of vertebra L3. We used reference values from an otherwise healthy Caucasian cohort to determine the presence or absence of visceral obesity and defined BMI categories according to the definition of the World Health Organization. We investigated the effect of visceral obesity on mortality during 90 days following ICU admission using logistic regression analysis. Odds ratios were adjusted for factors that may influence mortality such as age, gender, disease severity using APACHE II score, the presence of sarcopenia and muscle quality. For the assessment of the association between BMI and mortality we used the same variables.

We found a prevalence of visceral obesity of 48% in all patients with a similar distribution amongst males and females. There was no significant association between visceral obesity and mortality in the present cohort. After correction for possible confounders, the odds ratio for 90-day mortality showed even a non-significant association towards a better outcome. This non-significant association towards a better outcome was also seen in patients with overweight or obesity compared to patients with a normal weight.

We concluded that both the presence or absence of visceral obesity measured using CT scans and defined using sex specific reference values of the general population as BMI was not associated with increased mortality in critical illness. However, given the non-significant trend towards better outcome in patients with visceral obesity, these results do not fully exclude the existence of the obesity paradox. It therefore seems indicated to explore the association

between visceral obesity and clinical outcome in critical illness in more well-defined or even prospective cohorts.

Conclusion and future research

Outcome prediction in critical illness is a holy grail and reliable prediction instruments may help during consideration of an ICU admission of high-risk patients and in advance care planning. Unfortunately, the predictive value of currently available prediction tools is limited and frequently patients are given the benefit of the doubt, which results in futile ICU admissions in more than 60% of the patients that are considered to be at "high risk" [29].

Body composition, particularly sarcopenia is associated with poor outcome, although the causality is uncertain. Moreover, traditional physiological scoring systems such as APACHE and SOFA are still unsurpassed in predictive power.

There is currently increasing recognition of the power of artificial intelligence and machine learning to develop decision support tools that predict the clinical course after ICU admission. Particularly tools that assess "discharge readiness" are clinically tested [30]. It is to be expected that in the future such decision support tools may be developed that also can predict the adverse outcome of an ICU admission with acceptable reliability. To be able to take body composition into account in the development of these tools it is important to create a large body of high quality and comparable data on the association of body composition and outcome. To this end it is important to use standardized grouping definitions and outcome measures in future research. In addition, this facilitates the comparability of studies and helps to increase the understanding of mechanisms underlying the association between specific body types and clinical outcome.

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7

Samenvatting en algemene discussie

Samenvatting en algemene discussie

De meeste patiënten op de Intensive Care lijden aan een levensbedreigende functiestoornis van een of meer vitale organen [1]. Een IC-opname kan zowel op korte als op lange termijn een grote impact hebben op de fysieke, cognitieve en mentale gesteldheid van patiënten en hun naasten [2, 3]. Omdat de onzekerheid over de prognose stress veroorzaakt en vanwege de grote maatschappelijke impact van vergeefse IC opnames [4] is er behoefte aan een methode om de prognose van ernstig zieke patiënten betrouwbaar te kunnen voorspellen. Traditionele risico voorspellers zijn gebaseerd op orgaanfunctie en fysiologische parameters [5, 6]. De afgelopen jaren komt er echter steeds meer belangstelling voor de relatie tussen lichaamssamenstelling en uitkomst bij kritiek zieke patiënten [7-9]. Op dit moment zijn er vooral observationele data beschikbaar die de associatie tussen lichaamstype en uitkomst in kritieke ziekte beschrijven [10], het is echter grotendeels onbekend of deze associaties causale verbanden weergeven. Tot nu toe is er weinig aandacht besteed aan de pathofysiologische processen die deze associaties beïnvloeden [11], bovendien is de vergelijkbaarheid van studies naar lichaamssamenstelling in kritieke ziekte beperkt. Dit komt doordat er geen gestandaardiseerde definities zijn gebruikt van afwijkende lichaamstypes en doordat gestandaardiseerde uitkomstmaten ontbreken [12]. Voordat lichaamssamenstelling eventueel in de kliniek gebruikt kan worden om te beoordelen of patiënten in aanmerking komen voor IC opname, of voordat het gebruikt kan worden als therapeutisch doel, is het belangrijk dat er meer kennis komt over de relatie tussen lichaamssamenstelling en uitkomst bij IC patiënten.

Het doel van dit proefschrift was het bestuderen van epidemiologische en methodologische aspecten van lichaamssamenstelling bij ernstig zieke patiënten. In hoofdstuk 1 wordt de achtergrond van het proefschrift besproken en de kennis lacunes die er waren ten tijde van de start van dit promotieonderzoek. Hoofdstuk 2 en 5 bieden nieuwe inzichten in de associatie tussen skeletspierweefsel en klinische uitkomst (hoofdstuk 2) en de associatie tussen visceraal vetweefsel en klinische uitkomst (hoofdstuk 5) in kritiek zieke patiënten. Hoofdstuk 3 en 4 bespreken methodologische aspecten van het meten van spierverlies (hoofdstuk 3) en het meten van viscerale obesitas (hoofdstuk 4).

Hoofdstuk 3 richt zich op de betrouwbaarheid van Computed Tomography (CT) scans voor het kwantificeren van spierverlies in kritiek zieke patiënten. Hierbij hebben wij met name de invloed van oedeemvorming op het meten van spieroppervlakte met behulp van opeenvolgende CT scans in de acute fase van kritieke ziekte onderzocht. In hoofdstuk 4 hebben we getracht bij te dragen aan standaardisatie van onderzoek naar lichaamssamenstelling door geslacht

specifieke referentiewaarden voor viscerale obesitas gemeten met CT scans voor te stellen, gebaseerd op metabole risicoprofielen in de westerse populatie. In hoofdstuk 5 hebben we deze voorgestelde referentiewaarden gebruikt om de associatie tussen viscerale obesitas en ziekenhuissterfte bij intensive care patiënten te onderzoeken.

Sarcopenie: een oorzaak of een indicator voor hogere ziekenhuissterfte bij kritiek zieke patiënten?

Eerder onderzoek laat zien dat een lage spiermassa in een heterogene groep Intensive Care patiënten is geassocieerd met een verhoogde mortaliteit. [7-9]. De mogelijke causaliteit van deze associatie is echter nauwelijks onderzocht. Bovendien worden in studies verschillende definities van een lage spiermassa gebruikt, gebaseerd op de verdeling van spiermassa binnen het onderzochte cohort.

In hoofdstuk 2 hebben we een relatief homogene groep van 155 patiënten met abdominale sepsis retrospectief geanalyseerd. De spieroppervlakte werd gemeten door middel van CT scans ter hoogte van wervel L3. De spieroppervlakte werd gecorrigeerd voor lichaamslengte door de oppervlakte te delen door de lichaamslengte (Skeletal Muscle Index, SMI). Sarcopenie werd gedefinieerd als een SMI onder het 5e percentiel van de algemene bevolking [13]. We onderzochten de associatie tussen sarcopenie en ziekenhuissterfte door middel van univariabele en multivariabele analyses, waarbij werd gecorrigeerd voor leeftijd en comorbiditeiten die gepaard gaan met spierverlies zoals chronische nierinsufficiëntie, chronische cardiovasculaire insufficiëntie, COPD en kanker.

Univariabele analyse liet zien dat de prevalentie van sarcopenie hoger was in patiënten die niet overleefden tot ziekenhuisontslag, wat overeenkomt met eerdere bevindingen [7-9]. Echter, het bleek dat deze associatie werd beïnvloed door de aanwezigheid van chronische nierinsufficiëntie en kanker. Dit waren onafhankelijke risicofactoren voor ziekenhuissterfte bij patiënten met abdominale sepsis, terwijl sarcopenie dat niet was. We vonden geen associatie tussen spierkwaliteit, gemeten door middel van de radiation attenuation (RA), en ziekenhuismortaliteit. We concludeerden dat bij patiënten met abdominale sepsis sarcopenie waarschijnlijk een marker is voor ziekte in plaats van een directe oorzaak voor een hogere ziekhuissterfte.

De bevindingen in dit onderzoek benadrukken dat het in toekomstig onderzoek belangrijk is om rekening te houden met factoren die geassocieerd zijn met spierverlies. Dergelijke factoren kunnen ook aanwezig zijn bij onderzoek in andere vakgebieden, zoals bij de oncologie.

Sugimoto et al vonden een significante associatie tussen sarcopenie en een verminderd recidief vrije en totale overleving bij patiënten met een pancreascarcinoom. [14]. Hoewel er gecorrigeerd werd voor tumorgrootte en -uitbreiding, is het niet duidelijk of deze gevonden associatie een oorzakelijk verband weergeeft, of dat de sarcopenie een marker was van (microscopisch) gevorderde ziekte [15].

Het is belangrijk om de robuustheid van de resultaten uit retrospectief epidemiologisch onderzoek te evalueren in andere (prospectieve) databases [16]. Om reproduceerbaarheid en externe validatie mogelijk te maken zijn universeel toepasbare referentiewaarden noodzakelijk. Wij hebben gebruikt gemaakt van een afkapwaarde voor sarcopenie, welke bepaald is bij gezonde, levende nierdonoren [13]. We vonden dat deze externe referentiewaarde een betere voorspeller was voor ziekenhuismortaliteit dan een interne referentiewaarde uit het bestudeerde cohort. Hoewel deze observatie het gebruik van externe referentiewaarden lijkt te ondersteunen, dienen deze bevindingen nog wel in andere cohorten gevalideerd te worden.

De betrouwbaarheid van het meten van spierverlies tijdens kritieke ziekte

Tijdens de acute fase van kritieke ziekte lijden patiënten aan spierverlies [17]. In theorie kan spierverlies worden gekwantificeerd door sequentiële beeldvorming met behulp van echografie [17, 18] of CT-scans [19]. We hebben onderzocht of opeenvolgende CT scans gebruikt kunnen worden om spierverlies tijdens IC opname te meten. Dit is belangrijk omdat dit een mogelijkheid zou kunnen bieden om retrospectieve analyses van grote cohorten te verrichten waarbij sequentiële CT scans zijn gemaakt voor klinische doeleinden. Echter, in de acute fase van kritieke ziekte ontwikkelen patiënten gegeneraliseerd oedeem wat wordt veroorzaakt door capillaire lekkage [20]. Capillaire lekkage is een kenmerk van bijvoorbeeld sepsis en wordt verergerd door de grote hoeveelheid intraveneuze vloeistoffen die worden toegediend om een adequate bloeddruk te behouden [21]. Onze hypothese was dat oedeemvorming in weefsels en in het bijzonder spierweefsel, het meten van spierverlies door middel van sequentiële CT scans beïnvloedt.

In hoofdstuk 3 hebben we veranderingen in de SMI onderzocht met behulp van sequentiële CT scans ter hoogte van wervel L3 bij 77 patiënten met abdominale sepsis. De hoeveelheid oedeem werd beoordeeld door twee onafhankelijke onderzoekers en gescoord als (1) geen/minimaal oedeem, (2) matig oedeem en (3) ernstig oedeem en de verandering in oedeem tussen de sequentiële CT scans werd berekend. Daarnaast hebben we de radiation attenuation van spieren onderzocht wat wordt beschouwd als maat voor de spierkwaliteit [22]. De radiation attenuation kan dalen door zowel vet- als vloeistofinfiltratie in de weefsels. Tot slot

bestudeerden we de associatie tussen veranderingen in SMI en radiation attenuation, oedeem en ziekte ernst met behulp van de maximale Sequential Organ Failure Assessment (SOFA)-score.

Dit onderzoek liet zien dat SMI gemiddeld met 0.35% afnam. Echter, in 41.6% van de populatie werd een toename van SMI gemeten. Omdat het fysiologisch gezien zeer onwaarschijnlijk is dat deze observatie het gevolg was van spieranabolisme tijdens IC opname, hebben we de associatie tussen veranderingen in SMI en veranderingen in oedeem bestudeerd. We vonden dat een toename van SMI significant geassocieerd was met verhoogde oedeemvorming. Het was opvallend dat de vorming van oedeem ook significant geassocieerd was met een hogere maximale SOFA-score, wat wijst op ernstigere ziekte. De skeletspier radiation attenuation nam af tijdens kritieke ziekte, maar was niet significant geassocieerd met veranderingen in SMI of veranderingen in oedeem. Aangezien zowel oedeem als vetinfiltratie skeletspier radiation attenuation kunnen beïnvloeden, zijn de afzonderlijke effecten van deze factoren op de gemeten spierkwaliteit moeilijk te onderscheiden.

Concluderend vonden we dat het meten van spierverlies met behulp van CT scans tijdens kritieke ziekte beïnvloed wordt door de vorming van oedeem. Oedeem tijdens kritieke ziekte leidt tot een overschatting van de spieroppervlakte gemeten met CT-scans. De toename van oedeem was geassocieerd met een hogere SOFA-score, wat wijst op een hogere ziekte-ernst. Onderzoekers moeten zich bewust zijn van dit fenomeen en voorzichtig zijn bij de interpretatie van de resultaten wanneer abdominale CT scans gebruikt worden om veranderingen in spiermassa en spierkwaliteit te onderzoeken.

In niet acute situaties zoals bij kanker waar oedeemvorming geen rol speelt kan het relatieve verschil in spiermassa tussen opeenvolgende CT scans beperkt zijn [23]. De daadwerkelijke nauwkeurigheid van de meting van spieroppervlakte met CT-scans is nog niet vastgesteld. Om de betrouwbaarheid van de metingen van dergelijke kleine verschillen te kunnen bepalen, zou het interessant zijn om de foutmarge te onderzoeken. Het gebruik van sequentiële echografie om spierverlies tijdens kritieke ziekte te kwantificeren laat ook een aanzienlijk aantal patiënten zien met spiertoename [24]. Of dit wordt veroorzaakt door oedeemvorming of door verminderde reproduceerbaarheid bij deze onderzoeker afhankelijke techniek moet verder worden onderzocht.

Referentiewaarden voor het bepalen van viscerale obesitas met behulp van CT scans

Viscerale obesitas wordt geassocieerd met het metabool syndroom en een verhoogd risico op morbiditeit en mortaliteit [25]. Echter, er is ook onderzoek dat laat zien dat septische patiënten met een hogere BMI een betere overleving hebben dan patiënten met een normale BMI [26]. Deze observatie wordt ook wel "de obesitas paradox" genoemd. Gezien dit niet eenduidig in latere studies gereproduceerd kan worden blijft het bestaan ervan een onderwerp van discussie [27]. Mogelijk worden deze tegenstrijdige conclusies veroorzaakt doordat er gebruik is gemaakt van BMI om obesitas te definiëren. Er kan echter, vooral bij mannen, een discrepantie zijn tussen BMI en de hoeveelheid visceraal vet [28]. Aangezien met name viscerale obesitas is geassocieerd met het metabool syndroom was onze hypothese dat met name viscerale obesitas in plaats van BMI de uitkomst bij ernstig zieke patiënten bepaald. Zoals hierboven beschreven is het belangrijk om externe referentiewaarden gebruiken in onderzoek naar lichaamssamenstelling bij intensive care patiënten. Deze referentiewaarden waren echter niet beschikbaar. Daarom was ons doel om genderspecifieke afkapwaarden te maken voor visceraal vetweefsel gebaseerd op een verhoogd metabool risico.

In hoofdstuk 4 hebben we genderspecifieke referentie waarden voor viscerale obesitas in een westerse populatie onderzocht. De oppervlakte index van de hoeveelheid visceraal vetweefsel (VATI) op het niveau van wervel L3 werd geanalyseerd met behulp van CT-scans van 416 gezonde potentiële levende nierdonoren. Hierbij werden het gebruik van antihypertensiva en/of statines als indicatie voor een verhoogd metabool risico gebruikt. Met behulp van Receiver Operation Characteristic (ROC) curves werden met een sensitiviteit van ≥80% geslachtsspecifieke afkapwaarden voor VATI voor een verhoogd metabool risico bepaald. Daarnaast werden er aanvullende ROC-analyses uitgevoerd met Body Mass Index (BMI) om het voorspellend vermogen van VATI met BMI op het metabool risico te vergelijken. De oppervlakte onder de curve (AUC) van de ROC analyse werd gebruik als maat voor de kwaliteit van de voorspelling.

In dit onderzoek kwam naar voren dat een VATI waarde van ≥ 38,7 cm^2/m^2 voor mannen en ≥ 24,9 cm^2/m^2 voor vrouwen wijst op een verhoogd metabool risico en kan worden gebruikt als referentiewaarde voor het bepalen van viscerale obesitas op CT scans. Dit onderzoek liet ook zien dat voor zowel mannen als vrouwen viscerale obesitas een betere voorspeller is voor metabool risico dan BMI. Het is echter belangrijk om deze referentiewaarden in andere cohorten te valideren zoals bijvoorbeeld bij patiënten met diabetes en andere (inter)nationale westerse cohorten.

De invloed van viscerale obesitas op ziekenhuissterfte bij ernstig zieke patiënten

Zoals hierboven beschreven veronderstelden wij dat viscerale obesitas in plaats van BMI geassocieerd is met klinische uitkomst bij intensive care patiënten. Daarom hebben wij in hoofdstuk 5 de associatie tussen zowel viscerale obesitas als BMI op 90 dagen mortaliteit onderzocht. In een heterogeen cohort van 555 intensive care patiënten hebben we visceraal vet gemeten met behulp van CT scans ter hoogte van wervel L3. Om de aanwezigheid van viscerale obesitas te bepalen hebben wij referentiewaarden gebruikt van een gezond westers cohort en voor BMI hebben we gebruik gemaakt van de BMI categorieën van de wereld gezondheid organisatie. Het effect van viscerale obesitas op mortaliteit gedurende de eerste 90 dagen vanaf IC opname hebben we onderzocht door middel van logistische regressie analyse. Odds ratio's werden gecorrigeerd voor factoren die mortaliteit kunnen beïnvloeden zoals leeftijd, geslacht, ernst van ziekte volgens de APACHE II score, de aanwezigheid van sarcopenie en spierkwaliteit. Om de associatie tussen BMI en mortaliteit te onderzoeken werden dezelfde variabelen gebruikt.

In het onderzochte cohort vonden we een prevalentie van viscerale obesitas van 48%, waarbij de verdeling tussen mannen en vrouwen gelijk was. Er was geen significante associatie tussen viscerale obesitas en mortaliteit in het huidige cohort. Na correctie voor mogelijke beïnvloedende factoren liet de odds ratio voor 90 dagen mortaliteit zelfs een niet significante associatie tussen obesitas en klinische uitkomst zien. Deze niet significante associatie met een betere uitkomst werd ook waargenomen bij patiënten met overgewicht of obesitas vergeleken met patiënten met een normaal gewicht.

Hieruit kunnen we concluderen dat zowel de aanwezigheid als afwezigheid van viscerale obesitas, gemeten met CT scans en gedefinieerd volgens geslacht specifieke referentiewaarden uit de algemene populatie, als BMI niet waren geassocieerd met verhoogde mortaliteit bij kritiek zieke patiënten. Echter, gezien de niet significante trend naar betere uitkomst bij patiënten met viscerale obesitas, kan het bestaan van de obesitas paradox niet worden uitgesloten. Daarom is het belangrijk om de associatie tussen viscerale obesitas en klinische uitkomst bij kritiek zieke patiënten verder te onderzoeken in meer gedefinieerde of prospectieve cohorten.

Conclusie en toekomstig onderzoek

Het voorspellen van de uitkomst bij IC patiënten is zeer belangrijk en betrouwbare middelen om dit te voorspellen kunnen helpen bij de overwegingen om hoog risico patiënten wel of niet op de IC op te nemen en in het maken van beleidsbeperkende afspraken. Helaas is de voorspellende waarde van de momenteel beschikbare middelen beperkt. Vaak wordt patiënten

het voordeel van de twijfel gegeven wat ervoor zorgt dat in meer dan 60% van de opgenomen high risk patiënten IC opname tevergeefs is [29].

Lichaamssamenstelling en in het bijzonder sarcopenie is geassocieerd met slechte uitkomsten, echter de oorzaak hiervan is niet geheel bekend. Daarnaast zijn traditionele fysiologische scores zoals de APACHE en SOFA score nog niet overtroffen in voorspellende waarde.

Momenteel is er steeds meer belangstelling om met behulp van kunstmatige intelligentie en machine learning tools te ontwikkelen die kunnen helpen met het voorspellen van het klinisch beloop na IC opname en daarmee te helpen met het maken van beslissingen. Met name hulpmiddelen die beoordelen of patiënten klaar zijn voor ontslag, zijn klinisch getest [30]. Het is de verwachting dat er in de toekomst tools ontwikkeld worden die een ongunstige uitkomst van IC opname betrouwbaar kunnen voorspellen. Om lichaamssamenstelling mee te nemen in de ontwikkeling van deze tools is het belangrijk om een grote hoeveelheid hoogwaardige data over de associatie tussen lichaamssamenstelling en uitkomst te verzamelen. Daarom is het belangrijk om in toekomstig onderzoek gestandaardiseerde definities en uitkomstmaten te gebruiken. Bovendien vergroot dit de vergelijkbaarheid van onderzoeken en helpt het om de mechanismen die ten grondslag liggen aan de associatie tussen specifieke lichaamstypes en klinische uitkomst beter te begrijpen.

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Impact of the research

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Impact of critical illness

Every year more than 76.000 patients are admitted to Dutch ICU's. With a minimum cost of €2500 per admission, the total costs of Intensive Care Medicine exceeds 200 million euros. The in-hospital mortality of this entire population is 13% and from this it can be calculated that every day more than 25 patients die in Dutch hospitals after an ICU admission. An ICU admission is often associated with discomfort, pain and anxiety for the patient and emotional distress for the patient's relatives. For many relatives it is extra difficult to cope with this distress when the ICU admission has an adverse outcome and "all the suffering has been in vain". The aim of this thesis was to study the association between (changes in) body composition and outcome in critical illness and to provide the scientific field with new data and new tools that may advance the use of body composition analysis in the outcome prediction of patients with critical illness.

Associations and causal relations

In chapter 2 we confirmed previous observations that sarcopenia on ICU admission is associated with an increased hospital mortality. However, our research shows that this association is primarily determined by co-morbidities that are known to be associated with both muscle loss and high mortality, such as chronic renal insufficiency and cancer. Therefore, we concluded that, in our cohort, sarcopenia is not an independent risk factor for hospital mortality in critical illness. These findings underline the importance of carefully addressing confounding factors when studying the association between muscle mass and disease outcome. To improve pathophysiological and prognostic knowledge it is important to study associations between risk factors and outcome. In many cases specific risk factors are studied because a causal relation is presumed. Appealing hypotheses of causal relationships are often rapidly and broadly embraced and disseminated as without further challenging the actual causality of an association. Our findings remind researchers to keep challenging and deepen existing hypotheses, even if these are based on a plausible (patho)physiological background.

Reliability of sequential body composition analysis

Analysis of CT images at the level of vertebra L3 is an established method to determine muscle mass, muscle quality and fat mass. The interobserver agreement of the analysis of a single image is excellent. However, the coefficient of variation of a tissue area measured by CT is actually unknown. Sequential CT-scans are increasingly used to quantify changes in body composition over a period of time. In chapter 3 we observed a considerable spread in the measured changes in muscle area between individual patients over a relative short period

of time. Although this spread can be explained (partly) by pathophysiological variation, the question arises whether other physiological source of variation such as intestinal air content or even non-physiological sources of variation such as the position of a patient in the scanner affect the reliability of sequential CT scans for body composition analysis. Before sequential CT scans are widely implemented in body composition research, the coefficient of variation of sequential CT scans should be clarified. It can be conceived that changes in body composition can only be reliably measured when the coefficient of variation is much lower than the relative changes in tissue areas. It is also conceivable that edema affects point measurements of tissue areas in critically ill patients. To what extent this affects the interpretation of body composition remains to be seen.

Standardization of research methods

There is increasing awareness of the importance of standardization in clinical research. Standardization facilitates comparability and reproducibility of the results of different studies. Also, in the view of the growing importance of meta-analyses and in view of the advent of machine learning and other artificial intelligence tools standardization of methods and outcome parameters is important. In clinical research standardized core outcome sets are increasingly advocated and used. In order to optimally integrate the knowledge on the role of body composition in health and disease, yielded by different studies, it is important to develop generally accepted definitions and reference values. In chapter 3, we showed that the use of external reference values for sarcopenia leads to more accurate grouping and more robust conclusions than the use of reference values that are relative to a cohort under study. This probably holds true for many other epidemiological studies where the grouping factor has a skewed distribution within the studied cohort. In chapter 4 we propose a method to determine external reference values for visceral obesity measured using CT scans, these findings need to be validated but encourage the scientific field to take a further step towards standardization of definitions of advert body types. In chapter 5 we have used these reference values to study the association between visceral obesity and outcome in critical illness. We found no statistically significant association between visceral obesity and outcome following ICU admission. However, the results neither rule out the existence of the obesity paradox which states that (mild) obesity is protective in critical illness. These findings still warrant further investigation and validation in larger and more defined populations. In addition, pathophysiological explanations pointing at a possible causal relation between obesity and better outcome after critical illness should be investigated.

Appendices

Abbreviations

List of publications

Dankwoord

About the author

Abbreviations

APACHE	Acute Physiology and Chronic Health Evaluation
AUC	Area Under the Curve
BMI	Body Mass Index
CI	Confidence Interval
CT	Computed Tomography
HR	Hazard Ratio
HU	Hounsfield Unit
IC	Intensive Care
ICU	Intensive Care Unit
IQR	Inter Quartile Range
L3	Lumbar vertebra 3
OR	Odds Ratio
RA	Radiation Attenuation
ROC	Receiver Operating Characteristic
SAT	Subcutaneous Adipose Tissue
SATI	Subcutaneous Adipose Tissue Index
SD	Standard deviation
SMA	Skeletal Muscle Area
SMI	Skeletal Muscle Area Index
SOFA	Sequential Organ Failure Assessment
VAT	Visceral Adipose Tissue
VATI	Visceral Adipose Tissue Index

List of publications

Van Gassel RJJ, **Baggerman MR,** van de Poll MCG. Metabolic aspects of muscle wasting during critical illness. *Curr Opin Clin Nutr Metab Care. 2020 Mar;23(2):96-101.*

Baggerman MR, van Dijk DPJ, Winkens B, van Gassel RJJ, Bol ME, Schnabel RM, Bakers FC, Olde Damink SWM, van de Poll MCG. Muscle wasting associated co-morbidities, rather than sarcopenia are risk factors for hospital mortality in critical illness. *J Crit Care. 2020 Apr;56:31-36.*

Baggerman MR, van Dijk DPJ, Winkens B, van Gassel RJJ, Bakers FC, Bol ME, Schnabel RM, Olde Damink SWM, van de Poll MCG. Edema in critically ill patients leads to overestimation of skeletal muscle mass measurements using Computed Tomography scans. *Nutrition. 2021 Sep;89:111238.*

Baggerman MR, Dekker IM, Winkens B, Olde Damink SWM, Weijs PJM, van de Poll MCG. Computed tomography reference values for visceral obesity and increased metabolic risk in a Caucasian cohort. *Clin Nutr ESPEN. 2022 Apr;48:408-413.*

Baggerman MR, Dekker IM, Winkens B, Olde Damink SWM, Stapel SN, Weijs PJM, van de Poll MCG. Visceral obesity measured using Computed Tomography scans: no significant association with mortality in critically ill patients. *J Crit Care. 2023 Apr 26;77:154316.*

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About the author

Michelle Roanne Baggerman was born on 29th of March 1990 in Haarlem. She graduated from secondary school at Ichthus Lyceum in Driehuis. Thereafter she followed additional courses at Luzac College in Haarlem. From 2010-2011 she studied Health and Life sciences at VU University in Amsterdam. In 2011 she was selected to study Medicine at Maastricht University.

Her interest in scientific research started in 2015 during her first internship on the Intensive Care department of the Maastricht University Medical Center, where she started with research besides her medicine master. With the current research project she started in 2017 in which year she also graduated as medical doctor.

Because of her broad interest also in the organizational side of healthcare, she completed after her master in medicine a second master degree in Healthcare policy, Innovation and Management at Maastricht University in the year 2018. For her master thesis she conducted research at Spoedpost Zuid Kennemerland and the Emergency Department of the Spaarne Gasthuis hospital in Haarlem. In this hospital she worked for more than 10 years besides her study. First at the outpatient clinic and thereafter she graduated and worked as Triagist at the Emergency Department.

After obtaining her master in medicine and master in healthcare management she worked from 2018-2019 a year fulltime as researcher on the Intensive Care of the Maastricht University Medical Center. She continued with research besides her work as medical doctor in the Laurentius hospital in Roermond from 2019-2021 where she worked on the Intensive Care Unit and the Emergency Department during the COVID19 pandemic.

In 2022 she moved to Rotterdam and followed her career as Resident Anesthesiology in the Erasmus University Medical Center and Ikazia hospital in Rotterdam. In the meanwhile she completed her PhD trajectory.