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## FULL PAPER

# Visceral to subcutaneous fat ratio predicts short-term mortality in patients with Covid 19. A multicenter study

<sup>1</sup>ALEXEY SUROV, MD, <sup>2</sup>MAXIMILIAN THORMANN, MD, <sup>2</sup>HAKAN KARDAS, MD, <sup>2</sup>MATTES HINNERICHs, MD, <sup>2</sup>JAZAN OMARI, MD, <sup>3</sup>EDA CINGÖZ, MD, <sup>4</sup>MEHMET CINGÖZ, MD, <sup>3</sup>MEMDUH DURSUN, MD, <sup>5</sup>İNAN KORMAZ, MD, <sup>5</sup>ÇAĞRI ORHAN, MD, <sup>6</sup>ÖMER YILDIZ, MD, <sup>6</sup>ELIF HOC AOĞLU, MD, <sup>6</sup>ERCAN INCI, MD, <sup>7</sup>HAKAN ÖNDER, MD, <sup>7</sup>HAMDULLAH ERK, MD, <sup>8</sup>OU GKOUR CHOUSEIN, MD, <sup>8</sup>HADI SASANI, MD, <sup>8</sup>KORCAN AYSUN GÖNEN, MD, <sup>2</sup>MACIEJ PECH, MD and <sup>9</sup>ANDREAS WIENKE, PhD

<sup>1</sup>Department of Radiology,, Neuroradiology and Nuclear Medicine, Johannes Wesling University Hospital, Ruhr University Bochum, Bochum, Germany

<sup>2</sup>Clinic for Radiology and Nuclear Medicine, University Hospital Magdeburg, Magdeburg, Germany

<sup>3</sup>Istanbul Medical Faculty Radiology Department, Istanbul University, Istanbul, Turkey

<sup>4</sup>Department of Radiology, Istanbul Cam and Sakura City Hospital, Istanbul, Turkey

<sup>5</sup>Department of Radiology, Hatay Mustafa Kemal University, Antakya, Hatay, Turkey

<sup>6</sup>Radiology Department, University of Health Sciences, Bakirkoy Dr. Sadi Konuk Research and Training Hospital, Bakirkoy, Istanbul, Turkey

<sup>7</sup>Radiology Department, Health Science University, Prof. Dr. Cemil Tascioğlu City Hospital, Istanbul, Turkey

<sup>8</sup>Department of Radiology, Tekirdag Namik Kemal University, Tekirdag, Turkey

<sup>9</sup>Institute of Medical Epidemiology, Biometry, and Informatics, Martin- Luther- University, Halle-Wittenberg, Germany

Address correspondence to: Maximilian Thormann

E-mail: [maximilian.thormann@med.ovgu.de](mailto:maximilian.thormann@med.ovgu.de)

**Objective:** To evaluate the association of body composition parameters with outcomes in Covid-19.

**Methods:** 173 patients hospitalized for Covid-19 infection in 6 European centers were included in this retrospective study. Measurements were performed at L3-level and comprised skeletal muscle index (SMI), muscle density (MD), and adipose tissue measurements [visceral adipose tissue (VAT), subcutaneous adipose tissue (SAT), intramuscular adipose tissue (IMAT), visceral-to-subcutaneous-adipose-tissue-area-ratio (VSR)]. The association with mortality, the need for intubation (MV), and the need for admission to ICU within 30 days were evaluated.

**Results:** Higher SAT density was associated with a greater risk of MV (OR = 1.071, 95%CI=(1.034;1.110),  $p < 0.001$ ). Higher VAT density was associated with admission to ICU (OR = 1.068, 95%CI=(1.029;1.109),  $p <$

0.001). Higher MD was a protective factor for MV and ICU admission (OR = 0.914, 95%CI=(0.870;0.960),  $p < 0.001$ ; OR = 0.882, 95%CI=(0.832;0.934),  $p = 0.028$ ). Higher VSR was associated with mortality (OR = 2.147, 95%CI=(1.022;4.512),  $p = 0.044$ ). Male sex showed the strongest influence on the risk of ICU admission and MV. SMI was not associated with either parameter.

**Conclusion:** In patients hospitalized for Covid-19 infection, higher VSR seems to be a strong prognostic factor of short-term mortality. Weak associations with clinical course were found for MD and adipose tissue measurements. Male sex was the strongest prognostic factor of adverse clinical course.

**Advances in knowledge:** VSR is a prognostic biomarker for 30-day mortality in patients hospitalized for Covid-19 disease.

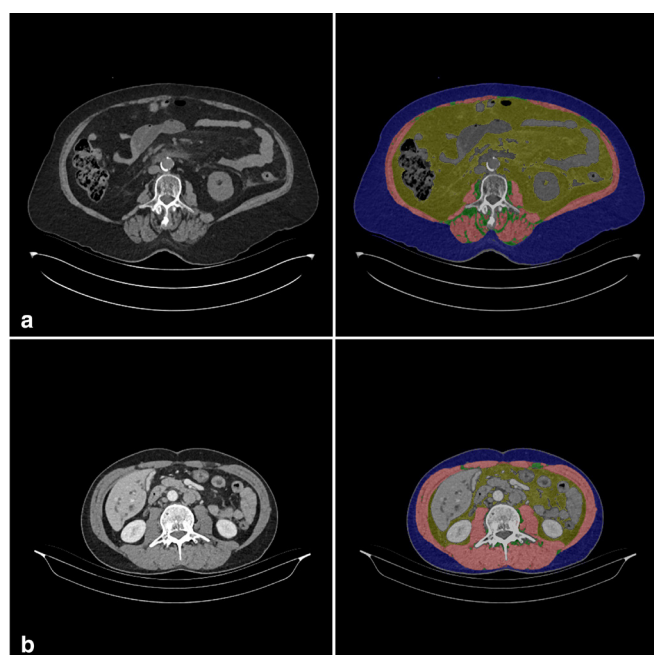
## INTRODUCTION

In coronavirus 2019 disease (Covid-19), body composition parameters are increasingly emerging as risk factors for clinical course and mortality.<sup>1-4</sup> Obesity and increased abdominal adipose tissue have been shown to be associated with severe clinical disease and mortality.<sup>1,5</sup> Likewise, low skeletal muscle mass, in clinical routine used as a surrogate marker for sarcopenia, seems to influence patient outcome.<sup>6,7</sup> However, the data on the role of body

composition are still mixed and results are contradictory, with other studies not finding a relevant association.<sup>8-10</sup>

Given the ongoing nature of the pandemic, prognosis of clinical course and mortality in Covid-19 disease remains essential. Age and sex are already established prognostic markers for Covid-19 patients and associated with mortality.<sup>11,12</sup> At the same time, standardized parameters that allow for better stratification are warranted. The use of CT-derived measurements of skeletal muscle and

Figure 1. Representative examples of abdominal CT scans with segmentation of skeletal muscle: intramuscular adipose tissue (green), visceral adipose tissue (yellow), subcutaneous adipose tissue (blue), skeletal muscle (red). (A) Patient 1 (female) had an SMA of 98.1 cm<sup>2</sup>, an SMI of 37.4 kg/cm<sup>2</sup>, a VAT of 314.2 cm<sup>2</sup>, and a VSR of 0.91 (1a). (B) Patient 2 (male) had a SMA of 140.3 cm<sup>2</sup>, an SMI of 46.4 kg/cm<sup>2</sup>, a VAT of 72.2 cm<sup>2</sup>, and a VSR of 0.72 (1b). SMA, skeletal muscle area; SMI, skeletal muscle index; VAT, visceral adipose tissue; VSR, visceral-to-subcutaneous adipose tissue area ratio.



abdominal fat tissue allows quantification of different body composition parameters in routine clinical use. For skeletal muscle mass, measurements of paraspinal, abdominal wall, and psoas muscles are usually performed at the L3 level.<sup>7</sup> For visceral adipose tissue measurements, the optimal level of measurement is not yet standardized.<sup>13</sup> Published studies have used different levels, both below and above the L3 level.

As fat depots are not distributed equally across the body and pose various cardiometabolic risks, different kind of fat tissues are usually evaluated. Fat tissue parameters like total adipose tissue (TAT), visceral adipose tissue (VAT), subcutaneous adipose tissue (SAT), and intramuscular adipose tissue (IMAT) have been associated with clinical course in different diseases.<sup>13–15</sup> Recently, it was shown that excess VAT, as expressed by the visceral-to-subcutaneous adipose tissue area ratio (VSR) was associated with the risk of ICU admission in Covid-19 patients.<sup>16</sup>

There is a paucity of studies assessing the association between a detailed set of standardized abdominal body composition parameters—including both muscle and adipose tissue measurements—and clinical outcomes and mortality in Covid-19 patients. The purpose of this study was therefore to determine the value of different body composition parameters to predict both Covid-19 severity (risk of ICU admission, invasive ventilation) and mortality within 30 days in a large multicenter cohort.

## METHODS

For the present study, data from the following six centers in Europe were retrospectively analyzed:

- Clinic for Radiology and Nuclear Medicine, University Hospital Magdeburg, Magdeburg, Germany ( $n = 25$ ).
- Istanbul Medical Faculty Radiology Department, Istanbul University, Istanbul, Turkey ( $n = 47$ ).
- Hatay Mustafa Kemal University, Faculty of Medicine, Department of Radiology, Antakya, Hatay, Turkey ( $n = 12$ ).
- Radiology Department, University of Health Sciences, Bakirkoy Dr Sadi Konuk Research and Training Hospital, Bakirkoy, Istanbul, Turkey ( $n = 23$ ).
- Radiology Department, Health Science University, Prof Dr Cemil Tascioğlu City Hospital, Istanbul, Turkey ( $n = 47$ ).
- Department of Radiology, Tekirdag Namik Kemal University, Tekirdag, Turkey ( $n = 19$ ).

Patients were identified from electronic hospital records from March 2020 to December 2021. The study was approved by the local ethic committees.

Inclusion criteria across all centers were:

- PCR confirmed Covid-19 disease.
- Hospitalization for symptoms or complications associated with Covid-19 disease.
- Available abdominal CT images with or without contrast medium injection.
- Available data regarding the following outcome variables: mechanical ventilation, admission to ICU, mortality within 30 days of admission.

Exclusion criteria were

- Missing clinical data.
- Hospitalization for other causes than Covid-19 disease.
- Missing abdominal CT scan on L3 level

The analyzed convenience sample comprised 173 patients, with 93 males and 80 females. Median age was 61 years (range 17–91).

## Measurement of body composition parameters

In all cases, the first opportunistic abdominal CT scan after hospital admission was used. Image analysis was standardized across all six centers. All body composition measurements were performed by two trained residents (with 2 and 3 years of experience, respectively) semi-automatically on axial images at the midsection of the third lumbar vertebra level (L3) in the soft tissue window (window of 45–250 HU) with the freely available ImageJ Software (v. 1.53, National Institute of Health, Bethesda, Maryland, USA) (Figure 1). Review of measurements and necessary corrections were performed by one experienced radiologist (MH, with 4 years of experience in muscle and fat demarcation) blinded to the clinical course of the patients. All measurements were performed on non-contrast images. The following parameters of body composition were estimated: skeletal muscle area (SMA), SAT, VAT, TAT, and IMAT were measured on cross-sectional images automatically by the software. The relative distribution of abdominal body fat was assessed by the VSR, which was calculated by dividing VAT by SAT. The skeletal muscle index (SMI) was calculated by dividing the SMA by the

patient’s height squared in cm. Adipose tissue indices were calculated in an analogous manner. Low skeletal muscle mass (LSMM) was defined as SMI <52.4 cm<sup>2</sup>/m<sup>2</sup> for males and <38.5 cm<sup>2</sup>/m<sup>2</sup> for females.<sup>17</sup> High VAT and high SAT were defined as an area >100 cm<sup>2</sup>. High VSR was defined as >1.1. Additionally, radiodensity of the analyzed body compartments was measured. Finally, fat-free mass (FFM) and fat mass (FM) were calculated using the following formulae<sup>18</sup> :

FFM (kg) = 0.30×[muscle L3 cross-sectional area] + 6.06;

FM (kg) = 0.042×[fat L3 cross-sectional area] + 11.2.

Statistical analysis

SPSS v. 25 was used for statistical analysis (IBM SPSS Statistics, NY). Mean and standard deviation as well as median and inter-quartile range (IQR) were calculated for continuous variables. Influence of body composition parameters on the risk of IMV, ICU admission, and mortality was assessed using logistic regression. Odds ratios are presented together with 95% confidence intervals (95% CI). The resulting *p*-values were interpreted in an exploratory sense.

RESULTS

Of the included patients, 52 were admitted to ICU, 46 required mechanical ventilation, and 33 patients died within the 30 day observation period.

Patients baseline characteristics and measurements of body composition parameters are summarized in Table 1.

30-day mortality

In univariable analysis, several body composition parameters were associated with mortality (Table 2). In multivariable analysis, IMAT, VSR, and VAT density showed a relevant influence on mortality. There was no association between SMI and mortality (Table 2).

Mechanical ventilation

Muscle density, SAT density, and BMI showed a relevant association with the risk of intubation. Male sex was also strongly associated with the risk of intubation. Neither adipose tissue parameter nor skeletal muscle parameter showed a relevant influence on the risk of intubation (Table 3).

ICU admission

In univariable analysis, numerous values of body compositions showed an influence on the risk of ICU admission (Table 4).

In multivariable analysis, muscle density, VAT density, SAT, and BMI were associated with the risk of ICU admission. Sex also showed a relevant influence (OR = 3.423, 95%CI=(1.294; 9.054), *p* = 0.013) (Table 4).

DISCUSSION

Our study indicates that higher VSR, IMAT and VAT density are prognostic factors of higher 30-day mortality when assessed on abdominal CT scans among patients hospitalized for Covid-19

Table 1. Baseline characteristics of included patients

| Variables           | Total N = 173                         |
|---------------------|---------------------------------------|
| Age, (range)        | 61 (17-91)                            |
| Male / female, n    | 93, 80                                |
| BMI                 | 27.4 kg/m <sup>2</sup>                |
| SMA                 | 118.2 cm <sup>2</sup>                 |
| SAT                 | 207.3 cm <sup>2</sup>                 |
| IMAT                | 15.6 cm <sup>2</sup>                  |
| VAT                 | 180.6 cm <sup>2</sup>                 |
| Muscle density      | 27.2 HU                               |
| SAT density         | −100.1 HU                             |
| IMAT density        | −61.5 HU                              |
| VAT density         | −90.1 HU                              |
| TAT                 | 419.6 cm <sup>2</sup>                 |
| SMI                 | 40.1 kg/cm <sup>2</sup>               |
| SATI                | 71.7 cm <sup>2</sup> /m <sup>2</sup>  |
| IMATI               | 5.4 cm <sup>2</sup> /m <sup>2</sup>   |
| VATI                | 59.2 cm <sup>2</sup> /m <sup>2</sup>  |
| TATI                | 141.3 cm <sup>2</sup> /m <sup>2</sup> |
| VSR                 | 0.81                                  |
| FFM                 | 41.5 kg                               |
| FM                  | 28.8 kg                               |
|                     |                                       |
| Low SMI, n          | 110 (63.6 %)                          |
| High VAT, n         | 136 (78.6 %)                          |
| High SAT, n         | 148 (85.5 %)                          |
| High VSR, n         | 48 (27.7 %)                           |
|                     |                                       |
| 30-day mortality, n | 33 (19.1 %)                           |
| 30-day IMV, n       | 46 (26.6 %)                           |
| 30-day ICU, n       | 52 (30.1 %)                           |

BMI, body mass index; FFM, fat free mass; FM, fat mass; HU, Hounsfield unit; IMAT, intramuscular adipose tissue; IMATI, intramuscular adipose tissue index; SAT, subcutaneous adipose tissue ; SATI, subcutaneous adipose index; SMA, skeletal muscle area; SMI, skeletal muscle index; TAT, total adipose tissue; TATI, total adipose tissue index; VAT, visceral adipose tissue; VATI, visceral adipose tissue index; VSR, visceral-to-adipose-tissue ratio.

Values are median, unless otherwise indicated.

infection. This association is independent of other known prognostic factors, such as age, sex, and BMI. VSR may therefore be used as a marker for adverse outcome.

Decreased muscle density, increased SAT density and BMI showed a weak association with the risk of intubation. Decreased muscle density and increased VAT density were also weakly associated with the risk of ICU admission, as was decreased SAT. However, none of these biomarkers may be used as a prognostic factor of clinical course. The strongest influence for

Table 2. Regression analysis for 30-day mortality

|                                          | Univariable |                |        | Multivariable |                |        |
|------------------------------------------|-------------|----------------|--------|---------------|----------------|--------|
| Variables                                | OR          | 95% CI         | p      | OR            | 95% CI         | p      |
| Continuous values                        |             |                |        |               |                |        |
| Age (years)                              | 1.034       | (1.008; 1.060) | 0.010  | 1.015         | (0.979; 1.053) | 0.408  |
| Sex (male vs female)                     | 2.300       | (1.020; 5.186) | 0.045  | 2.891         | (0.915; 9.132) | 0.070  |
| BMI, (kg/m <sup>2</sup> )                | 1.013       | (0.936; 1.096) | 0.749  | 1.030         | (0.941; 1.128) | 0.521  |
| SMA (cm <sup>2</sup> )                   | 0.997       | (0.986; 1.008) | 0.611  |               |                |        |
| SMI (kg/cm <sup>2</sup> )                | 0.995       | (0.958; 1.032) | 0.777  |               |                |        |
| Muscle density (HU)                      | 0.935       | (0.901; 0.971) | <0.001 |               |                |        |
| VAT (cm <sup>2</sup> )                   | 1.001       | (0.997; 1.005) | 0.642  |               |                |        |
| SAT (cm <sup>2</sup> )                   | 0.996       | (0.992; 1.000) | 0.035  |               |                |        |
| TAT (cm <sup>2</sup> )                   | 0.999       | (0.997; 1.001) | 0.321  |               |                |        |
| IMAT (cm <sup>2</sup> )                  | 1.042       | (1.011; 1.073) | 0.008  | 1.083         | (1.035; 1.133) | <0.001 |
| VSR                                      | 1.918       | (1.114; 3.305) | 0.019  | 2.147         | (1.022; 4.512) | 0.044  |
| VATI (cm <sup>2</sup> /m <sup>2</sup> )  | 1.004       | (0.993; 1.015) | 0.534  |               |                |        |
| SATI (cm <sup>2</sup> /m <sup>2</sup> )  | 0.990       | (0.980; 1.000) | 0.054  |               |                |        |
| TATI (cm <sup>2</sup> /m <sup>2</sup> )  | 0.998       | (0.992; 1.003) | 0.416  |               |                |        |
| IMATI (cm <sup>2</sup> /m <sup>2</sup> ) | 1.109       | (1.023; 1.203) | 0.012  |               |                |        |
| VAT density (HU)                         | 1.038       | (1.008; 1.068) | 0.011  | 1.090         | (1.046; 1.136) | <0.001 |
| SAT density (HU)                         | 1.049       | (1.018; 1.081) | 0.002  |               |                |        |
| IMAT density (HU)                        | 1.069       | (1.005; 1.138) | 0.034  |               |                |        |
| SMI/TAT                                  | 3.296       | (0.06; 173.83) | 0.556  |               |                |        |
| SMA/TAT                                  | 1.448       | (0.365; 5.743) | 0.598  |               |                |        |
| SMA/VAT                                  | 0.864       | (0.567; 1.318) | 0.498  |               |                |        |
| FFM (kg)                                 | 0.990       | (0.955; 1.028) | 0.611  |               |                |        |
| FM (kg)                                  | 0.975       | (0.927; 1.025) | 0.321  |               |                |        |
| Dichotomized values                      |             |                |        |               |                |        |
| SMI (low vs high)                        | 0.647       | (0.260; 1.605) | 0.347  | 0.299         | (0.089; 1.008) | 0.051  |
| VAT (high vs low)                        | 1.013       | (0.401; 2.560) | 0.978  |               |                |        |
| SAT (high vs low)                        | 0.344       | (0.136; 0.869) | 0.024  |               |                |        |
| VSR (high vs low)                        | 2.196       | (1.014; 4.755) | 0.046  |               |                |        |

BMI, body mass index; FFM, fat free mass; FM, fat mass; HU, Hounsfield unit; IMAT, intramuscular adipose tissue; IMATI, intramuscular adipose tissue index; SAT, subcutaneous adipose tissue; SATI, subcutaneous adipose index; SMA, skeletal muscle area; SMI, skeletal muscle index; TAT, total adipose tissue; TATI, total adipose tissue index; VAT, visceral adipose tissue; VATI, visceral adipose tissue index; VSR, visceral-to-adipose-tissue ratio.

both outcomes was found for sex. To our knowledge, this is to date the largest study performing a comprehensive analysis of both adipose tissue and musculature parameters on different outcomes in patients hospitalized for Covid-19 disease.

Several studies have shown an influence of different body composition parameters on outcomes in Covid-19 disease. In a small cohort with 51 patients, Chandarana et al showed that patients requiring hospitalization for Covid-19 disease had a higher VAT at the L3 level than those who did not require hospitalization.<sup>19</sup> Similarly, higher VAT was associated with the risk of

ICU admission in an Italian cohort.<sup>20</sup> Higher VAT was predictive of the cumulative outcome of severe disease or death in a large American cohort.<sup>21</sup> Similarly, visceral fat area was associated with higher risk of ICU admission and 30 day mortality in a UK cohort.<sup>22</sup> The studies did not investigate other parameters such as adipose tissue densities, IMAT, or VSR. Molwitz et al did not find an influence of either adipose tissue parameter and muscle density on clinical outcomes in a German cohort.<sup>23</sup> The study by Viddeleer et al showed an association between increased IMAT and 21-day mortality.<sup>24</sup> A recent meta-analysis found an influence of LSMM and high VAT on in-hospital mortality.<sup>25</sup>

Table 3. Regression analysis for need for intubation

|                                          | Univariable |                |        | Multivariable |                |        |
|------------------------------------------|-------------|----------------|--------|---------------|----------------|--------|
| Variables                                | OR          | 95% CI         | p      | OR            | 95% CI         | p      |
| Continuous values                        |             |                |        |               |                |        |
| Age (years)                              | 1.032       | (1.010; 1.055) | 0.005  | 0.995         | (0.961; 1.031) | 0.788  |
| Sex (male vs female)                     | 1.679       | (0.840; 3.356) | 0.142  | 4.138         | (1.610; 10.63) | 0.003  |
| BMI, (kg/m <sup>2</sup> )                | 1.081       | (1.006; 1.161) | 0.033  | 1.117         | (1.011; 1.233) | 0.029  |
| SMA (cm <sup>2</sup> )                   | 0.996       | (0.986; 1.006) | 0.384  |               |                |        |
| SMI (kg/cm <sup>2</sup> )                | 0.991       | (0.958; 1.024) | 0.584  |               |                |        |
| Muscle density (HU)                      | 0.925       | (0.894; 0.958) | <0.001 | 0.914         | (0.870; 0.960) | <0.001 |
| VAT (cm <sup>2</sup> )                   | 1.002       | (0.998; 1.005) | 0.346  |               |                |        |
| SAT (cm <sup>2</sup> )                   | 0.998       | (0.995; 1.001) | 0.155  |               |                |        |
| TAT (cm <sup>2</sup> )                   | 1.000       | (0.998; 1.002) | 0.766  |               |                |        |
| IMAT (cm <sup>2</sup> )                  | 1.038       | (1.009; 1.067) | 0.009  |               |                |        |
| VSR                                      | 1.760       | (1.053; 2.943) | 0.019  |               |                |        |
| VATI (cm <sup>2</sup> /m <sup>2</sup> )  | 1.006       | (0.996; 1.016) | 0.246  |               |                |        |
| SATI (cm <sup>2</sup> /m <sup>2</sup> )  | 0.996       | (0.988; 1.004) | 0.274  |               |                |        |
| TATI (cm <sup>2</sup> /m <sup>2</sup> )  | 1.000       | (0.995; 1.005) | 0.992  |               |                |        |
| IMATI (cm <sup>2</sup> /m <sup>2</sup> ) | 1.106       | (1.025; 1.193) | 0.009  |               |                |        |
| VAT density (HU)                         | 1.038       | (1.011; 1.066) | 0.005  |               |                |        |
| SAT density (HU)                         | 1.059       | (1.029; 1.091) | <0.001 | 1.071         | (1.034; 1.110) | <0.001 |
| IMAT density (HU)                        | 1.087       | (1.026; 1.151) | 0.004  |               |                |        |
| SMI/TAT                                  | 0.753       | (0.015; 39.03) | 0.888  |               |                |        |
| SMA/TAT                                  | 0.856       | (0.218; 3.360) | 0.824  |               |                |        |
| SMA/VAT                                  | 0.811       | (0.527; 1.247) | 0.339  |               |                |        |
| FFM (kg/m <sup>2</sup> )                 | 0.985       | (0.954; 1.018) | 0.384  |               |                |        |
| FM (kg)                                  | 0.994       | (0.952; 1.037) | 0.766  |               |                |        |
| Dichotomized values                      |             |                |        |               |                |        |
| SMI (low vs high)                        | 0.754       | (0.326; 1.744) | 0.510  |               |                |        |
| VAT (high vs low)                        | 1.163       | (0.502; 2.695) | 0.725  |               |                |        |
| SAT (high vs low)                        | 0.482       | (0.199; 1.167) | 0.106  |               |                |        |
| VSR (high vs low)                        | 1.802       | (0.898; 3.613) | 0.097  |               |                |        |

BMI, body mass index; FFM, fat free mass; FM, fat mass; HU, Hounsfield unit; IMAT, intramuscular adipose tissue; IMATI, intramuscular adipose tissue index; SAT, subcutaneous adipose tissue; SATI, subcutaneous adipose index; SMA, skeletal muscle area; SMI, skeletal muscle index; TAT, total adipose tissue; TATI, total adipose tissue index; VAT, visceral adipose tissue; VATI, visceral adipose tissue index; VSR, visceral-to-adipose-tissue ratio.

Regarding VSR, the available data are yet sparse. In an American cohort with 124 patients by Bunnell et al, a higher VAT/SAT ratio was associated with the composite outcome of ICU admission or death.<sup>1</sup> Measurements were carried out at the mid-portion of the L4 level. Battisti et al showed that higher VAT/SAT ratio, measured at the L2 level, was a predictor of ICU admission.<sup>16</sup> In a Chinese cohort with 143 patients, high VAT/SAT ratio and low muscle density were independent risk factors for ICU admission or mechanical ventilation, yet no association with mortality was found.<sup>26</sup> Inversing the ratio, Favre et al found that the subcutaneous to visceral fat ratio was lower in patients with severe

Covid-19.<sup>2</sup> In contrast, Nobel et al were not able to find a relevant influence of an increased VAT/SAT ratio on clinical outcomes.<sup>10</sup>

In our cohort, VSR showed a relevant influence on 30-day mortality. This supports the hypothesis that fat distribution rather than total abdominal fat tissue may be a more appropriate risk parameter for outcomes in patients with Covid-19 disease. When controlled for other body composition parameters, we did not find a significant association between VSR and either the risk of intubation or ICU admission. The associations between adipose tissue and unfavorable course in Covid-19 disease is manifold.



Table 4. Regression analysis for need for admission to ICU

|                                          | Univariable |                |        | Multivariable |                |        |
|------------------------------------------|-------------|----------------|--------|---------------|----------------|--------|
| Variables                                | OR          | 95% CI         | p      | OR            | 95% CI         | p      |
| Continuous values                        |             |                |        |               |                |        |
| Age (years)                              | 1.032       | (1.010; 1.054) | 0.004  | 0.975         | (0.939; 1.012) | 0.183  |
| Sex (male vs female)                     | 1.574       | (0.811; 3.053) | 0.180  | 3.423         | (1.294; 9.054) | 0.013  |
| BMI, (kg/m <sup>2</sup> )                | 1.069       | (0.997; 1.145) | 0.061  | 1.199         | (1.070; 1.344) | 0.002  |
| SMA (cm <sup>2</sup> )                   | 0.994       | (0.985; 1.004) | 0.226  |               |                |        |
| SMI (kg/cm <sup>2</sup> )                | 0.985       | (0.954; 1.018) | 0.371  |               |                |        |
| Muscle density (HU)                      | 0.928       | (0.897; 0.959) | <0.001 | 0.882         | (0.832; 0.934) | <0.001 |
| VAT (cm <sup>2</sup> )                   | 1.001       | (0.997; 1.004) | 0.761  |               |                |        |
| SAT (cm <sup>2</sup> )                   | 0.997       | (0.994; 1.000) | 0.049  | 0.993         | (0.987; 0.999) | 0.028  |
| TAT (cm <sup>2</sup> )                   | 0.999       | (0.997; 1.001) | 0.311  |               |                |        |
| IMAT (cm <sup>2</sup> )                  | 1.030       | (1.003; 1.058) | 0.029  |               |                |        |
| VSR                                      | 1.665       | (1.007; 2.755) | 0.047  |               |                |        |
| VATI (cm <sup>2</sup> /m <sup>2</sup> )  | 1.003       | (0.993; 1.012) | 0.597  |               |                |        |
| SATI (cm <sup>2</sup> /m <sup>2</sup> )  | 0.994       | (0.986; 1.002) | 0.113  |               |                |        |
| TATI (cm <sup>2</sup> /m <sup>2</sup> )  | 0.998       | (0.994; 1.003) | 0.513  |               |                |        |
| IMATI (cm <sup>2</sup> /m <sup>2</sup> ) | 1.085       | (1.009; 1.168) | 0.028  |               |                |        |
| VAT density (HU)                         | 1.050       | (1.022; 1.078) | <0.001 | 1.068         | (1.029; 1.109) | <0.001 |
| SAT density (HU)                         | 1.068       | (1.036; 1.101) | <0.001 |               |                |        |
| IMAT density (HU)                        | 1.095       | (1.036; 1.159) | 0.001  |               |                |        |
| SMI/TAT                                  | 4.818       | (0.14; 164.76) | 0.383  |               |                |        |
| SMA/TAT                                  | 1.523       | (0.449; 5.161) | 0.500  |               |                |        |
| SMA/VAT                                  | 1.038       | (0.960; 1.123) | 0.350  |               |                |        |
| FFM (kg)                                 | 0.980       | (0.950; 1.012) | 0.226  |               |                |        |
| FM (kg)                                  | 0.978       | (0.938; 1.021) | 0.311  |               |                |        |
| Dichotomized values                      |             |                |        |               |                |        |
| SMI (low vs high)                        | 0.933       | (0.407; 2.141) | 0.871  |               |                |        |
| VAT (high vs low)                        | 1.020       | (0.461; 2.258) | 0.961  |               |                |        |
| SAT (high vs low)                        | 0.330       | (0.139; 0.785) | 0.012  |               |                |        |
| VSR (high vs low)                        | 1.731       | (0.882; 3.398) | 0.111  |               |                |        |

BMI, body mass index; FFM, fat free mass; FM, fat mass; HU, Hounsfield unit; ICU, intensive care unit ; IMAT, intramuscular adipose tissue; IMATI, intramuscular adipose tissue index; SAT, subcutaneous adipose tissue; SATI, subcutaneous adipose index; SMA, skeletal muscle area; SMI, skeletal muscle index; TAT, total adipose tissue; TATI, total adipose tissue index; TATI, total adipose tissue index ; VAT, visceral adipose tissue; VATI, visceral adipose tissue index; VSR, visceral-to-adipose-tissue ratio.

The inverse relation between SAT and clinical outcomes has been described in the literature. Studies have shown that visceral and subcutaneous fat have different metabolic and endocrine characteristics.<sup>27</sup> Visceral fat is metabolically active and releases pro-inflammatory cytokines such as IL-6 and is linked with various diseases.<sup>28</sup> Subcutaneous fat excretes anti-inflammatory cytokines such as adiponectin.<sup>29,30</sup> Disproportionate visceral adipose tissue might modify metabolism and cell-mediated immune response, by increasing macrophage accumulation and decreasing adiponectin.<sup>29,31,32</sup>

Interestingly, neither skeletal muscle parameter showed a relevant association with either outcome in our cohort. This is somewhat contradictory to the literature published so far. Schiaffino et al have indicated that LSMM is associated with higher risk of ICU admission and increased mortality.<sup>4</sup> Measurements of paravertebral muscle area were not performed on the L3 level, but on T5 and T12, different to our cohort. Measuring on T12, Kim et al found an association between LSMM and prolonged hospital stay, but not with mortality.<sup>33</sup> Other authors did not find any relationship between muscle parameters and clinical outcomes.<sup>8,23</sup>

Furthermore, most of the literature concentrated either on the musculature or adipose tissue parameters. There are only few studies that analyze both. The novelty of our study is therefore a comprehensive comparative analysis of the influence of different kinds of body composition measurements. For both ICU admission and intubation, higher muscle density and higher SAT seem to be protective in hospitalized Covid-19 patients. Muscle density is considered to be a proxy for muscle lipid content and representative of muscle quality and capacity.<sup>31,34</sup> However, their influence is too weak to be routinely applied as relevant biomarkers in clinical routine. It seems that, when controlled for different parameters, male sex is still the best-established risk factor for adverse clinical course, but not for mortality.

Body composition parameters can be assessed on opportunistic CT scans in clinical routine. Compared to X-ray absorptiometry and body impedance assessment, CT scans are more objective and easy to acquire.<sup>35</sup> CT scans are frequently performed in hospitalized patients and measurements can be performed as a byproduct of radiological diagnostics. The literature on CT-based body composition parameters is large. For the musculature, most studies use the level L3, where the highest correlation of the skeletal muscle with body muscle volume has been described.<sup>36</sup> For MRI measurements, there is a good correlation between L3 cross-sectional adipose tissue and total tissue volume.<sup>37</sup> We therefore chose to perform our measurements on the same level to achieve standardization. Our data suggest that semi-automated CT body composition measurements should be included into clinical routine to identify patients at risk and provide best nutritional and physical therapy to patients with changes in muscle and adipose tissue density.

Our study has several limitations. It was a retrospective cohort analysis and only patients that underwent an abdominal CT

scan at the discretion of the treating physician were included. We did not consider the impact of different virus subtypes on clinical course in our analysis. We did not control for comorbidities. However, this is to date the largest multicenter cohort investigating the spectrum of body composition parameters on outcomes in Covid-19 patients with a standardized measurement level at L3.

In conclusion, VSR is a prognostic biomarker for 30-day mortality in patients hospitalized for Covid-19 disease. Sex is more strongly associated with the risk of intubation and ICU admission than adipose tissue variables. Increased muscle density is a protective factor for adverse clinical course. There was no impact of musculature parameters on either outcome.

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## AUTHOR CONTRIBUTIONS

AS, MT: study design, data acquisition, data analysis drafting and revision, final approval; HK, MH, JO: data acquisition, data analysis, revision; EC, MC, MD, IK, CO, ÖY, EH, EI, HÖ, HE, OC, HS, KAG: data acquisition and interpretation, revision; MP: data analysis and interpretation; AW: study conception and design, data interpretation, drafting and revision.

## CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

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