Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Metabolism Clinical and Experimental 113 (2020) 154378

Contents lists available at ScienceDirect

Metabolism Clinical and Experimental

journal homepage: www.metabolismjournal.com

Obesity in patients with COVID-19: a systematic review and meta-analysis

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ARTICLE INFO

Article history:
Received 5 August 2020
Received in revised form 15 September 2020
Accepted 19 September 2020

Keywords:
Obesity
Coronavirus disease 2019
Visceral adipose tissue
Intensive care
Invasive mechanical ventilation
Mortality

ABSTRACT

Background: Obesity is common in patients with coronavirus disease 2019 (COVID-19). The effects of obesity on clinical outcomes of COVID-19 warrant systematical investigation.
Objective: This study explores the effects of obesity with the risk of severe disease among patients with COVID-19.
Methods: Body mass index (BMI) and degree of visceral adipose tissue (VAT) accumulation were used as indicators for obesity status. Publication databases including preprints were searched up to August 10, 2020. Clinical outcomes of severe COVID-19 included hospitalization, a requirement for treatment in an intensive care unit (ICU), invasive mechanical ventilation (IMV), and mortality. Risks for severe COVID-19 outcomes are presented as odds ratios (OR) and 95% confidence interval (95%CI) for cohort studies with BMI-defined obesity, and standardized mean difference (SMD) and 95%CI for controlled studies with VAT-defined excessive adiposity.
Results: A total of 45, 650 participants from 30 studies with BMI-defined obesity and 3 controlled studies with VAT-defined adiposity were included for assessing the risk of severe COVID-19. Univariate analyses showed significantly higher ORs of severe COVID-19 with higher BMI: 1.76 (95%: 1.21, 2.56, $P = 0.003$) for hospitalization, 1.67 (95%CI: 1.26, 2.21, $P<0.001$) for ICU admission, 2.19 (95%CI: 1.56, 3.07, $P<0.001$) for IMV requirement, and 1.37 (95%CI: 1.06, 1.75, $P = 0.014$) for death, giving an overall OR for severe COVID-19 of 1.67 (95%CI: 1.43, 1.96; $P<0.001$). Multivariate analyses revealed increased ORs of severe COVID-19 associated with higher BMI: 2.36 (95%CI: 1.37, 4.07, $P = 0.002$) for hospitalization, 2.32 (95%CI: 1.38, 3.90, $P = 0.001$) for requiring ICU admission, 2.63 (95%CI: 1.32, 5.25, $P = 0.006$) for IMV support, and 1.49 (95%CI: 1.20, 1.85, $P<0.001$) for mortality, giving an overall OR for severe COVID-19 of 2.09 (95%CI: 1.67, 2.62; $P<0.001$). Compared to non-severe COVID-19 patients, severe COVID-19 cases showed significantly higher VAT accumulation with a SMD of 0.49 for hospitalization (95% CI: 0.11, 0.87; $P = 0.011$), 0.57 (95% CI: 0.33, 0.81; $P<0.001$) for requiring ICU admission and 0.37 (95% CI: 0.03, 0.71; $P = 0.035$) for IMV support. The overall SMD for severe COVID-19 was 0.50 (95% CI: 0.33, 0.68; $P<0.001$).
Conclusions: Obesity increases risk for hospitalization, ICU admission, IMV requirement and death among patients with COVID-19. Further, excessive visceral adiposity appears to be associated with severe COVID-19 outcomes. These findings emphasize the need for effective actions by individuals, the public and governments to increase awareness of the risks resulting from obesity and how these are heightened in the current global pandemic.

1. Introduction

The world is witnessing a global pandemic of coronavirus disease 2019 (COVID-19), which is considered to be related to infection by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Most people with COVID-19 appear to develop mild to moderate illness characterized by fever, dry cough and tiredness, and recover without intensive care unit (ICU) admission [1]. In some individuals, however, it may progress to serious conditions such as pneumonia and respiratory

Abbreviations: COVID-19, Coronavirus Disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; ICU, intensive care unit; BMI, body mass index; CNKI, Chinese National Knowledge Infrastructure; MeSH, Medical Subject Headings; VAT, Visceral adipose tissue; IMV, invasive mechanical ventilation; OR, odds ratio; 95% CI, 95% confidence interval; SMD, standardized mean difference; NOS, Newcastle-Ottawa Scale; CT, computed tomography; IAV, Influenza A virus; ACE2, angiotensin-converting enzyme 2; SAT, subcutaneous adipose tissue; DKD, diabetic kidney disease.

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https://doi.org/10.1016/j.metabol.2020.154378
0026-0495/

failure. As of 10 August 2020, there were 19, 718, 030 confirmed cases and 728, 013 confirmed deaths reported in 216 countries, areas or territories [2]. As the crisis of COVID-19 continues, worldwide efforts have been underway to investigate the disease severity and health complications. Early studies have shed light on risk factors that might drive the disease to be life threatening [3,4]. Patients who are older and have pre-existing chronic medical conditions, including obesity, cardiovascular diseases, diabetes, cancers and chronic respiratory diseases and kidney diseases were found to be vulnerable to severe COVID-19 [3,4].

Of concern, most chronic medical conditions often co-exist with obesity even in patients younger than 60 years of age. As a public health epidemic, obesity affects more than 650 million adults (about 13% of the world's adult population) and 124 million children and adolescents worldwide [5]. Moreover, much clinical research from different affected countries and areas suggests a strong relationship between body mass index (BMI) defined obesity and increased risk of testing positive for SARS-CoV-2 [6], as well as increased risk of severe disease among patients with COVID-19 [7–10]. In a prospective cohort study of 233 patients hospitalized with COVID-19 in Italy, patients with obesity had a 3-fold higher risk of death as compared to those with a BMI<30 kg/m^2 [11]. Among 200 patients with COVID-19 in the Bronx borough of New York City, severe obesity (defined as BMI ≥ 35 kg/m^2) was associated with higher in-hospital mortality independent of other pertinent potentially confounding factors [12]. However, a prospective cohort study of 1150 adults hospitalized with COVID-19 in New York did not show that severe obesity was an independent risk factor for in-hospital mortality [13]. Other preliminary studies have suggested that increased visceral fat is associated with a worse prognosis among patients with COVID-19 [14,15], implicating a potential positive association between visceral obesity and COVID-19 severity. Therefore, the effects of obesity on the clinical outcomes of COVID-19 warrant systematical investigation. We conducted this systematic review and meta-analysis to investigate the impact of obesity on disease severity and fatality among patients with COVID-19.

2. Material and methods

2.1. Literature search

Medical articles published or preprinted up to August 10, 2020 were searched through databases including PubMed, EMBASE, Web of Science, Chinese National Knowledge Infrastructure (CNKI), Wanfang Data, SinoMed, and the preprint service for the medicine and health sciences of medRxiv, with no restriction on the language used. We searched databases of published articles with text-words in Medical Subject Headings (MeSH) and the text-words are as follows: ("coronavirus disease 2019" or "covid-19" or "2019 novel coronavirus" or "2019-ncov" or "novel coronavirus 2019 infection" or "2019-ncov infection" or "severe acute respiratory syndrome coronavirus 2" or "sars-cov-2") AND "obesity" or "overweight" or "body mass index" or "BMI" or "visceral fat" or "excessive fat" or "abdominal fat" or "visceral adipose tissue" or "visceral adiposity" or "central adiposity" or "waist circumference" or "risk factors" or "factor" or "risk factor" or "clinical characteristics" or "clinical features". For medRxiv searching, we used the term of "covid-19 and obesity" as the strategy to identify the potentially most relevant articles for our study.

BMI and VAT levels were used as indicators to reflect obesity status in the present analysis. The amount of VAT was measured by using computed tomography (CT), and all defined-indicators of quantification of VAT among studies were accepted. Severe COVID-19 was defined by four clinical outcomes including three levels of care that a patient required, and the worst outcome of death. The three levels of care were hospitalization, ICU admission, and invasive mechanical ventilation (IMV) support. Death related to COVID-19 was defined as being a lab-confirmed case of COVID-19 death during the study period and the follow-up period of a study, regardless of where or not the death occurred in a hospital. Diagnostic criteria for cases of COVID-19 in studies required a laboratory-confirmed positive SARS-CoV-2 infection as a necessary condition. All diagnostic criteria for obesity among studies were accepted. Based on these criteria, we searched for cohort studies on COVID-19 among published articles and other publicly available research that met the following eligibility criteria: (a) BMI or VAT amount or obesity status provided in the data of demographic characteristics; and (b) Reported clinical outcomes included hospitalization, ICU admission, IMV requirement, and death for study participants with COVID-19. We excluded medical literatures with the following characteristics: (a) participants in the control group for cohort study were people without COVID-19; (b) pregnant women with COVID-19 were the object of study; (c) participants of a study included suspected cases of COVID-19 which were not confirmed by SARS-CoV-2 diagnostic tests. (d) no defined obesity group data or BMI data were provided as continuous variables rather than categorical that indicated obesity status; (e) no available data were provided for the calculation of odds ratio (OR) and 95% confidence interval (95%CI) when indicating the strength of association between BMI and aforementioned clinical outcomes; (f) composited outcomes rather than separate outcomes were provided.

2.2. Data abstraction

The following data were abstracted by three reviewers (LY, HYM and HY) from all included eligible studies: author, publication year, country, study type, sample size and valid participants numbers, study period, mean age or median age, age range, numbers of males, measure of obesity, numbers of participants with obesity, and defined clinical outcomes. Risks of severe COVID-19 were presented as OR and 95% CI for cohort studies with BMI-defined obesity and standardized mean difference (SMD) and 95%CI for controlled studies with VAT-defined excessive adiposity.

2.3. Quality assessment

The Newcastle–Ottawa Scale (NOS) was used in this study to assess quality of all included cohort studies. Since age is a well-established risk factor for COVID-19 severity, we selected age as the most important factor for comparability of cohorts on the basis of the design or analysis. Studies with more than 7 stars, 5–7 stars, and 0–4 stars had high, moderate, and low quality, respectively.

2.4. Statistical analysis

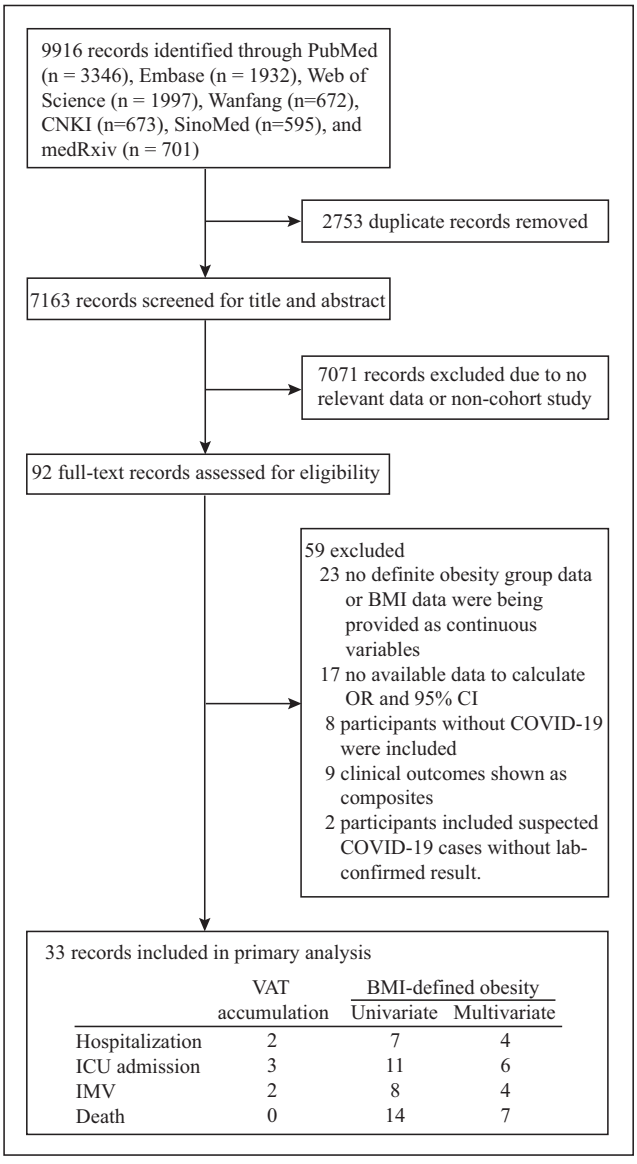
For included studies that provided data about BMI-defined obesity group and corresponding clinical outcomes rather than OR and 95%CI, we performed Chi-square test and risk estimation statistics using SPSS 22.0 to calculate *P* value, related OR and 95%CI that applied to univariate analysis. For each study that provided age-specific or BMI-specific OR and 95%CI for association between obesity and defined outcomes, we conducted the effect size combination for all age subgroups as well as all obesity groups and non-obesity group using Stata/SE 12.0. We then conducted the effect size combination for all included studies. Pooled OR and 95%CI estimates were calculated using Stata/SE 12.0 to address the relationship between BMI-defined obesity and the risk of defined outcomes among patients with COVID-19. For continuous outcome variables, SMD is a measure of distance between two group means in terms of one or more variables and used as a summary statistic when outcome from each study is measured using several different scales [16]. Since all defined-indicators of quantification of VAT among studies were accepted in our meta-analysis, SMD was used as a summary statistic for included studies to evaluate VAT difference between severe COVID-19 and non-severe COVID-19 groups. The I^2 statistic was used to describe the degree of heterogeneity among the studies. $I^2 > 50\%$ was considered as high heterogeneity and this allowed us to use the random-effects model, while $I^2<50\%$ allowed us to run the fixed-effects model.

Potential publication bias was evaluated by visual inspection of funnel plots. Egger's tests were used to assess the symmetry of a funnel plot. The level of statistical significance was defined as $P < 0.05$.

3. Results

3.1. Included studies

A total of 9, 916 articles were identified using the search strategies (Fig. 1). After removing 2, 753 duplicated records, 7, 163 studies were then screened for title and abstract and 7, 071 were excluded due to having no relevant data or being a non-cohort study. The remaining 92 articles were fully reviewed and 33 studies which met inclusion criteria were included. Among 33 included studies, 30 studies were analyzed to assess the association between BMI and severe COVID-19 while the remaining 3 studies were analyzed to evaluate the association between VAT and severe COVID-19. From 92 full-text articles that were assessed for eligibility, we excluded 59 studies (Supplementary appendix A) owing to no available definite obesity group data or BMI data being provided as continuous variables ($n = 23$), no available data to calculate OR and 95% CI ($n = 17$), where the study included participants without COVID-19 ($n = 8$), where participants of a study included suspected cases of COVID-19 which were not confirmed by SARS-CoV-2 diagnostic tests ($n = 2$) or where clinical outcomes of the study shown as composited and could not be analysis separately ($n = 9$). Thirty included studies which reported BMI as a variable, were assigned to different groups according to various specified outcomes. For univariate analysis, there were seven studies included to estimate the risk of hospitalization, eleven studies to estimate the risk of ICU admission, eight studies to estimate the need for IMV and fourteen to estimate the risk of death. For multivariate analysis, there were four studies included to estimate the risk of hospitalization, six studies to estimate the risk of ICU admission, four studies the risk of requiring IMV and seven studies the risk of death. We identified one study from the Bronx borough of New York City reporting a positive association between BMI ≥ 35 kg/m^2 and worse in-hospital outcomes among 200 patients with COVID-19 [12]. In this retrospective cohort study, BMI ≥ 35 kg/m^2 (reference: BMI 25–34 kg/m^2) was independently associated with increased risks of intubation (OR: 3.87; 95%CI: 1.47, 10.18; $P = 0.006$) and in-hospital mortality (OR: 3.78; 95% CI: 1.45, 9.83; $P = 0.006$). However, this valuable study provided no available data on defined obesity group (BMI ≥ 30 kg/m^2) and therefore was not included in our meta-analysis. Among the other three included studies reporting VAT as variable, there were two studies included to estimate the risk of hospitalization, three studies the risk of ICU admission, two studies the risk of needing IMV and no studies to estimate the risk of death. We identified only one article reporting an association between VAT area and death related to COVID-19 [15]. However, this research was finally excluded from our study as there was no available data of VAT area for the survivor group.



	VAT accumulation	BMI-defined obesity	
		Univariate	Multivariate
Hospitalization	2	7	4
ICU admission	3	11	6
IMV	2	8	4
Death	0	14	7

Fig. 1. Flowchart of screened and included studies. In the box of included records, column headings represent obesity condition including VAT accumulation and BMI-defined obesity; Rowheadings represent clinical outcomes including hospitalization, ICU admission, IMV and death. Abbreviation: CNKI, Chinese National Knowledge Infrastructure; BMI, body mass index; OR, odds ratio; 95%CI, 95% confidence interval; COVID-19, Coronavirus Disease 2019; VAT, visceral adipose tissue; ICU, intensive care unit; IMV, invasive mechanical ventilation.

3.2. Characteristics and quality assessment

The included studies involved 9 countries over the world including USA, Italy, China, Spain, The state of Kuwait, Mexico, France, Switzerland and Greece. A total of 45, 650 participants were finally included into analysis. Nearly two third of the studies (18/33) were from USA, the current epicenter of the coronavirus pandemic. A retrospective study design was used in the majority of included studies (87.9%, 29/33). We identified five studies, which didn't report their study type as retrospective studies according to their study methods [7,9,17–19]. Only one of the included studies was designed as a retrospective and prospective study [20]. Patients mainly participated in these studies between February to May. The participants in 20 studies were all adults, over 18 years of age, while 11 studies did not report the age range of their participants in detail. Only one study included exclusively children with a median age of 13.1 (0.4–19.3) [21]. Except for this study, the median age of participants ranges from 40.5 (31.5–52.1) to 72 (60–80) years, with fourteen studies reporting a mean age or no statistical description for their age range. Obesity criteria among 24 studies were defined as a level of BMI of 30 kg/m^2 or more. One study from China defined a BMI of 28 kg/m^2 or more as obesity in accordance to obesity criteria of Chinese adults [9], another study from Italy defined a BMI of over 29 kg/m^2 as obesity [22]. It should be noted that one study emphasized that the World Health Organization defined obesity as abnormal or excessive fat accumulation that presents a risk to health [14]. No obesity definition was given in six studies [17,20,23–26]. The percentage of people with obesity among valid participants of all but one of the included studies ranged from 10.9% to 61.3%, with only one study below 10% (Table 1). Among three studies that aimed to evaluate the association between VAT and severe COVID-19, a CT measurement was performed to quantify VAT. One study defined VAT as the greatest

Table 1
Characteristics of included studies.

Study author, year	Country	Study type	Sample size	No. of valid participants	Median age	Age range	Male (%)	Study period	Measure of Obesity	No. of participants with obesity (%)	Outcomes
Giacomelli et al., 2020 [11]	Italy	Prospective	233	233	61(50–72)	18–95	161 (69.1)	21/2–19/5	BMI ≥ 30	38(16.3)	Death
Borobia et al., 2020 [17]	Spain	Retrospective	2226	2226	61 (46–78)	18–90	1074 (48.2)	25/2–19/4	NA	242(10.9)	Death
Kalligeros et al., 2020 [68]	USA	retrospective	103	103	60 (50–72)	≥18	63 (61.2)	17/2–5/4	BMI ≥ 30	49(47.5)	ICU admission, IMV
Chao et al., 2020 [21]	USA	Retrospective	46	46	13.1 (0.4–19.3)	1 month to 21 years	31 (67.4)	15/3–13/4	BMI>30	12(26.1)	ICU admission
Giorgi Rossi et al., 2020 [23]	Italy	Prospective	2653	2407	63.2	NA	1328 (50.1)	27/2–2/4	NA	65(2.7)	Hospitalization, death
Goyal et al., 2020 [69]	USA	Retrospective	393	380	62.2 (48.6–73.7)	≥18	238 (60.6)	5/3–27/3	BMI ≥ 30	136(35.8)	IMV
Argenziano et al., 2020 [70]	USA	Retrospective	1000	781	63.0 (50–75)	≥18	596 (59.6)	1/3–5/4	BMI > 30	352(41.6)	ICU admission
Al-Sabah et al., 2020 [71]	The State of Kuwait	Retrospective	1158	727	40.5 (31.5–52.1)	NA	945 (81.6)	24/2–7/4	BMI ≥ 30	148(20.4)	ICU admission
Petrilli et al., 2020 [72]	USA	Prospective	5279	5040	54 (38–66)	≥19	2615 (49.5)	1/3–8/4	BMI ≥ 30	1865(37.0)	Hospitalization
Mejia-Vilet et al., 2020 [73]	Mexico	Prospective	329	329	49 (41–60)	>18	211 (64)	16/3–8/5	BMI > 30	132(40.1)	ICU admission
Hur et al., 2020 [74]	USA	Retrospective	486	486	59(47–69)	≥18	271 (55)	1/3–8/4	BMI ≥ 30	259(53.3)	IMV
Robilotti et al., 2020 [75]	USA	Retrospective	423	423	NA	NA	212 (50)	10/3–7/4	BMI ≥ 30	130(30.7)	Hospitalization
Carrillo-Vega et al. [24]	Mexico	Retrospective	10,544	9946	48.15 ± 14.35§	NA	6082 (57.7)	27/2–23/4	NA	2053 (20.64)	Hospitalization, death
Simonnet et al., 2020 [8]	France	Retrospective	124	124	60(51–70)	NA	90 (72.6)	27/2–5/4	BMI > 30	59(47.6)	IMV
Shekhar et al., 2020 [20]	USA	Retrospective& prospective	50	50	55.5 (20–85)	≥18	23(46)	19/1–24/4	NA	20/39(51)	ICU admission
Klang et al., et al., 2020 [40]	USA	Retrospective	3406	3406	NA	≥18	1961 (57.6)	1/3–17/5	BMI ≥ 30	1231(36.1)	Death
Cai et al., 2020 [9]	China	Retrospective	383	383	NA	≥18	183 (47.5)	11/1–26/3	BMI ≥ 28	41(10.7)	ICU admission, death
Regina et al., 2020 [76]	Switzerland	Retrospective	200	200	70(55–81)	≥18	120 (60)	1/3–25/3	BMI > 30	54(27)	IMV
Lighter et al., 2020 [10]	USA	Retrospective	3615	3615	NA	≥18	NA	3/3–4/4	BMI ≥ 30	547(15.1)	ICU admission
Petrilli et al., 2020 [7]	USA	Retrospective	4103	4103	52(36–65)	NA	2072 (50.5)	1/3–2/4	BMI ≥ 30	1100(26.8)	Hospitalization
Kim et al., 2020 [18]	USA	Retrospective	2491	2491	62(50–75)	≥18	1326 (53.2)	1/3–2/5	BMI ≥ 30	1154/2332 (49.7)	ICU admission, death
Gaibazzi et al., 2020 [22]	Italy	Retrospective	279	279	72 (60–80)	NA	169 (61)	5/3–15/3	BMI>29	29/181(16)	Death
Ebinger et al., 2020 [19]	USA	Retrospective	442	442	52.7 ± 19.7§	NA	256 (58)	26/2–21/3	BMI ≥ 31	71(16.1)	Hospitalization, ICU admission, IMV
Daniel et al., 2020 [77]	USA	Retrospective	172	172	53 (33.5–68)	NA	96 (55.8)	12/3–8/5	BMI>30	89(51.7)	Death
Murillo-Zamora et al., 2020 [78]	Mexico	Retrospective	5393	5393	NA	≥18	3432 (63.6)	4/3–5/5	BMI ≥ 30	1197(22.2)	Death
Halvatsiotis et al., 2020 [79]	Greece	Retrospective	90	86	65.5 (56–73)	NA	72(80)	10/3–13/4	BMI>30	30(34.4)	Death
Rottoli et al., 2020 [80]	Italy	Retrospective	516	482	66.2 ± 16.8§	≥18	302 (62.7†)	1/3–20/4	BMI ≥ 30	104(21.6)	ICU admission, death
Steinberg et al., 2020 [81]	USA	Retrospective	210	210	NA	18–45	NA	8/3–4/4	BMI>30	NA	Hospitalization, IMV, death
Pettit et al., 2020 [35]	USA	Retrospective	238	238	58.5 ± 17§	NA	113 (47.5)	1/3–18/4	BMI ≥ 30	146(61.3)	ICU admission, IMV, death
Nakeshbandi et al., 2020 [82]	USA	Retrospective	504	504	68 ± 15§	≥18	263 (52)	10/3–13/4	BMI ≥ 30	215(30)	IMV, death
Chandarana et al., 2020 [26]	USA	Retrospective	51	51	59.8 ± 14.9§	20–88	38 (70.4)	19/3–19/4	VAT deposition	NA	Hospitalization, ICU admission, IMV
Battisti et al., 2020 [25]	Italy	Retrospective	441	144	60.3 ± 17.0§	NA	NA	26/2–6/4	VAT deposition	NA	ICU
Watanabe et al., 2020 [14]	Italy	Retrospective	150	150	64.15 ± 15.69§	22–97	97 (64.7)	1/3–31/3	VAT deposition	NA	Hospitalization, ICU admission, IMV

BMI = Weight (kg)/Height^2(m^2) and is expressed in units of **kg/m^2**. Abbreviation: BMI, body mass index; NA, not available; ICU, intensive care unit; IMV, invasive mechanical ventilation; VAT, visceral adipose tissue.
§ Statistical description of age was presented as Mean ± Standard Deviation.
¶ We identified these five studies, which didn't report their study type as retrospective studies according to their study methods.
† Proportion of male among total valid participants.

distance between the inner muscular wall and the anterior liver surface and therefore assessed VAT amount by thickness [25], whereas two other studies [14,26] assessed VAT amount by area (Table B. Supplementary appendix B). In the two studies, VAT content was evaluated at different abdominal levels of CT scan: the first slice where lung bases were no longer visible at the thoracoabdominal level in one study [14] and the axial slice at the superior end plate of L3 vertebral body in the other study [26].

Using the NOS method, studies included in the present analysis had an average score of 8, with 22 studies achieved 8 or 9 scores and were then considered as cohort study of high quality. Eleven studies achieved scores of 5 to 7 and thus were considered as moderate quality (Table 2).

3.3. Univariate analysis of association between BMI-defined obesity and severe COVID-19

Pooled effects of univariate analysis of included studies indicated that BMI-defined obesity increased risk of severe disease among patients with COVID-19, as shown in Fig. 2. COVID-19 patients with obesity had a significantly increased risk of needing hospitalization (OR: 1.76, 95% CI: 1.21, 2.56, $P = 0.003$) and ICU admission (OR: 1.67, 95% CI: 1.26, 2.21, $P<0.001$). Similarly, obesity also increased risk of death for patient with COVID-19 (OR: 1.37, 95% CI: 1.06, 1.75, $P = 0.014$). Moreover, obesity was in particular found to be associated with an over twofold significantly increased risk of IMV among patients with COVID-19 (OR:2.19, 95%CI: 1.56, 3.07, $P<0.001$). The overall risk estimation of univariate analyses showed significant OR of obesity with COVID-19 severity: 1.67 (95%CI: 1.43, 1.96, $P<0.001$). Furthermore, since Paleodimos and colleagues reported the importance of severe obesity as a critical component to COVID-19 severity in the cohort of the Bronx borough of New York City [12], we included their study in our meta-analysis and performed a summary estimation (Table C. Supplementary appendix C). The pooled OR and 95%CI estimates did not change appreciably: an OR of 2.22 (95%CI: 1.62, 3.03; P<0.001) by univariate association between BMI-defined obesity and IMV requirement among COVID-19 patients, an OR of 1.41 (95%CI: 1.11, 1.81; $P = 0.006$) between BMI-defined obesity and COVID-19 mortality and an overall OR of 1.70 (95%CI: 1.45, 1.99; P<0.001) between BMI-defined obesity and the risk of COVID-19 severity.

3.4. Multivariate analysis association between BMI-defined obesity and COVID-19 severity

Pooled summary effects of multivariate analysis of included studies also suggested that BMI-defined obesity increased risk of severe disease and death among patients with COVID-19, as shown in Fig. 3. After adjusting for covariate factors, COVID-19 patients with obesity were also at a high risk of needing hospitalization (OR: 2.36, 95%CI: 1.37, 4.07, $P = 0.002$) and ICU admission (OR: 2.32, 95%CI: 1.38, 3.90, $P = 0.001$). Compared to univariate analysis, and after multivariate adjustment, obesity added a nearly 3-fold increased risk of needing IMV among patients with COVID-19 (OR: 2.63, 95%CI: 1.32, 5.25, $P = 0.006$). However, in multivariate analysis, there were only minor changes of increased risk of death that obesity added to patients with COVID-19(OR: 1.49, 95%CI: 1.20, 1.85, $P<0.001$). The overall risk estimation of multivariate analyses

Table 2
Quality assessment of included studies using the Newcastle–Ottawa Scale (NOS).

Study ID	Selection				Comparability		Outcome		
	Representativeness of the exposed cohort	Selection of the non exposed cohort	Ascertain-ment of exposure	Demonstration that outcome of interest was not present-at start of study	Comparability of cohorts on the basis of the design or analysis		Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow-up of cohorts
Giacomelli et al., 2020	☆	☆	☆	☆	☆	☆	☆	☆	☆
Borobia et al., 2020	☆	☆	☆	☆	☆	☆	☆	☆	☆
Kalligeros et al., 2020	☆	☆	☆	☆	☆	☆	☆	☆	☆
Chao et al., 2020	☆	☆	☆	☆			☆		☆
Giorgi Rossi et al., 2020	☆	☆	☆	☆	☆	☆	☆	☆	☆
Goyal et al., 2020	☆	☆	☆	☆			☆		☆
Argenziano et al., 2020	☆	☆	☆	☆			☆		☆
Al-Sabah et al., 2020	☆	☆	☆	☆	☆	☆	☆	☆	☆
Petrilli et al., 2020	☆	☆	☆	☆	☆	☆	☆	☆	☆
Mejia-Vilet et al., 2020	☆	☆	☆	☆	☆	☆	☆	☆	☆
Hur et al., 2020	☆	☆	☆	☆	☆	☆	☆	☆	☆
Robilotti et al., 2020	☆	☆	☆		☆		☆	☆	☆
Carrillo-Vega et al	☆	☆	☆		☆	☆	☆		
Simonnet et al., 2020	☆	☆	☆	☆	☆	☆	☆		☆
Shekhar et al	☆	☆	☆	☆			☆		☆
Klang et al., et al., 2020	☆	☆	☆	☆	☆	☆	☆		☆
Cai et al., 2020	☆	☆	☆	☆	☆	☆	☆	☆	☆
Regina et al	☆	☆	☆	☆	☆	☆	☆	☆	☆
Lighter et al., 2020	☆	☆	☆	☆			☆		
Petrilli et al., 2020	☆	☆	☆		☆	☆	☆	☆	☆
Kim et al., 2020	☆	☆	☆	☆	☆	☆	☆	☆	☆
Gaibazzi et al., 2020	☆	☆	☆	☆	☆	☆	☆	☆	☆
Ebinger et al., 2020	☆	☆	☆	☆	☆	☆	☆	☆	☆
Daniel et al., 2020	☆	☆	☆	☆	☆	☆	☆	☆	
Murillo-Zamora et al., 2020	☆	☆	☆	☆	☆	☆	☆	☆	☆
Halvatsiotis et al., 2020	☆	☆	☆	☆			☆	☆	☆
Rottoli et al., 2020	☆	☆	☆	☆	☆	☆	☆	☆	☆
Steinberg et al., 2020	☆	☆	☆					☆	☆
Pettit et al., 2020	☆	☆	☆	☆	☆	☆	☆	☆	☆
Nakeshbandi et al., 2020	☆	☆	☆	☆	☆	☆	☆	☆	☆
Chandarana et al., 2020	☆	☆	☆	☆			☆	☆	☆
Watanabe et al., 2020	☆	☆	☆	☆	☆	☆	☆	☆	☆
Battisti et al., 2020	☆	☆	☆		☆	☆		☆	☆

showed a significant OR of severe COVID-19 with obesity: 2.09 (95% CI: 1.67, 2.62, $P<0.001$). When the Paleodimos study were included in our meta-analysis, the pooled OR and 95%CI estimates slightly increased (Table C. Supplementary appendix C): an OR of 2.79 (95%CI: 1.54, 5.04; $P = 0.001$) by multivariate association between BMI-defined obesity and IMV requirement among COVID-19 patients, an OR of 1.57 (95%CI: 1.25, 1.98; P<0.001) between BMI-defined obesity and COVID-19 mortality and an overall OR of 2.17 (95%CI: 1.74, 2.70; P<0.001) between BMI-defined obesity and the risk of COVID-19 severity.

3.5. Increased VAT accumulation among patients with severe COVID-19

Compared to the non-severe COVID-19 group, VAT accumulation levels were significantly higher in COVID-19 patients with a severe condition. For the hospitalized group versus those not hospitalized, the

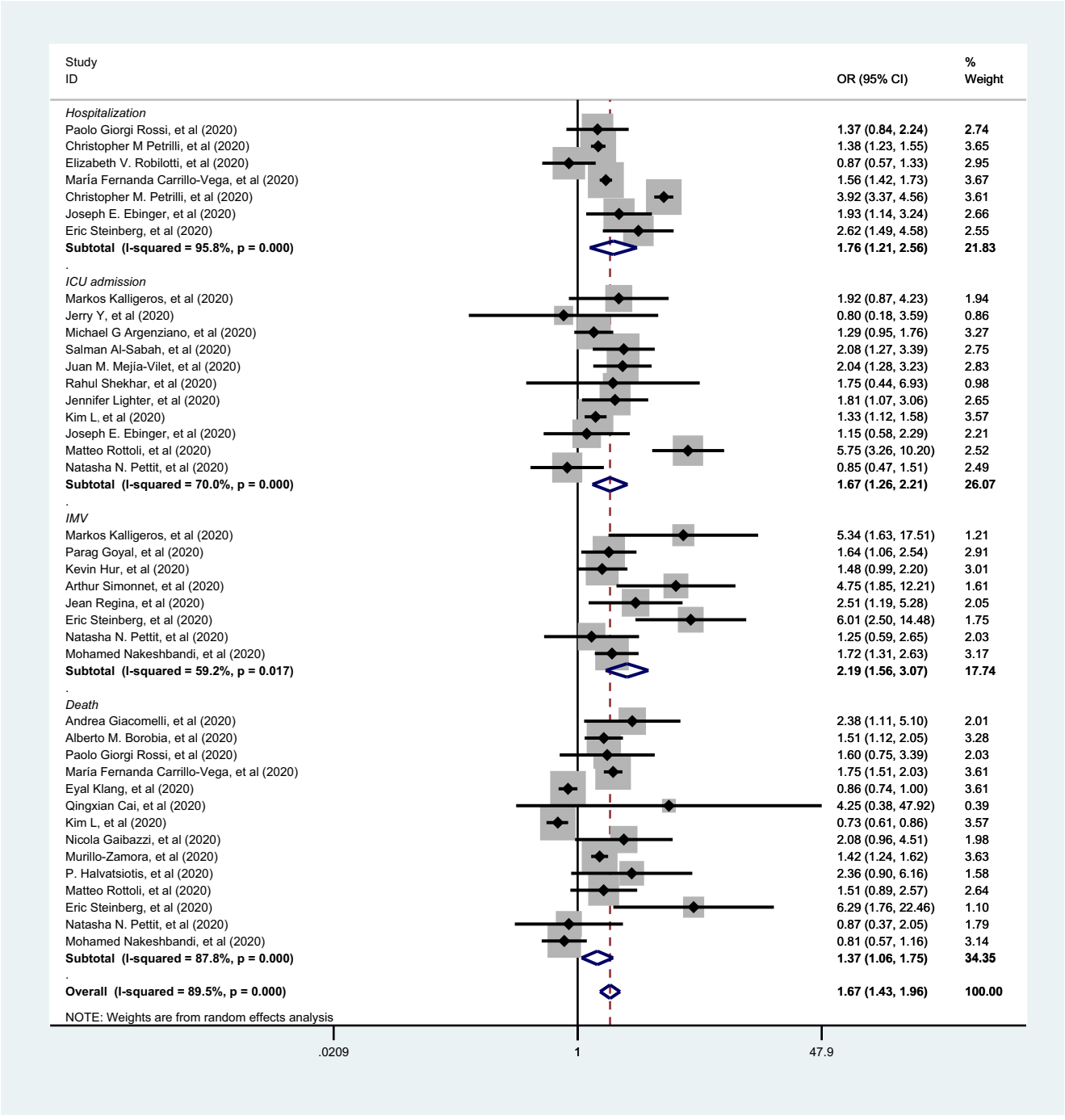


Fig. 2. Forest plots of univariate association between BMI-defined obesity and the risk of COVID-19 severity using the random-effects model. Clinical outcome of each subgroup is marked in italics. The gray squares show the estimated effect of each single study and their sizes reflected the weight of each single study on the summary effect. The larger the size, the greater the weight. The diamonds represent the overall summary effects with their widths reflecting the length of the 95% CI. A wider diamond means a wider 95% CI. The horizontal black lines through the gray squares also represent the length of the 95% confidence interval of individual studies. The longer the line, the wider the 95% CI. The solid vertical black line is the line of no effect. The region to the left of the line of no effect indicates no association while the region to the right indicates association. When the diamond touches the solid vertical black line, this indicates no statistical difference. The dotted black line is the line of the overall summary effect. Subtotal effect estimate results and the overall results are marked in bold. I-squared indicates the degree of heterogeneity within the studies. Abbreviation: OR, odds ratio; 95%CI, 95% confidence interval; ICU, intensive care unit; IMV, invasive mechanical ventilation; COVID-19, Coronavirus Disease 2019.

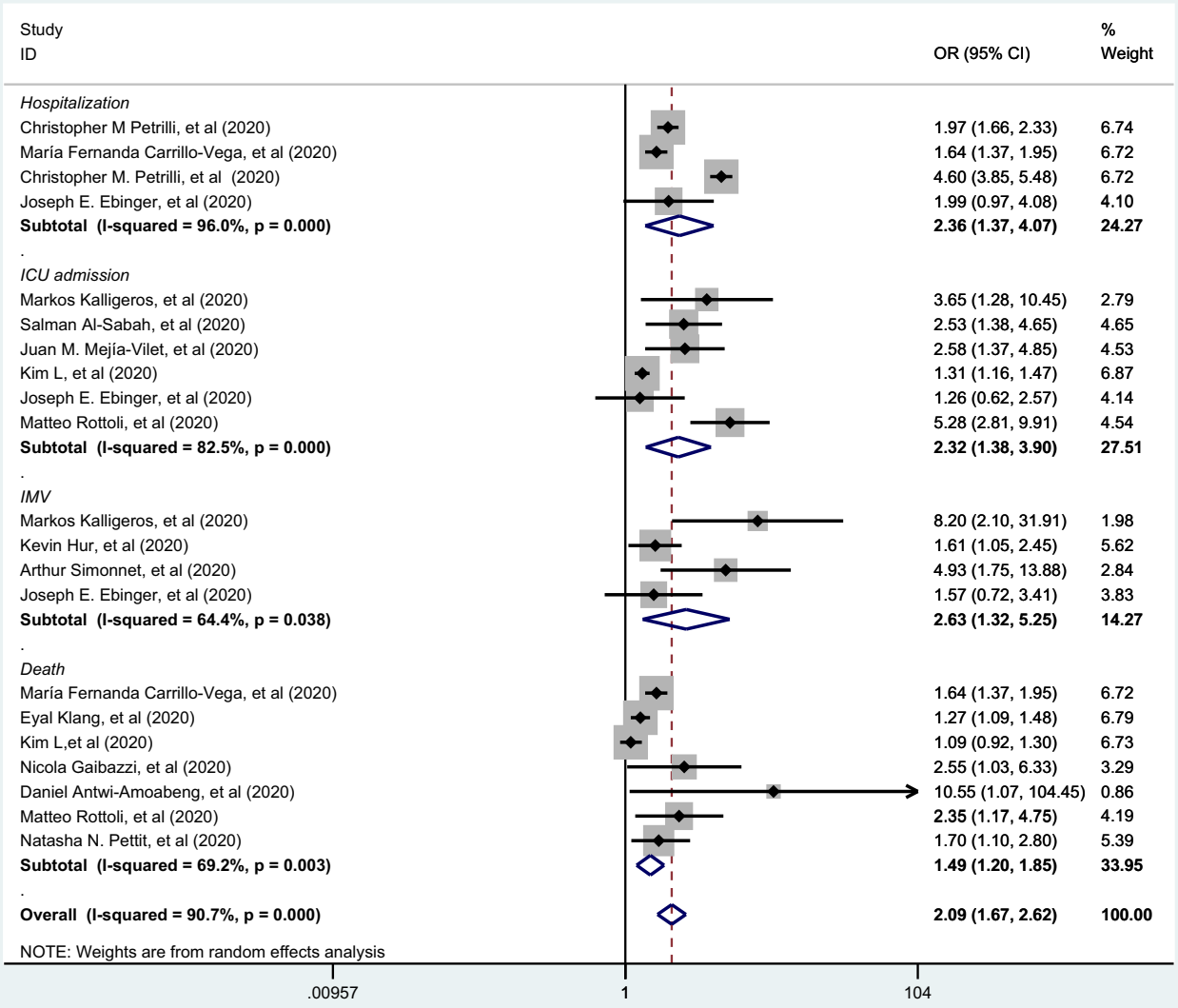


Fig. 3. Forest plots of multivariate association between BMI-defined obesity and the risk of COVID-19 severity using the random-effects model. Clinical outcome of each subgroup is marked in italics. The gray squares show the estimated effect of each single study and their sizes reflect the weight of each single study on the summary effect. The larger the size, the greater the weight. The diamonds represent the overall summary effects with their widths reflecting the length of the 95% CI. A wider diamond means a wider 95% CI. The horizontal black lines through the gray squares also represent the length of the 95% CI of individual studies. The longer the line, the wider the 95% CI. The solid vertical black line is the line of no effect. The region to the left of the line of no effect indicates no association while the region to the right indicates association. When the diamond touches the solid vertical black line, this indicates no statistical difference. The dotted black line is the line of the overall summary effect. Subtotal effect estimate results and the overall results are marked in bold. I-squared indicates the degree of heterogeneity within the studies. Abbreviation: OR, odds ratio; 95%CI, 95% confidence interval; ICU, intensive care unit; IMV, invasive mechanical ventilation; COVID-19, Coronavirus Disease 2019.

SMD was 0.49 (95% CI: 0.11, 0.87; $P = 0.011$), For the ICU admission group versus those not admitted to ICU, the SMD was 0.57 (95% CI: 0.33, 0.81; $P<0.001$) and for the IMV group versus those not needing IMV, the SMD was 0.37 (95% CI: 0.03, 0.71; $P = 0.035$) (Fig. 4). The overall estimated effect was statistically significant (SMD = 0.50, 95% CI: 0.33, 0.68; $P<0.001$) (Fig. 4), indicating that the more VAT accumulation a COVID-19 patient had, the more severe the clinical condition they might develop.

3.6. Assessment of publication bias

No significant publication bias was shown in the funnel plots (Fig. 5.) and the result was confirmed by Egger's test (Egger's tests: Fig. 5a. $P = 0.332$; Fig. 5b. $P = 0.132$; Fig. 5c. $P = 0.438$).

4. Discussion

Our study confirms that obesity may increase the risks of hospitalization, ICU admission, the necessity for IMV, and death among patients with COVID-19. An early systematic review addressed that obesity was a predictor for a worse prognosis of COVID-19 with a total of three cohort studies included [27]. Previous meta-analysis studies indicated that COVID-19 patients with higher BMI were at a greater risk of medical complications [28], ICU admission [29,30], IMV intervention [29,30], death [31,32] and poor composite outcomes [31,33,34]. Findings in our study are consistent with those reports, suggesting a positive relationship between higher BMI and increased risk of disease severity among patients with COVID-19.

In terms of method, both univariate and multivariate analyses of the association between high BMI and clinical outcomes were performed in

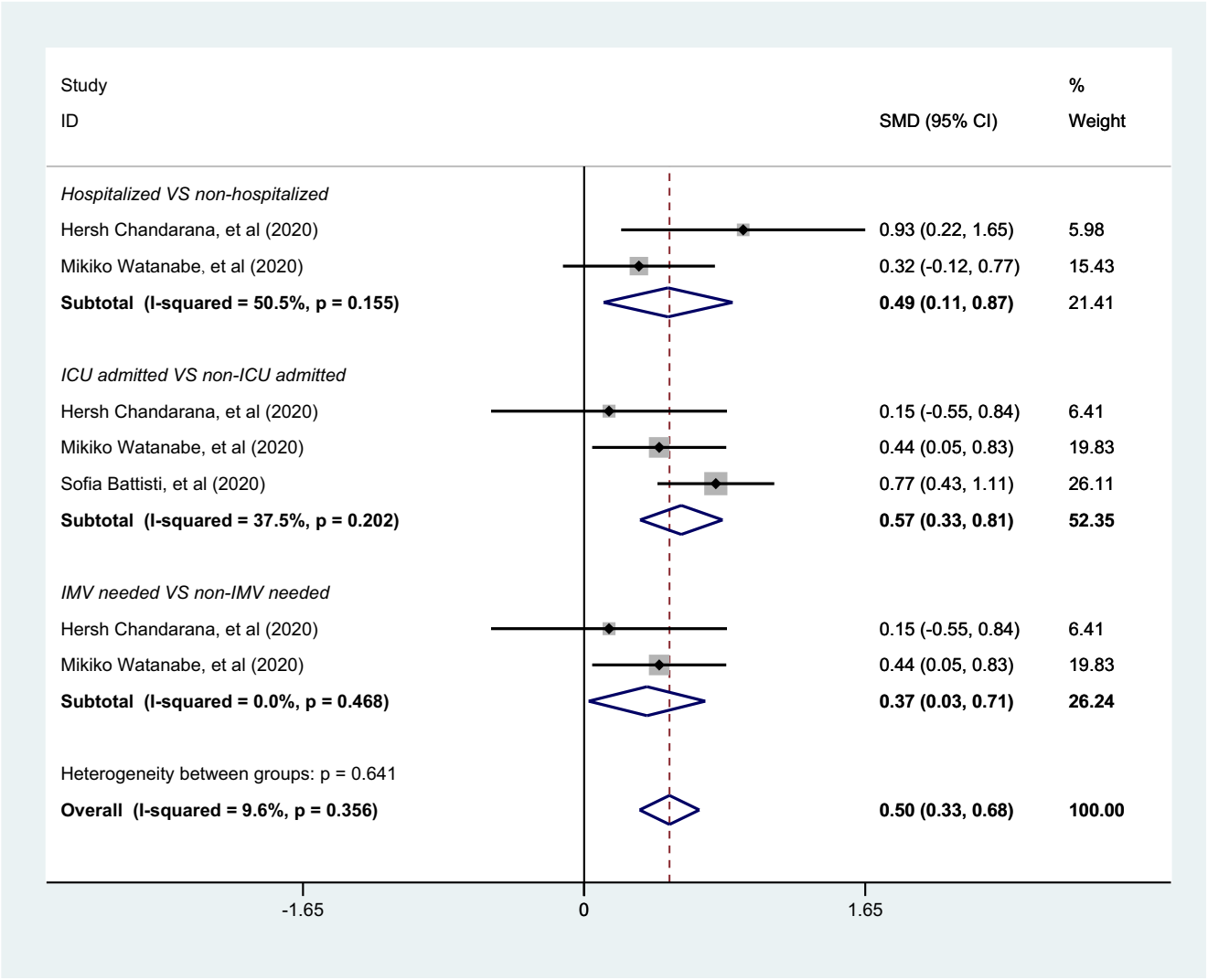


Fig. 4. Forest plots of VAT amount between severe group and non-severe group among COVID-19 patients using the fixed-effects model. The gray squares show the estimated effect of each single study and their sizes reflect the weight of each single study on the summary effect. The larger the size, the greater the weight. The diamonds represent the overall summary effects with their widths reflecting the length of the 95% CI. A wider diamond means a wider 95% CI. The horizontal black lines through the gray squares also represent the length of the 95% CI of individual studies. The longer the line, the wider the 95% CI. The solid vertical black line is the line of no effect. The region to the left of the line of no effect indicates a lower mean value for the experimental group versus the control group while the region to the right indicates a higher mean value for the experimental group versus the control group. When the diamond touches the solid vertical black line, this indicates no statistical difference. The dotted black line is the line of the overall summary effect. Subtotal effect estimate results and the overall results are marked in bold. I-squared indicates the degree of heterogeneity within the studies. Abbreviation: SMD, Standardized Mean Difference; 95%CI, 95% confidence interval; ICU, intensive care unit; IMV, invasive mechanical ventilation; VAT, visceral adipose tissue;COVID-19, Coronavirus Disease 2019.

our meta-analysis to provide a contrast among study results, which differs from previous similar meta-analyses. Moreover, previous meta-analyses focused mainly on the association between BMI-defined obesity and COVID-19 severity. However BMI does not reflect the distribution of body fat and therefore these research analyses fail to demonstrate the impact of excess body fat in different parts of the body on COVID-19 severity. To the best of our knowledge, this is the first meta-analysis to identify a positive relationship between high VAT accumulation and severe COVID-19.

Obesity prevalence among hospitalized COVID-19 patients can reach up to 61.3%, according to an American study from our included articles [35]. In addition to the impact of obesity on the risk of hospitalization, this may also due to high prevalence of obesity in American population. The prevalence of obesity among adults in the USA was 42.4%, with severe obesity in 9.2% in 2017–2018 [36]. By 2016, obesity had reached 27.8% in the UK, 19.9% in Italy, 6.2% in China, 4.7% in Korea, 3.9% in India, 22.1% in Brazil, 23.8% in Spain, 21.6% in France and 28.9% in Mexico [37]. Of particular note is that BMI threshold differs between Asian and Caucasian populations, and health risks among these two groups can be different at any given BMI. Despite the lower prevalence of BMI-defined obesity, awareness of a potentially similar obesity-related risk of COVID-19 should be not be delayed by Asian countries.

Since older age has been well recognized as an important risk factor of suffering a severe condition of COVID-19, we should be cautious about applying the findings of our meta-analysis to children. Most infected children appear to experience more favorable outcomes than adults [38]. The study we included that examined children had a relatively small subject number and did not find an association between obesity and increased likelihood of pediatric intensive care unit admission [21]. However, a significant inverse correlation between age and BMI was reported among 265 patients admitted to ICU, meaning that obesity could shift severe COVID-19 disease to younger ages [39]. On the other hand, two studies we included found that the effect of BMI ≥30 kg/m^2 on COVID-19 severity or death among adults was age-

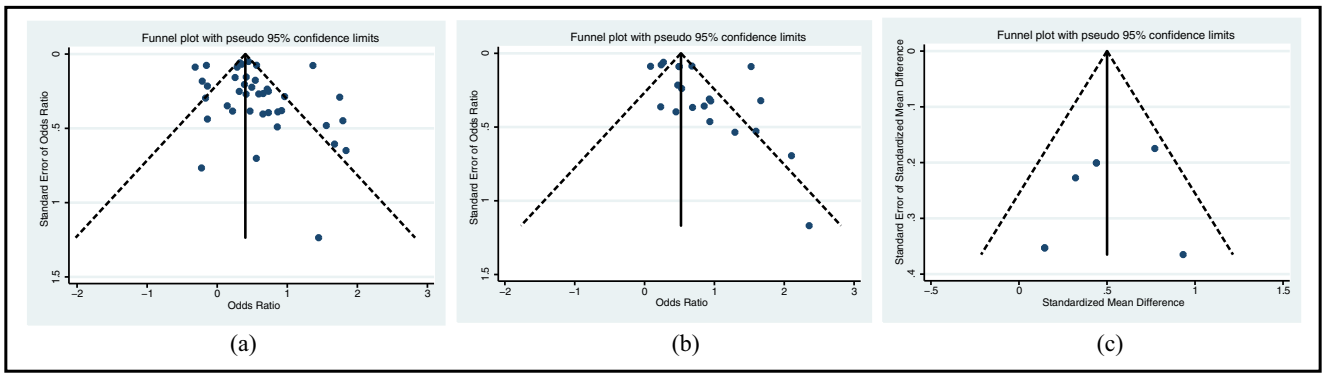


Fig. 5. Funnel plot of included studies for publication bias. a. Funnel plot of included studies using univariate analysis between BMI-defined obesity and COVID-19 severity; b. Funnel plot of included studies using multivariate analysis between BMI-defined obesity and COVID-19 severity; c. Funnel plot of included studies that assessed the association between VAT accumulation and severe COVID-19.

dependent [10,40]. Compared to younger patients, older COVID-19 patients with BMI ≥ 30 kg/m^2 appeared to develop a less severe condition [10,40]. Nevertheless, it's worth noting that the gradient of risk of severe COVID-19 in relation to BMI might be more gradual among older patients when compared to younger individuals [41]. This may be attributed to the fact that BMI is a less accurate predictor of excess fat in older adults with lower muscle mass, together with a shift from subcutaneous fat to VAT and increased relative fat mass among them [14]. A more precise measurement of excess fat may help predict more reliable health risks in this group with obesity. The positive relationship between VAT and severe COVID-19 in our meta-analysis may provide an important insight.

The underlying mechanism by which obesity increases the risk of severe covid-19 remains unknown. Previous research has shown that obesity was related to a worse outcome as a result of infection and disease progression for certain kinds of infectious virus diseases, such as influenza in the 1918 "Spanish" influenza pandemic [42,43], the 1957 pandemic, the 1968 pandemic and the 2009 Influenza A virus (IAV) H1N1 pandemic [44,45]. People with obesity tend to have respiratory dysfunction at various levels [46] and may be mildly hypoxaemic [47]. A greater oxygen cost of breathing was needed for patients with obesity when compared to those without obesity, even at rest [47]. In a recently published meta-analysis, dyspnea rather than fever was shown to be significantly associated with the risk of mortality among COVID-19 patients [48]. One study we included found that BMI ≥ 30 kg/m^2 were associated with the risk of hypoxemia upon hospital admission among patients with COVID-19 (OR: 1.7, 95%CI: 1.3, 2.1; $P < 0.0005$) [35]. A BMI ≥ 35 kg/m^2 was even a significant predictor for increasing oxygenation requirement in a cohort of COVID-19 patients in the Bronx borough of New York City [12]. In the children-included study [21], shortness of breath was found to be the only clinical symptom that was associated with pediatric intensive care unit admission. Patients diagnosed with obesity hypoventilation syndrome developed typical hypoxaemia and hypercapnia, and may suffer a higher risk of severe condition when infected with SARS-CoV-2 [49]. Therefore, obesity-related hypoxaemia might be an important contributor to COVID-19 severity among those with obesity. This may explain why COVID-19 patients with obesity were at a greater risk of needing IMV, as shown by results in our study.

Obesity also increases the risk of many common non-communicable diseases such as diabetes mellitus, cardiovascular disorders, cancers and non-alcoholic fatty liver disease, and often co-exists with them in a single individual. These co-existing co-morbidities are considered to increase the likelihood of severe illness from COVID-19 for people with obesity [50–52]. Excessive adipose tissue including ectopic fat may serve as reservoirs for angiotensin-converting enzyme 2 (ACE2) and microbes such as coronavirus, influenza A virus and *Mycobacterium tuberculosis* [53]. Beyond disease severity, obesity increased the duration of influenza A virus shedding to hasten virus spreading mainly for person-to-person transmission [54]. Moreover, college volunteers with symptomatic seasonal influenza who had higher BMI have been found to generate more infectious aerosols [55]. These findings may also extend to COVID-19.

Above all, combined adipose tissue-mediated immune and metabolic dysfunctions might play a key role in the pathophysiological pathways that lead obesity to influence COVID-19 prognosis [46,56,57]. Low-grade systemic inflammation and increasing insulin resistance commonly exists in people with obesity [58,59]. and this immune and metabolic phenomena is strongly associated with presence of excess VAT [60]. Excess VAT is believed to be the main culprit in the inflammatory diseases of obesity [60], which in turn might induce severe complications on top of the viral infection itself, such as development of thrombosis [56]. Visceral obesity-related impaired immune response can also lead to systemic metabolic dysfunction [43,56] and increase risks of metabolic disorders and cardiovascular diseases, as well as their complications [61–63]. Furthermore, while BMI on its own does not reflects any particular distribution of body fat, VAT is a marker of increased ectopic fat that might contribute to increased atherosclerosis and cardiometabolic risk [64]. Excessive visceral adiposity may provide additional important information about COVID-19 risk, which is not captured in BMI. Evidence of value from two recent studies, which were not included in our analysis due to our study design and eligibility criteria, suggests that visceral adiposity increases the likelihood of severe COVID-19 [15,65]. Central obesity is defined as a state of excessive VAT accumulation [66]. Patients with central obesity evidenced by waist circumference or waist-to-hip ratio were also found to be more likely to develop severe COVID-19 (P<0.001) in a large population-based cohort [67]. Our primary analysis also demonstrates a more VAT accumulation among patients with severe COVID-19. For the sake of comparison, we also extracted data on subcutaneous adipose tissue (SAT) from the included 3 controlled studies with VAT-defined adiposity, and performed a separate meta-analysis to evaluate SAT accumulation with the risk of severe COVID-19 (Table D & Fig. D. Supplementary appendix D). The overall estimated SMD was −0.05 (95% CI: −0.22, 0.13; $P = 0.601$), indicating that there might have no significant difference of SAT accumulation between severe group and non-severe group among COVID-19 patients. Therefore, compared to SAT, VAT accumulation might be a stronger contributor to COVID-19 severity.

The present study assesses the risk of severe COVID-19 with obesity, using not only BMI but also VAT measures, and this is the main strength of our study. There are also several limitations to be acknowledged. First, some participants we included might overlap, because some of our included studies are from the same affected area or city and both single-center and multi-center studies were included in our meta-analysis. Second, despite our study seeking to investigate the role of

VAT accumulation in the risk of severe COVID-19, diagnostic cut-off points by VAT amount for obesity of the three included studies could not be set in our meta-analysis since no accepted standards of diagnostic criteria by VAT quantification for obesity were available. Third, while fat mass can be classified as VAT, SAT, ectopic fat (intra-muscular fat, myocardial steatosis, fatty liver, atheroma, et al), and blood lipids (dyslipidemia) we have only evaluated the impact of VAT and SAT on COVID-19 prognosis. A comprehensive assessment of the relationship between excess fat mass and the risk of severe COVID-19 will require a thorough literature search and extensive future investigation. Fourth, in our study, the effects of combining all included studies could lead to a bias due to the adjusted confounders for BMI or obesity state varying between the included studies, particularly in the absence of adjusting for some unrecognized factors. Last, since the vast majority of included studies were designed as retrospective, a causal relationship between obesity and COVID-19 severity and death should not be identified.

5. Conclusions

Our study suggests that obesity increases risk for hospitalization, ICU admission, need for IMV and death among patients with COVID-19. Further, excessive visceral adiposity appears to be associated with severe COVID-19 outcomes. The clinical outcomes of communicable disease such as COVID-19 might also depend on obesity status. These findings emphasize the need for effective actions by individuals, the public and governments to increase awareness of the risks resulting from obesity and how these are heightened in the current global pandemic.

Funding

This work was supported by grants from the National Natural Science Foundation of China (81471054, 81660150), the Innovation Project of Guangxi Graduate Education (JGY2015128) and Seeding Fund of the Center for Diabetic Systems Medicine, Guangxi Key Laboratory of Excellence (203030401902). The funders had no role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript.

CRediT authorship contribution statement

Yi Huang: Data curation, Formal analysis, Writing - original draft. **Yao Lu:** Data curation, Validation, Investigation. **Yan-Mei Huang:** Data curation. **Min Wang:** Formal analysis. **Wei Ling:** Formal analysis. **Yi Sui:** Writing - review & editing. **Hai-Lu Zhao:** Conceptualization, Methodology, Writing - review & editing.

Declaration of competing interest

We declare no competing interests.

Acknowledgement

We are grateful to Dr. Phil Griffiths for his work revising the written English in our text.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.metabol.2020.154378.

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