Original Article
CLINICAL TRIALS AND INVESTIGATIONS

Obesity

Visceral Adiposity Elevates the Risk of Critical Condition in COVID-19: A Systematic Review and Meta-Analysis

Mária Földi [1,2,3], Nelli Farkas[1,4], Szabolcs Kiss [1,2,3], Fanni Dembrovszky [1,2], Zsolt Szakács[1,2], Márta Balaskó[1,2], Bálint Erőss[1,2], Péter Hegyi[1,2,3], and Andrea Szentesi [1,2,3]

Objective: A higher BMI has become acknowledged as one of the important risk factors for developing critical condition in coronavirus disease 2019 (COVID-19). In addition to BMI, body composition, and particularly visceral adiposity, might be an even more accurate measure to stratify patients. Therefore, the aim of this study was to evaluate the association between the distributions of computed-tomography-quantified fat mass and critical condition of patients with COVID-19.

Methods: A systematic search was conducted in five databases for studies published until November 17, 2020. In the meta-analysis, pooled mean difference (standardized mean difference [SMD]) of visceral fat area (VFA; in square centimeters) was calculated between patients in the intensive care unit and those in general ward and between patients with the requirement for invasive mechanical ventilation (IMV) and those without the IMV requirement.

Results: The quantitative synthesis revealed that patients requiring intensive care had higher VFA values (SMD = 0.46, 95% CI: 0.20-0.71, $P < 0.001$) compared with patients on the general ward. Similarly, patients requiring IMV had higher VFA values (SMD = 0.38, 95% CI: 0.05-0.71, $P = 0.026$) compared with patients without the IMV requirement.

Conclusions: VFA values were found to be significantly higher in patients with critical condition. Therefore, abdominal adiposity seems to be a risk factor in COVID-19, and patients with central obesity might need special attention.

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Study Importance

What is already known?

- A higher BMI was found to be a risk factor for developing critical condition in COVID-19.
- Because the prevalence of obesity is increasing worldwide, it is vital to identify patients at a higher risk.
- Several studies have proposed that visceral adiposity might be a risk factor.

What does this study add?

- We performed a comprehensive search, selection, and quantitative and qualitative analysis concerning the association between computed-tomography-quantified fat mass distribution and critical condition among COVID-19 patients.
- Pooled analysis of three studies revealed that patients requiring intensive care or invasive mechanical ventilation had higher visceral fat area values compared with patients without the need for them.

How might these results change the direction of research or the focus of clinical practice?

- Although BMI is widely used to define obesity, further phenotyping of patients, for example by assessing body composition and central obesity, might be recommended.
- Considering the potential role of visceral adipose tissue, it might also be worth studying adipose-tissue-related substances as potential pharmacological targets.

Introduction

With the escalation of the pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), recognizing risk factors is of utmost importance. Among other risk factors such as age and comorbidities (1,2), a higher BMI has been acknowledged as a risk factor for developing critical condition in coronavirus disease 2019 (COVID-19) in our former analysis and in other articles since then (3-6). Because the obesity epidemic is rapidly spreading worldwide, it is vital to accurately identify patients with a higher risk for developing critical condition in COVID-19.

[1] Institute for Translational Medicine, Medical School, University of Pécs, Pécs, Hungary. Correspondence: Andrea Szentesi (szentesiai@gmail.com) [2] Szentágothai Research Centre, University of Pécs, Pécs, Hungary [3] Centre for Translational Medicine, Department of Medicine, University of Szeged, Szeged, Hungary [4] Institute of Bioanalysis, Medical School, University of Pécs, Pécs, Hungary.

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Although BMI is widely used to diagnose obesity (7), body composition, and especially visceral adiposity, might be an even more accurate measure to stratify patients (8-12). Therefore, we aimed to evaluate the association between the distributions of computed tomography (CT)-quantified fat mass and critical condition of patients with COVID-19.

Methods

We report this meta-analysis and systematic review according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Statement (13).

Search strategy

A systematic search was conducted in MEDLINE (via PubMed), Embase, Cochrane Library (CENTRAL), Scopus, and Web of Science for studies published until November 17, 2020. The following search terms were used in all databases: ((“covid 19”) OR (“Wuhan virus”) OR (“coronavirus”) OR (“2019 nCoV”) OR (“SARS-cov-2”)) AND ((fat OR obes* OR adipos*) AND (visceral OR intraabdominal OR abdominal OR central)). There was no restriction applied to the search.

Selection and eligibility criteria

We selected clinical studies reporting on patients hospitalized with confirmed SARS-CoV-2 infection (based on the World Health Organization case definition) and on the distribution of body fat mass assessed by CT. Studies were included in the meta-analysis if data on the following variables were reported: the number of patients with and without critical condition (defined as the need for invasive mechanical ventilation [IMV] or admission to intensive care unit [ICU]) and distribution of body fat mass (total adipose tissue [TAT], visceral adipose tissue [VAT], subcutaneous adipose tissue [SAT]). The latter parameters could be reported as thickness (millimeters), area (square centimeters), or volume (cubic centimeters). Abstracts and grey literature (preprints and other non-peer-reviewed material) were excluded from the analysis.

The yield of the search was combined in a reference manager software (EndNote X9; Clarivate Analytics, Philadelphia, Pennsylvania). After automatic and manual removal of duplicate records, full texts of all studies were evaluated by two independent review authors. Two review authors decided to include a study in the meta-analysis if they agreed. A third author resolved the disagreements. Reference lists of the included studies were screened for additional eligible articles.

Data extraction

Two independent review authors extracted data into a standardized data collection form (Microsoft Excel 365, Microsoft Corporation, Redmond, Washington). The following data were extracted from each eligible article: first and second authors; publication year; study site; sex; age; the number of patients with and without critical condition; and the means, standard deviations, medians, ranges, and interquartile ranges related to body fat mass (the article provided thickness in millimeters, area in square centimeters, and volume in cubic centimeters of TAT, VAT, and SAT). Odds ratios (ORs) and risk ratios (with the corresponding confidence intervals) relating to the association between body fat mass and critical condition were also extracted. A third party resolved discrepancies. The authors of the eligible articles were not contacted for further information.

Quality assessment

Quality of the eligible studies was evaluated by using the Quality in Prognosis Studies (QUIPS) tool by two independent review authors (14). Any disagreement was resolved by third-party arbitration.

Statistical analysis

Cohen’s kappa coefficient (κ) was calculated to measure interrater reliability during the selection process. $\kappa \leq 0$ is interpreted as no agreement, 0.01-0.20 as none to slight agreement, 0.21-0.40 as fair agreement, 0.41-0.60 as moderate agreement, 0.61-0.80 as substantial agreement, 0.81-1.00 as almost perfect agreement, and 1.00 as perfect agreement (15).

We calculated pooled mean difference (standardized mean difference [SMD]) for continuous variables because the CT examinations were performed at different vertebral levels among studies. We used random effect model with the DerSimonian-Laird estimation (16). Statistical heterogeneity was calculated performing the I^2 test, and we also carried out χ^2 tests to acquire probability values: $P<0.1$ indicated significant heterogeneity. The interpretation of I^2 was as follows: 0% to 40%: not important; 30% to 60%: moderate heterogeneity; 50% to 90%: substantial heterogeneity; and 75% to 100%: considerable heterogeneity (17). If the mean with standard deviation could not be extracted, we estimated them from median, interquartiles, and range using the method by Wan et al. (18).

Results

Systematic search and selection

The results of the systematic search and selection are shown in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Flowchart (Figure 1). The calculated κ value based on the full-text selection was 1.00, which was interpreted as perfect agreement. On completion of the selection, six studies, including data from 560 patients, were eligible. The characteristics of the studies included are summarized in Table 1. Five out of six studies, including 509 patients, reported on ICU admission rate, which ranged between 18.5% and 43.3%. Three studies with 208 patients reported on IMV requirement in the association with body composition metrics. The visceral fat area (VFA; in cubic centimeres) values ranged between 70.9 cm^2 and 240 cm^2. The results of the quantitative and qualitative synthesis are shown in Table 1, Table 2, and Figure 2.

VAT mass and COVID-19

Our quantitative synthesis revealed that patients requiring intensive care had higher VFA values (SMD = 0.46, 95% CI: 0.20-0.71, $P<0.001$) compared with patients on the general ward. Similarly, patients requiring IMV had higher VFA values (SMD = 0.38, 95% CI: 0.05-0.71, $P=0.022$) compared with patients without IMV requirement. Statistical heterogeneity might not be important in any analysis ($I^2=0.0\%$, $P=0.637$ and $I^2=0.0\%$, $P=0.747$ for ICU admission and IMV, respectively). These results are depicted in Figure 2. Two studies found, in age- and gender-adjusted analyses, that an increased VFA carries a higher risk for ICU admission (11,19). Yang et al. did

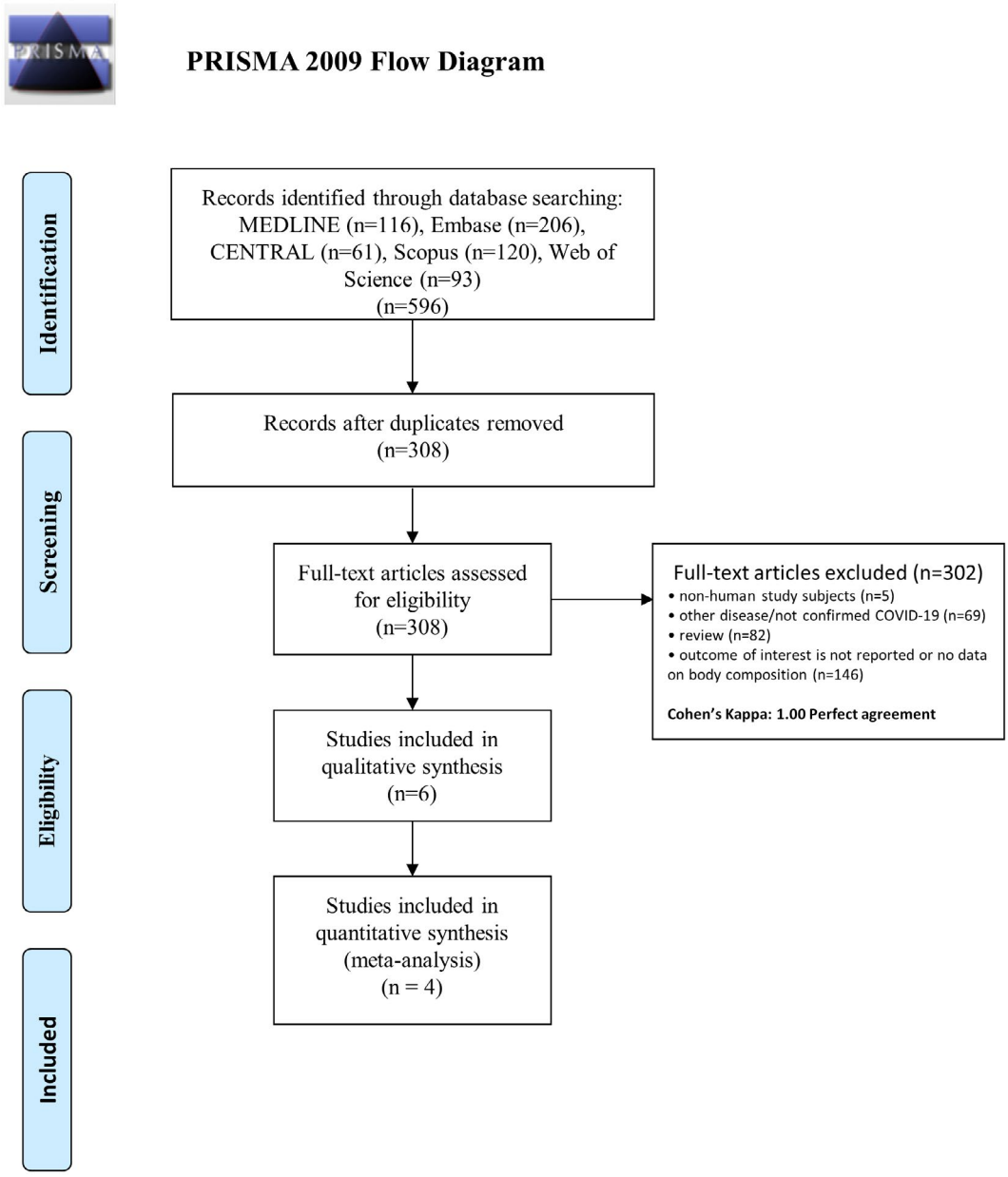

Figure 1 PRISMA flowchart for the study selection process. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses. [Color figure can be viewed at wileyonlinelibrary.com]

not identify VFA > 100 mm^2 as a significant risk factor for ICU admission (OR = 1.94, 95% CI: 0.95-4.05). (32). Battisti et al. also found a higher visceral fat thickness (in millimeters) among patients admitted to the ICU compared with patients on the general ward (13.1 ± 6 mm vs. 17.9 ± 6.5 mm, $P < 0.001$) (8).

SAT mass and COVID-19

Watanabe et al. found that an increased subcutaneous fat area (SFA) is not associated with a higher risk for ICU admission (19). Yang et al. did not identify SFA > 100 mm^2 as a risk factor for ICU admission (OR = 1.06, 95% CI: 0.52-2.17) (32). However, a high VFA/SFA ratio was found to be associated with an increased risk for ICU admission (OR = 2.47, 95% CI = 1.05-5.98) (9).

TAT mass and COVID-19

Two studies evaluated total fat area (TFA) in COVID-19 patients. Petersen et al. revealed that every additional 10 cm^2 of TFA carries 1.13 times (95% CI: 1.03-1.29) and 1.28 times (95% CI: 1.06-1.80) additional risk for ICU admission and IMV requirement, respectively (11). Another study identified an increased TFA as a risk factor for ICU

TABLE 1 Characteristics of the studies included in the quantitative and qualitative analyses

Study first author and year	Study site	Period of enrollment	Sample size	Demographic data	Event	Body composition in the event group	Body composition in the non-event group
Battisti S et al. (2020) (8)	Trauma Center Public Hospital Bufalini, Cesena, Italy	26 Feb-6 Apr 2020	144	Mean BMI: 26.2 ± 4, Mean age: 60.3 ± 17 y, 39.6% female	ICU	Mean BMI (kg/m^2): 29.6 ± 5.8 Mean VAT (mm): 17.9 ± 6.5 Mean SAT (mm): 15.6 ± 7.4 Mean VAT/SAT: 1.53 ± 1.04	Mean BMI (kg/m^2): 25.8 ± 4.3 Mean VAT (mm): 13.1 ± 6.0 Mean SAT (mm): 19.2 ± 9.7 Mean VAT/SAT: 0.90 ± 0.73
Chandarana H et al. (2020) (9)	New York, USA	19 Mar-19 Apr 2020	51	BMI: n.r., Age: n.r., 19.5% female	IMV	Mean BMI (kg/m^2): 27.6 ± 10.4 Mean VAT (cm^2): 240.6 ± 101.2 Mean SAT (cm^2): 179.6 ± 56 Mean TAT (cm^2): 420.2 ± 134.7 Mean VAT/TAT: 0.56 ± 0.08	Mean BMI (kg/m^2): 30.4 ± 7.8 Mean VAT (cm^2): 224.2 ± 115.9 Mean SAT (cm^2): 231.5 ± 142.2 Mean TAT (cm^2): 455.7 ± 201 Mean VAT/TAT: 0.5 ± 0.16
Deng et al. (2020) (12)	Zhongnan Hospital of Wuhan University, China	Until 13 Mar 2020	65	BMI: n.r., Age: n.r., 44.6% female	ICU	Median BMI (kg/m^2): 29.2 (IQR: 27.5-31.1) Median SAT (mm): 12 (IQR: 9.5-20)	Median BMI (kg/m^2): 22.8 (IQR: 19.5-24.6) Median SAT (mm): 11 (IQR: 9.7-13)
Petersen et al. (2020) (11)	Level-one medical center in Berlin, Germany	27 Mar-27 Apr 2020	30	Mean BMI: 26.4 ± 3.0, Mean age: 65.6 ± 13.1 y, 40.0% female	ICU	Mean BMI (kg/m^2): 26.8 ± 2.1 Mean VAT (cm^2): 96.9 ± 33.5 Mean SAT (cm^2): 107.57 ± 72.8 Mean TAT (cm^2): 204.4 ± 86.9	Mean BMI (kg/m^2): 26.1 ± 3.4 Mean VAT (cm^2): 70 ± 28.2 Mean SAT (cm^2): 56.2 ± 33.8 Mean TAT (cm^2): 136 ± 61.8
		27 Mar-27 Apr 2020	30	Mean BMI: 26.4 ± 3.0, Mean age: 65.6 ± 13.1 y, 40.0% female	IMV	Mean BMI (kg/m^2): 26.4 ± 2.2 Mean VAT (cm^2): 124.2 ± 65.9 Mean SAT (cm^2): 73 ± 59.7 Mean TAT (cm^2): 237.3 ± 134.3	Mean BMI (kg/m^2): 26.8 ± 2.1 Mean VAT (cm^2): 96.6 ± 33.5 Mean SAT (cm^2): 107.57 ± 72.8 Mean TAT (cm^2): 204.4 ± 86.9
Watanabe et al. (2020) (19)	Emergency Department of Sant'Andrea Hospital, Rome, Italy	Mar 2020	127	BMI: n.r., Mean age: 64.15 ± 15.69 y, 63.0% female	ICU/IMV	BMI (kg/m^2): n.r. Mean VAT (cm^2): 173.4 ± 95.6 Mean SAT (cm^2): 155 ± 93.8 Mean TAT (cm^2): 328.4 ± 148.7	BMI (kg/m^2): n.r. Mean VAT (cm^2): 136.8 ± 78.1 Mean SAT (cm^2): 132.6 ± 81.2 Mean TAT (cm^2): 269.4 ± 134.2

(Continued)

TABLE 1 (continued).

Study first author and year	Study site	Period of enrollment	Sample size	Demographic data	Event	Body composition in the event group	Body composition in the non-event group
Yang Y et al. (2020) (32)	Tongji Hospital in Wuhan, China	1 Jan-30 Mar 2020	143	Median BMI: 23.4 (IQR: 21.9-25.3), Median age: 66 y (IQR: 56-73.5), 51.0% female	ICU	Median BMI (kg/m^2): 24.8 (IQR: 22.5-26.1) Median VAT (cm^2): 131.9 (IQR: 79.2-185.7) Median SAT (cm^2): 108.2 (IQR: 66-138.5) Median VAT/SAT: 1.31 (IQR: 0.79-1.76)	Median BMI (kg/m^2): 23.0 (IQR: 21.4-24.8) Median VAT (cm^2): 90.5 (IQR: 51.3-156.1) Median SAT (cm^2): 108.8 (IQR: 83.2-175.2) Median VAT/SAT: 1.31 (IQR: 0.79-1.76)

ICU, intensive care unit admission; IMV, invasive machanical ventilation; IQR, interquartile range; n.r., not reported; SAT, subcutaneous adipose tissue; TAT, total adipose tissue; VAT, visceral adipose tissue.

admission in univariate and age- and sex-adjusted multivariate logistic regression analysis (19).

Risk of bias assessment

The overall risk of bias was low to moderate in the studies included. Detailed results of the quality assessment are found in Supporting Information.

Discussion

Our most important finding is that VFA was higher in patients admitted to the ICU and requiring IMV, which draws attention to the importance of abdominal adiposity in COVID-19.

A recent meta-analysis by Huang et al. has come to the same conclusion (20); they have found higher VAT values in patients with critical condition, as well. However, their search interval was shorter, and we included two additional studies in the meta-analyses (9,11). They did not change the direction of the results but rather confirmed the previous findings. A further strength of our study is that, unlike Huang et al., we pooled only those studies that reported on VFA (in square centimeters), whereas we excluded from the meta-analysis those studies that reported visceral fat thickness (in millimeters), preventing biases resulting from combining values reported in different units of measures. Thereby, the possible distortion owing to indirectness was minimized. In addition, we performed a qualitative synthesis concerning the effects of fat distribution (VAT, SAT, and TAT values) on the outcomes.

There are several theories proposed to explain how abdominal obesity leads to adverse outcomes in COVID-19.

The malfunction of VAT can impair the immune system by producing different inflammatory substances and adipokines (21). The unhealthy expansion of adipose tissue is associated with endoplasmic reticulum stress, adipose tissue fibrosis, and localized hypoxia (22). In turn, it is associated with adipocyte cell death and inflammatory response initiation (23). An increase in monocyte chemoattractant protein-1 in VAT contributes to macrophages' infiltration, predominantly M1 macrophages, which promote inflammation, generate reactive oxygen species, and release pro-inflammatory cytokines, such as tumor necrosis factor-α and interleukin-6. In contrast, lean adipose tissue contains M2 macrophages predominantly, showing anti-inflammatory activity. Besides, in obesity, inflammation-inducing leptin release increases, whereas protective adiponectin production declines.

The emerging low-grade chronic inflammation may contribute to the "cytokine storm" in severe COVID-19 cases (24) and increases the vulnerability to infections as well as to metabolic and cardiovascular complications, such as insulin resistance, type 2 diabetes mellitus, microvascular disorders, or progressive atherosclerosis (25). These diseases are also recognized as risk factors in COVID-19 (1). Angiotensin-converting enzyme 2 receptors are also abundant in adipose tissue, contributing to more severe infection and disease course (26).

Moreover, visceral obesity is associated with a complex pro-coagulant and a suppressed fibrinolytic profile (because of, among other reason, extensive endothelial damage, enhanced estrogen, and plasmin activator inhibitor-1 production), which can lead to thrombotic complications in COVID-19 (27).

TABLE 2 Summary of the qualitative synthesis and results of the individual studies

Study first author and year	Risk factor	Outcome	Sample size	Results of the study
Battisti et al. (2020) (8**)**	VAT thickness (per mm increase)	ICU	144	OR = 1.16 (95% CI: 1.07-1.26)* *Multivariate analysis: adjusted for gender, age, and BMI
	20% VAT/SAT increase	ICU	144	OR = 1.25 (95% CI: 1.1-1.42)* *Multivariate analysis: adjusted for gender, age, and BMI
Deng et al. (2020) (12**)**	SAT higher than 10 mm	ICU	65	*P* = 1.0
	VAT CT density higher than 107 HU	ICU	65	*P* = 0.706
Petersen et al. (2020) (11**)**	VAT (per 10 cm^2)	ICU	30	OR = 1.36 (95% CI: 1.08-1.86) OR = 1.37 (95% CI: 1.07-1.89)* *Multivariate analysis: adjusted for gender and age
	TAT (per 10 cm^2)	ICU	30	OR = 1.11 (95% CI: 1.02-1.28) OR = 1.13 (95% CI: 1.03-1.29)* *Multivariate analysis: adjusted for gender and age
	VAT (per 10 cm^2)	IMV	30	OR = 1.30 (95% CI: 1.05-1.81) OR = 1.32 (95% CI: 1.04-1.91)* *Multivariate analysis: adjusted for gender and age
	TAT (per 10 cm^2)	IMV	30	OR = 1.08 (95% CI: 0.99-1.19) OR = 1.28 (95% CI: 1.06-1.80)* *Multivariate analysis: adjusted for gender and age
Watanabe et al. (2020) (19**)**	VAT (mm^2)	ICU/IMV	127	OR = 3.13 (95% CI: 1.36-7.19) OR = 1.57 (95% CI: 1.0.5-2.37)* OR = 2.47 (95% CI: 1.02-6.02)** *Multivariate analysis: adjusted for gender and age **Multivariate analysis: adjusted for age, gender, diabetes, hypertension, ACEi/ARB use
	SAT (mm^2)	ICU/IMV	127	OR = 1.6 (95% CI: 0.73-3.5)
	TAT (mm^2)	ICU/IMV	127	OR = 2.22 (95% CI: 0.99-4.93) OR = 1.59 (95% CI: 1.06-2.39)* *Multivariate analysis: adjusted for gender and age
Yang Y et al. (2020) (32**)**	>100 cm^2 VAT	ICU	143	OR = 1.94 (95% CI: 0.95-4.05)
	>100 cm^2 SAT	ICU	143	OR = 1.06 (95% CI: 0.52-2.17)
	High VAT/SAT ratio	ICU	143	OR = 2.32 (95% CI: 1.13-4.89) OR = 2.47 (95% CI: 1.05-5.98)* *Multivariate analysis: adjusted for age and gender

ACEi/ARB, angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers; CI, confidence interval; CT, computed tomography; HU, Hounsfield unit; ICU, intensive care unit admission; IMV, invasive mechanical ventilation; OR, odds ratio; SAT, subcutaneous adipose tissue; TAT, total adipose tissue; VAT, visceral adipose tissue.

Severe abdominal obesity also leads to restrictive ventilator disorders with decreased chest compliance and low respiratory reserve (reduced vital capacity and forced expiratory volume in 1 second), which may aggravate lung complications in COVID-19 (28).

In addition to CT-quantified VAT, other indicators of abdominal obesity, such as waist circumference and waist-hip ratio, would be worth further investigation since they are easily applicable in routine clinical practice (10,11,29-31).

Our study has some limitations. First, this difference mentioned earlier is difficult to interpret without adjusting for BMI and other risk factors such as age, gender, or comorbidities. Nonetheless, most of the included studies performed multivariate analysis, and they mostly agreed on that visceral adiposity might be an independent risk factor for adverse outcomes. Second, we could not perform meta-analyses related to TAT, SAT, VAT/TAT ratio, or VAT/SAT ratio in the absence of a sufficient number of studies. However, our qualitative synthesis suggested that SAT does not carry a risk of critical condition. Third, we could only combine those studies in the meta-analysis that evaluated VAT by area, which resulted in the exclusion of a study reporting on VAT thickness (8). Finally, the small number of included studies remained a limitation.

In summary, we found that VFA values were significantly higher in patients with critical condition. In light of the high prevalence of

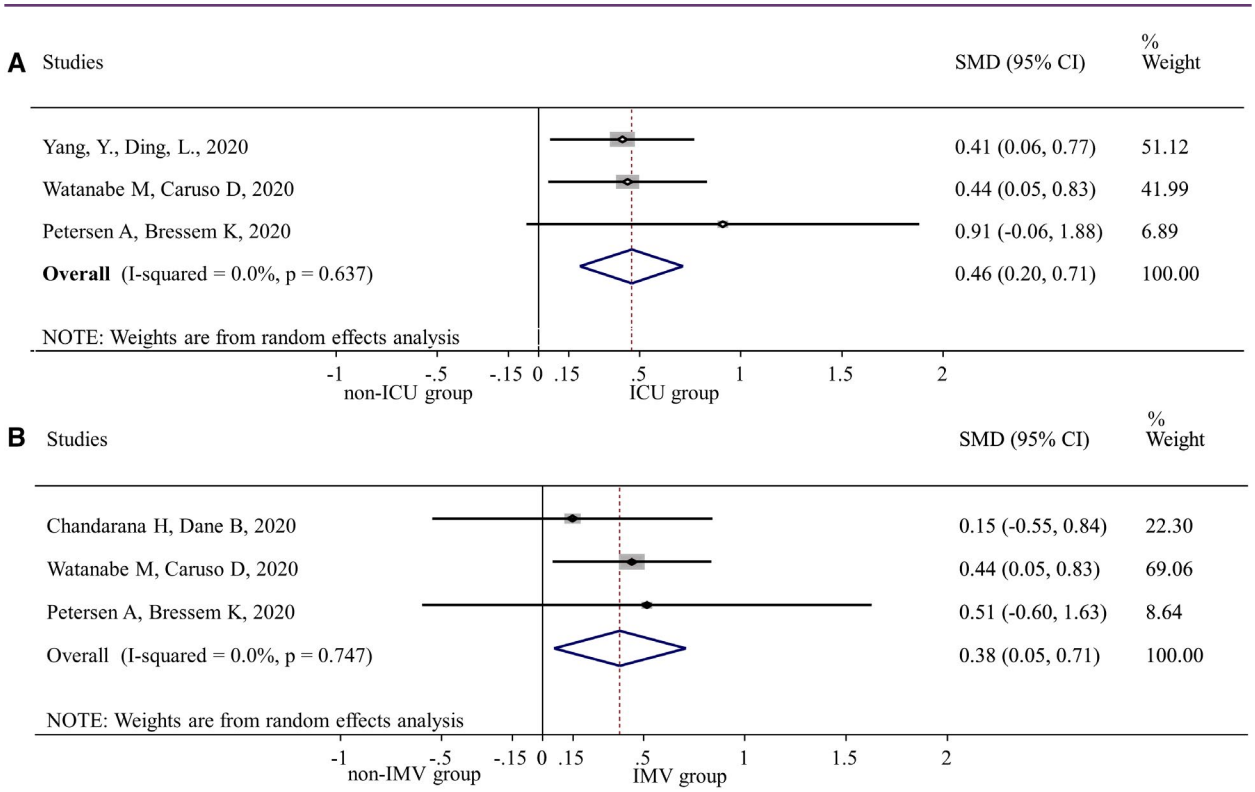

Figure 2 SMD of visceral adipose tissue in patients needing ICU or IMV compared with visceral adipose tissue in patients not needing these. (**A**) Non-ICU versus ICU. (**B**) Non-IMV versus IMV. ICU, intensive care unit; IMV, invasive mechanical ventilation; SMD, standardized mean difference. [Color figure can be viewed at wileyonlinelibrary.com]

obesity, this area of research should be further investigated. Besides the distribution of body fat, adipose-tissue-related substances as potential pharmacological targets might be worth studying as well.O

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Supporting information: Additional Supporting Information may be found in the online version of this article.

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