Systematic Review and Meta-Analysis

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Obesity or increased body mass index and the risk of severe outcomes in patients with COVID-19

A protocol for systematic review and meta-analysis

Yaxian Yang, BM[a], Liting Wang, MS[a,b], Jingfang Liu, MD[a,b,*], Songbo Fu, MD[a,b], Liyuan Zhou, BM[b], Yan Wang, BM[b]

Abstract

Background: To assess the effect of obesity or a high body mass index (BMI) on the risk of severe outcomes in patients with coronavirus disease 2019 (COVID-19).

Methods: Studies on the relationship between BMI or obesity and COVID-19 since December 2019. The odds ratio (OR) and weighted mean difference (WMD) with their 95% confidence intervals (CIs) were used to assess the effect size.

Results: BMI was significantly increased in COVID-19 patients with severe illness (WMD: 1.18; 95% CI: 0.42–1.93), who were admitted to an intensive care unit (ICU) (WMD: 1.46; 95% CI: 0.96–1.97), who required invasive mechanical ventilation (IMV) (WMD: 2.70, 95% CI: 1.05–4.35) and who died (WMD: 0.91, 95% CI: 0.02–1.80). In Western countries, obesity (BMI of ≥30 kg/m^2) increased the risk of hospitalization (OR: 2.08; 95% CI: 1.22–3.54), admission to an ICU (OR: 1.54; 95% CI: 1.29–1.84), need for IMV (OR: 1.73, 95% CI: 1.38–2.17), and mortality (OR: 1.43; 95% CI: 1.17–1.74) of patients with COVID-19. In the Asian population, obesity (BMI of ≥28 kg/m^2) increased the risk of severe illness (OR: 3.14; 95% CI: 1.83–5.38). Compared with patients with COVID-19 and a BMI of <25 kg/m^2, those with a BMI of 25–30 kg/m^2 and ≥30 kg/m^2 had a higher risk of need for IMV (OR: 2.19, 95% CI: 1.30–3.69 and OR: 3.04; 95% CI: 1.76–5.28, respectively). The risk of ICU admission in patients with COVID-19 and a BMI of ≥30 kg/m^2 was significantly higher than in those with a BMI of 25–30 kg/m^2 (OR: 1.49; 95% CI: 1.00–2.21).

Conclusion: As BMI increased, the risks of hospitalization, ICU admission, and need for IMV increased, especially in COVID-19 patients with obesity.

Ethics and dissemination: This systematic review and meta-analysis does not require an ethics approval as it does not collect any primary data from patients.

Abbreviations: ACE2 = angiotensin-converting enzyme 2, BMI = body mass index, CAD = coronary artery disease, CHD = coronary heart disease, CIs = confidence intervals, CKD = chronic kidney diseases, COVID-19 = coronavirus disease 2019, CVD = cerebrovascular disease, DM = diabetes mellitus, HTN = hypertension, ICU = intensive care unit, IL = interleukin, IMV = invasive mechanical ventilation, NA = not available, NOS = Newcastle–Ottawa Scale, OR = odds ratio, SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2, SD = standard deviation, TNF = tumor necrosis factor, WMD = weighted mean difference.

Keywords: BMI, COVID-19, intensive care unit, invasive mechanical ventilation, mortality, obesity

1. Introduction

Coronavirus disease (COVID-19) has spread to several countries around the world since 2019 and poses a significant threat to the health and property of people around the world. COVID-19 is caused by infection by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a membrane-wrapped, single-stranded ribonucleic acid virus.[1]

COVID-19 mainly manifests with respiratory symptoms (fever, fatigue, and cough), but some patients experience gastrointestinal symptoms, such as diarrhea, vomiting, and

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The data that support the findings of this study are available from the corresponding author upon reasonable request.

[a] The First Clinical Medical College, Lanzhou University, Lanzhou, Gansu, P.R. China, [b] Department of Endocrinology, The First Hospital of Lanzhou University, Lanzhou, Gansu, P.R. China.

[*] Correspondence: Jingfang Liu, Department of Endocrinology, The First Hospital of Lanzhou University, 1 Donggang West Road, Lanzhou, Gansu 730000, P.R. China (e-mail: ljf824168@126.com).

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anorexia. Approximately 10% of patients with COVID-19 who present with gastrointestinal symptoms have no signs of fever or respiratory infections.[2] Patients with severe COVID-19 can experience respiratory failure and multiple organ failure, leading to death. COVID-19 is primarily symptomatic, with no specific drug for treatment currently identified.

Humans are generally susceptible to SARS-CoV-2 infections. The World Health Organization declared COVID-19 a global pandemic on March 11, 2020.[1] As it is an emerging infectious disease, many mechanisms of COVID-19 remain unknown. The understanding of the disease and its risk factors are key factors for implementing public health policies at present. Previous studies have shown that hypertension, diabetes mellitus, cardiovascular and cerebrovascular diseases, pulmonary diseases, age, and gender affect the prognosis and outcome of patients with COVID-19.[3] Obesity is a risk factor for many diseases such as heart disease, diabetes, and hypertension, with the number of people with obesity worldwide increasing annually. The prevalence of obesity in the United States was 39.8% from 2015 to 2016 and is projected to be 48.9% by 2030.[4] In developing countries such as China also, obesity is on the rise, with a considerable number of patients with COVID-19 being obese.[5] Therefore, at present, researchers need to pay attention to whether obesity in patients with COVID-19 increases the risk of adverse outcomes and whether a high BMI will affect the outcomes in patients with COVID-19. In this meta-analysis, the influence of different BMI values of patients with COVID-19 on their adverse clinical outcomes was investigated to provide a reference for the treatment of these patients in clinical practice.

2. Methods

2.1. Literature retrieval

We performed this systematic review and meta-analysis according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement,[6] and it was registered on the PROSPERO International Prospective Register of Systematic Reviews (registration number: CRD42021260770). This systematic review and meta-analysis does not require an ethics approval as it does not collect any primary data from patients. The PubMed, Embase, and China National Knowledge Infrastructure databases were searched for all studies since December 2019. We also included the relevant references of selected studies. The search strategy of matching keywords with free words was adopted, and the search terms were as follows: ("coronavirus disease 2019" or "2019 novel coronavirus" or "covid-19" or "2019-ncov" or "novel coronavirus 2019 infection" or "severe acute respiratory syndrome coronavirus 2" or "sars-cov-2") AND ("obesity" or "overweight" or "body mass index" or "BMI" or "risk factors" or "factor" or "risk factor" or "clinical characteristics" or "clinical features")

2.2. Inclusion and exclusion criteria

The following studies were included:

(1) studies on patients diagnosed with COVID-19 confirmed via polymerase chain reaction,
(2) retrospective or prospective studies without language restrictions,
(3) studies containing information on COVID-19 and BMI or obesity,
(4) studies with original data provided and the indicators, such as the number of patients with obesity in the experimental and control groups, not adjusted for, and
(5) studies mentioning the clinical outcomes of patients with COVID-19.

The following studies were excluded:

(1) studies involving populations without COVID-19,
(2) studies based on animals,
(3) case reports or reviews, and
(4) studies with incomplete data or poor quality (Newcastle–Ottawa Scale [NOS] score of ≤ 3).

2.3. Data extraction

Two researchers independently searched for relevant literature and decided whether the selected studies met the inclusion criteria. Any discrepancies were resolved via discussion. The following variables were extracted from each study if available: first author's name, country, single-center or multi-center, age of the study population, percentage of men in the population, sample of participants, different outcomes of patients with COVID-19, BMI levels with different clinical outcomes, number of patients with obesity who had different clinical outcomes, number of patients with different clinical outcomes at different BMI classes, rates of different comorbidities such as hypertension, diabetes mellitus, heart disease, dyslipidemia, and chronic kidney disease in patients with COVID-19.

2.4. Quality assessment

The NOS was used to assess the quality of the studies included in the meta-analysis. The scale consists of eight items under three dimensions: selection (4 items, maximum score 4), comparability (1 item, maximum score 2), and outcome (3 items, maximum score 3).[7] The highest score was 9. A total score of higher than 7 indicates high quality, 5–6 indicates moderate quality, and 0–4 indicates low quality.

2.5. Statistical analysis

In this meta-analysis, the following clinical adverse outcome events in patients with COVID-19 patients were used:

(1) hospitalization,
(2) severe illness,
(3) invasive mechanical ventilation (IMV) needed during hospitalization,
(4) admission to an intensive care unit (ICU) during hospitalization, and
(5) mortality during hospitalization.

First, the total number of patients in the experimental group (with the above outcome events) and the control group (without the above outcome events) were extracted, as well as their respective BMI; the original data in the included studies were mostly given as median values with interquartile ranges of BMI. We used the statistical method described by Luo et al[8] to calculate the mean and standard deviation (mean $\pm$ SD) of BMI based on the median values with interquartile ranges. The weighted mean difference (WMD) and 95% confidence interval (CI) were calculated according to the mean $\pm$ SD of BMI in each group. When the WMD was 0 or its 95% CI contained 0, the diamond-shaped box representing the combined

effect size intersected with the equivalent line in the forest map, suggesting that there was no statistically significant difference between the experimental and control groups in terms of the relevant outcome indicators. When the WMD was greater than 0 and the lower limit of 95% CI was greater than 0, the diamond-shaped box of the forest map was located to the right of the equivalent line, indicating that BMI was higher in the experimental group than in the control group. When the WMD was less than 0 and the upper limit of the 95% CI was less than 0, the diamond-shaped box of the forest map was located to the left of the equivalent line, indicating that BMI in the experimental group was lower than that in the control group.

Second, the criterion for obesity in the Asian population was a BMI of $\geq 28\,kg/m^2$,[9] whereas for non-Asians, obesity was defined as a BMI of $\geq 30\,kg/m^2$.[10] We analyzed the studies from these two populations according to the respective obesity standards. The total number of patients in the experimental group and control groups (without relevant outcome events) and the number of patients with obesity in the experimental group and the control group were extracted. Using STATA 12.0, odds ratios (OR) and 95% CIs were calculated. When the OR value was equal to 1 or the 95% CI was 1, BMI was not associated with the risk of adverse outcomes in patients with COVID-19. When the OR value was greater than 1 or the lower limit of 95% CI was greater than 1, BMI was positively associated with the risk of adverse outcomes in patients with COVID-19. When the OR value was less than 1 or the upper limit of the 95% CI was less than 1, BMI was inversely associated with the risk of adverse outcomes in patients with COVID-19.

At present, BMI is used to measure the degree of body fat and thinness and whether a person is healthy or not. In our study, a BMI of $\geq 30\,kg/m^2$ in Western countries and a BMI of $\geq 28\,kg/m^2$ in the Asian population were considered to indicates obesity, and the risks of relevant clinical outcomes were analyzed. In addition, BMI was stratified into three classes: $<25\,kg/m^2$, 25–30 kg/m^2, and $\geq 30\,kg/m^2$.[11] BMI $\geq 30\,kg/m^2$ by extracting the number of COVID-19 patients at different BMI classes who had related clinical outcomes and those who did not have relevant clinical outcomes in relevant studies. The three different classes were compared, and the OR values and 95% CI for different clinical outcomes were calculated using STATA 12.0 software.

In this meta-analysis, STATA 12.0 was used to draw forest maps. A fixed effect model or a random effect model was adopted according to the heterogeneity of the included studies, and Cochran Q and I^2 statistics were used to test the heterogeneity. A fixed-effects model was used when $I^2 < 50\%$. Otherwise, a random-effects model was chosen. In the subgroup analysis, $P < .05$ was considered statistically significant.

3. Results

3.1. Search results

A total of 3717 studies describing the correlations between COVID-19 and BMI or obesity were retrieved (1840 in PubMed, 1016 in Embase, and 861 in the China National Knowledge Infrastructure databases). By reading the titles and abstracts, we screened the studies, and 346 duplicates were eliminated. As a result, 3371 studies remained, and after skimming the titles, abstracts, and reading the full texts, 204 studies were obtained. After carefully reading the 204 studies, 57 studies were finally selected.[12–67] The details of the screening process are presented in Figure 1.

3.2. Basic characteristics of the included studies

The basic characteristics of 57 studies are shown in Table 1. The studies were from different parts of the world including China, the United States, and Europe. There were 49 retrospective cohort studies,[12–25,27–30,32–38,40–41,43–60,62,64,65,67] 8 prospective cohort studies,[26,31,39,42,51,61,63,66] 43 single-center studies,[12,15,16,18–21,23–47,49,52,53,55–58,60–62,66] and 14 multi-center studies.[13,14,17,22,48,50,51,54,59,63–65,67] Among these, 29 stud-

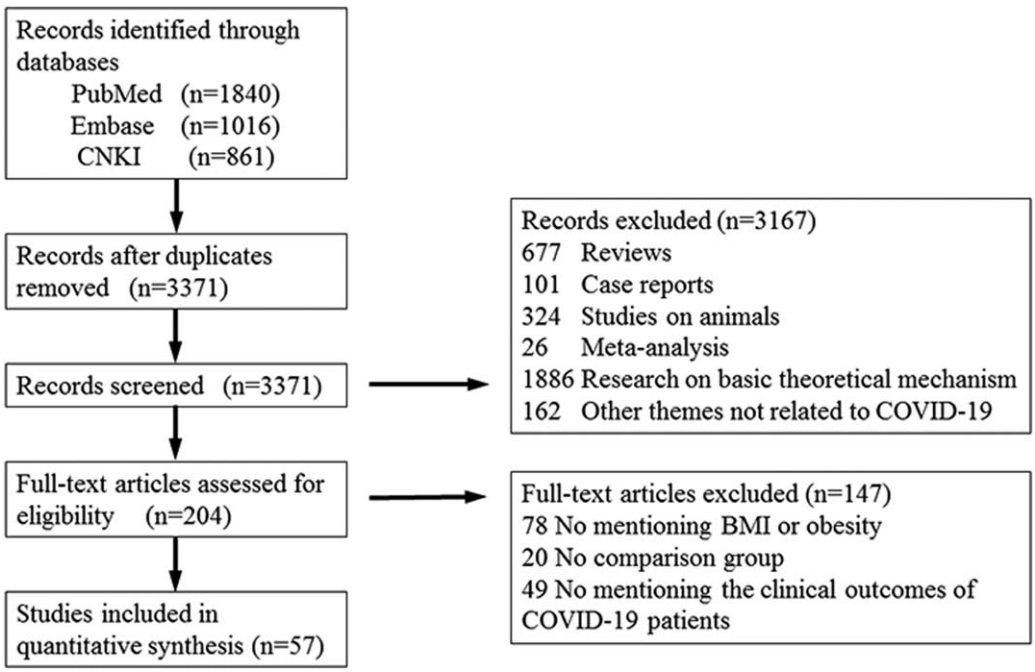

Figure 1. Flow diagram of the study selection.

Table 1

Basic characteristics of the included studies.

Study	Country	Study type	Center (single-/ multi-)	Sample (severe group/non severe group)	Primary outcomes	Age (yr)	Male (%)	Comorbidities (%)
Cai[25]2020	China	Retrospective	Single	298 (58/240)	Severe illness	47.5	48.7	HTN 15.8, DM 6.04, CVD 8.39
Bhatla[28]2020	USA	Retrospective	Single	700 (79/621)	ICU	50	45	HTN 50, CHD 11, DM 26, CKD 11
Chao[29]2020	USA	Retrospective	Single	46 (13/33)	ICU	13.1	69.6	NA
Wei[12]2020	China	Retrospective	Single	276 (14/262)	Severe illness	51.0	56.2	HTN 17, DM 5.1, CHD 4.0, CVD 2.2
Li[26]2020	China	Prospective	Single	548 (269/279)	Severe illness	60	50.9	HTN 30.3, DM 15.1, CHD 6.2, CKD 1.8
Almazeedi[30]2020	Kuwait	Retrospective	Single	1096 (42/1054)	ICU	41	81	HTN 16.1, DM 14.1, Dyslipidemia 5.9, CAD 3.7, CKD 1.0, CVD 0.6
Huang[13]2020	China	Retrospective	Multi	202 (23/179)	Severe illness	44	57.4	HTN 14.4, DM 9.4, CAD 2.5, CVD 1.5
Wu[14]2020	China	Retrospective	Multi	280 (83/197)	Severe illness	43.1	53.9	CVD20.36, CKD 1.07
Xiang[15]2020	China	Retrospective	Single	49 (9/40)	Severe illness	42.9	67.3	HTN 12.2, DM 4.1
Chen[16]2020	China	Retrospective	Single	145 (43/102)	Severe illness	47.5	54.4	HTN 15.2, DM 9.7, CKD 2.1, Hyperlipidemia 2.3
Xiong[17]2020	China	Retrospective	Multi	131 (30/101)	Severe illness	63.2	57.3	CAD 68.7, DM 22.9
Sun[18]2020	China	Retrospective	Single	57 (45/12)	Severe illness	NA	50.9	Chronic disease history 59.6
Mejía-Vilet[31]2020	Mexico	Prospective	Single	329 (115/214)	ICU	49	64	HTN 27, DM 24, CKD 6
Mejía-Vilet[31]2020	Mexico	Prospective	Single	240 (115/125)	ICU	52	69	HTN 31, DM 33, CKD 5
Liu[19]2020	China	Retrospective	Single	30 (4/26)	Severe illness	35	33	NA
Peng[20]2020	China	Retrospective	Single	112 (16/96)	Severe illness	62	47.3	HTN 82.14, DM 20.54, CHD 55.36
Simonnet[34]2020	France	Retrospective	Single	124 (85/39)	IMV	60	73	HTN 49, DM 23, Dyslipidemia 28
Dreher[35]2020	Germany	Retrospective	Single	50 (24/26)	IMV	65	66	HTN 70, DM 59, CKD 20, CVD 14
Regina[36]2020	Switzerland	Retrospective	Single	200 (37/163)	IMV	70	60	HTN 43.5, DM 21.5, CAD 17.5, CKD 14
Zhang[21]2020	China	Retrospective	Single	52 (21/31)	Severe illness	65.5	63.5	HTN 65.4, DM 100, CHD 26.9, CKD 5.8
Huang[22]2020	China	Retrospective	Multi	60 (8/52)	Severe illness	57	58.3	HTN 23.3, DM 16.7, CAD 5.0, CKD 1.7
Petrey[27]2021	USA	Retrospective	Single	22 (8/14)	Severe illness	NA	59	HTN 50, DM 50
Argenziano[33]2020	USA	Retrospective	Single	850 (236/614)	ICU	63	60.1	HTN 59.8, DM 39.2, CKD 13.7, CAD 13.5
Brill[37]2020	UK	Retrospective	Single	410 (173/237)	Death	72	60	HTN 43, DM 30
Cao[38]2020	China	Retrospective	Single	102 (17/85)	Death	54	52	HTN 27.5, DM 10.8, CAD 4.9, CKD 3.9
Garcia[39]2020	Switzerland	Prospective	single	398 (97/301)	Death	63	75.1	HTN 44.1, DM 23, CHD 23.8
Gayam[40]2021	USA	Retrospective	Single	408 (132/276)	Death	67	56.6	HTN 66.42, DM 43.24, CAD 13.24, Dyslipidemia 16.18
Krishnan[41]2020	USA	Retrospective	Single	152 (92/60)	Death	68	62.5	HTN 73, DM 65, CAD 15, Hypercholesterolemia 61, CKD 14
Masetti[42]2020	Italy	Prospective	Single	229 (33/196)	Death	60.7	64.6	HTN 38, DM 18.8, CHD 9.2, CKD 4.8
Salacup[43]2021	USA	Retrospective	Single	242 (52/190)	Death	66	49	HTN 74, DM 49, CAD 19, CKD 17
Auld[44]2020	USA	Retrospective	Single	209 (62/147)	Death	64.0	54.2	HTN 61.7, DM 45.6, CAD 14.3, CKD 26.7
Luo[45]2021	China	Retrospective	Single	85 (12/73)	Death	63.0	56.5	HTN 35.29, CHD 11.76, DM 14.12
Zhang[46]2020	China	Retrospective	Single	43 (12/31)	Death	NA	NA	NA
Klang[47]2020	USA	Retrospective	Single	572 (60/512)	Death	NA	69.4	HTN 29.5, DM 25.2, CAD 5.1, CKD 10.4, Hyperlipidemia 12.3
Klang[47]2020	USA	Retrospective	Single	2834 (1076/1758)	Death	NA	58.9	HTN 71.7, DM 47.7, CAD 20.4, CKD 17.0, Hyperlipidemia 40.0
Halvatsiotis[48]2020	Greece	Retrospective	Multi	86 (26/60)	Death	65.5	80	HTN 50, DM 18.9, CAD 21.1, CKD 4.4
Halasz[49]2020	Italy	Retrospective	Single	242 (78/164)	Death	64	80.2	HTN 45.5, DM 15.3, CAD 14.5
Giacomelli[61]2020	Italy	Prospective	Single	233 (48/185)	Death	61	69.1	NA
Borobia[62]2020	Spain	Retrospective	Single	2226 (460/1766)	Death	61	48.2	HTN 41.3, DM 17.1, CKD 7.8, CHD 19.3
Rossi[63]2020	Italy	Prospective	Multi	1292 (217/1075)	Death	63.2	50.1	HTN 18.1, DM 12, CKD 2.5, CHD 12.9, Dyslipidemia 5
Carrillo-Vega[50]2020	Mexico	Retrospective	Multi	9946 (963/8983)	Death	48.15	57.7	HTN 21.74, DM 17.65, CHD 2.99, CKD 2.13
Murillo-Zamoraa[64]2021	Mexico	Retrospective	Multi	5393 (1735/3658)	Death	NA	63.6	HTN 36.6,DM 31.1,CKD 5.5
Baqui[65]2020	Brazil	Retrospective	Multi	7371 (3328/4043)	Death	NA	58.2	DM 25.7, CHD 33.9, CKD 5.3
Rodríguez[66]2020	Spain	Prospective	Single	38 (10/28)	Death	NA	NA	DM 18.6, CHD 9.3, CKD 4.7
Amit[67]2020	USA	Retrospective	Multi	109 (56/53)	Death	72	69	HTN 54.5, DM 39.7, CHD 32.1, CKD 15.4, Dyslipidemia 15.4
Goyal[58]2020	USA	Retrospective	Single	380 (129/251)	IMV	62.2	60.6	HTN 50.1,DM 25.2
Hur[59]2020	USA	Retrospective	Multi	486 (138/348)	IMV	59	55.8	HTN 54.9, DM 32.9, CHD 22.8, CKD 8.6
Carrillo-Vega[50]2020	Mexico	Retrospective	Multi	9946 (3922/6024)	Hospitalization	48.15	57.7	HTN 21.74, DM 17.65, CHD 2.99, CKD 2.13
Shekhar[52]2020	USA	Retrospective	Single	39 (27/12)	ICU	55	46	HTN 34
Ebinger[53]2020	USA	Retrospective	Single	214 (77/137)	ICU	52.72	63.1	HTN 36.4
Ebinger[53]2020	USA	Retrospective	Single	77 (52/25)	IMV	52.72	74.0	HTN 36.4
Ferguson[54]2020	USA	Retrospective	Multi	72 (21/51)	ICU	60.4	52.8	CHD 59.7, CKD 5.6
Lodigiani[55]2020	Italy	Retrospective	Single	363 (57/306)	ICU	66	68	HTN 47.2, DM 22.7, CHD 13.9, CKD 15.1, Dyslipidemia 19.6
Hu[23]2020	China	Retrospective	Single	294 (164/130)	Severe illness	61	51.4	HTN 32.5, DM 14.6,CKD 2.2
Itelman[56]2020	Israel	Retrospective	Single	162 (26/136)	ICU	52	65	HTN 30.2, DM 18.5, CHD 7.4, CKD 1.2
Petrilli[51]2020	USA	Prospective	Multi	5279 (2741/2538)	Hospitalization	54	49.5	HTN 42.7, DM 22.6, CHD 52.1, CKD 12.3, Dyslipidemia 32.5
Petrilli[51]2020	USA	Retrospective	Multi	4103 (1999/2104)	Hospitalization	NA	50.5	HTN 24, CKD 5.2, DM 15, CHD 8.9, CKD 12.3, Dyslipidemia 18
Al-Sabah[32]2020	Kuwait	Retrospective	Single	1158 (104/1054)	ICU	40.5	81.6	HTN 20.4,DM 23.4
Caussy[60]2020	France	Retrospective	Single	291 (170/121)	IMV	NA	NA	NA
Kalligeros[57]2020	USA	Retrospective	Single	103 (44/59)	ICU	60	61.1	HTN 64, DM 36.8, CHD 24.2, CKD 10.6
Wang[24]2021	China	Retrospective	Single	482 (93/389)	Severe illness	52	54.7	HTN 24.77, DM 8.69, CAD 5.36

CAD = coronary artery disease, CHD = coronary heart disease, CKD = chronic kidney diseases, CVD = cerebrovascular disease, DM = diabetes mellitus, HTN = hypertension, ICU = intensive care unit, IMV = invasive mechanical ventilation, and NA = not available.

ies[13,24,31–34,36,47–67] with original data related to the dichotomous variable (obesity), 36 studies[12–22,25–49] with original data related to continuous data (BMI), and 9 studies[23,32–34,49,55,57,60,67] with BMI stratification could be carried out. The clinical outcomes of patients with COVID-19 in the included studies were hospitalization, ICU admission, need for IMV, and mortality; in 14 studies,[12–22,25–27] the clinical outcome was severe illness. In three of these studies,[25–27] the criteria for severe illness was based on the American Thoracic Society/Infectious Diseases Society of America guidelines,[68] while in the other 11 studies,[12–22] the criteria for severe illness was according to the National Health Commission of China classification.[69] In two studies,[31,47] the population was divided into two cohorts according to the time of hospitalization and age; therefore, we analyzed the two cohorts separately.

Table 2

Quality assessment of included studies (NOS).

Study	Selection			Comparability		Outcome			Total
	Representation of the exposed cohort	Selection of the non exposed cohort	Ascertainment 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	
Cai[25]2020	1	1	1	1	2	1	1	1	9
Bhatla[28]2020	1	1	1	1	1	1	1	1	8
Chao[29]2020	1	1	1	1		1		1	6
Wei[12]2020	1	1	1	1		1	1	1	7
Li[26]2020	1	1	1	1	1	1	1	1	8
Almazeedi[30]2020	1	1	1	1	2	1	1	1	9
Huang[13]2020	1	1	1	1	1	1		1	7
Wu[14]2020	1	1	1	1	1	1		1	7
Xiang[15]2020	1	1	1	1	1	1		1	7
Chen[16]2020	1	1	1	1		1		1	6
Xiong[17]2020	1	1	1	1	2	1		1	8
Sun[18]2020	1	1	1	1	1	1		1	7
Mejía-Vilet[31]2020	1	1	1	1	2	1	1	1	9
Liu[19]2020	1	1	1	1	2	1	1	1	9
Peng[20]2020	1	1	1	1	2	1		1	8
Simonnet[34]2020	1	1	1	1	2	1		1	8
Dreher[35]2020	1	1	1	1		1		1	6
Regina[36]2020	1	1	1	1	2	1	1	1	9
Zhang[21]2020	1	1	1	1	1	1		1	7
Huang[22]2020	1	1	1	1	1	1		1	7
Al-Sabah[32]2020	1	1	1	1	2	1	1	1	9
Petrey[27]2021	1	1	1	1	2	1		1	8
Argenziano[33]2020	1	1	1	1		1		1	6
Brill[37]2020	1	1	1	1	1	1	1	1	8
Cao[38]2020	1	1	1	1	1	1		1	7
Garcia[39]2020	1	1	1	1	2	1		1	8
Gayam[40]2021	1	1	1	1	1	1	1	1	8
Krishnan[41]2020	1	1	1	1		1	1	1	7
Masetti[42]2020	1	1	1	1		1		1	6
Salacup[43]2021	1	1	1	1	2	1		1	8
Auld[44]2020	1	1	1		1	1		1	6
Luo[45]2021	1	1	1	1	2	1	1	1	9
Zhang[46]2020	1	1			1	1	1	1	6
Klang[47]2020	1	1	1	1	2	1		1	8
Halvatsiotis[48]2020	1	1	1	1	2	1	1	1	9
Halasz[49]2020	1		1	1	1	1		1	6
Giacomelli[61]2020	1	1	1	1	2	1		1	8
Borobia[62]2020	1	1	1	1	2	1	1	1	9
Rossi[63]2020	1	1	1	1	2	1	1	1	9
Murillo-Zamoraa[64]2021	1	1	1	1	2	1	1	1	9
Baqui[65]2020	1	1	1	1	2	1	1	1	9
Rodríguez[66]2020	1	1	1		1	1		1	6
Amit[67]2020	1	1	1	1	1	1	1	1	8
Goyal[58]2020	1	1	1	1		1		1	6
Petrilli[51]2020	1	1	1	1	2	1	1	1	9
Hur[59]2020	1	1	1	1	2	1	1	1	9
Carrillo-Vega[50]2020	1	1	1		2	1			6
Shekhar[52]2020	1	1	1	1		1		1	6
Petrilli[51]2020	1	1	1	1	2	1	1	1	9
Ebinger[53]2020	1	1	1	1	2	1	1	1	9
Ferguson[54]2020	1	1	1		1	1		1	6
Lodigiani[55]2020	1	1	1		2	1	1	1	8
Hu[23]2020	1	1	1	1		1	1	1	7
Itelman[56]2020	1	1	1		2	1	1	1	8
Caussy[60]2020	1		1			1	1	1	5
Kalligeros[57]2020	1	1	1	1	2	1	1	1	9
Wang[24]2021	1	1			2	1		1	6

The number in the table represents the score.

3.3. Quality assessment of the included studies

The NOS was used to assess the quality of the studies. The results are shown in Table 2. All studies included in this study were of moderate or high quality.

3.4. Associations between elevated BMI and different clinical outcomes

A total of 36 studies[12–22,25–49] mentioned BMI and different clinical outcomes in patients with COVID-19. Among them, 14

studies[12–22,25–27] compared BMI of severe illness group and non-severe illness group, and 6 studies[28–33] were on the difference in BMI between the ICU group and non-ICU group. There were 3 studies[34–36] comparing BMI of patients with COVID-19 requiring IMV and not requiring IMV, while there were 14 studies[30,37–49] comparing BMI between the death group and survival group. The WMD and 95% CI were calculated according to the total number of patients in the experimental and control groups in each study and the mean ± SD of BMI in each group by the random effect model.

As shown in Figure 2A, compared with patients in the control group, those who had severe illness, were admitted to an ICU, and required IMV had significantly higher BMI (severe illness: WMD: 1.18, 95% CI: 0.42–1.93; admission to ICU: WMD: 1.46, 95% CI: 0.96–1.97; IMV acquirement: WMD: 2.70, 95% CI: 1.05–4.35), there was also significant difference in BMI between the death group and survival group (WMD: 0.91, 95% CI: 0.02–1.80) (Figure 2B).

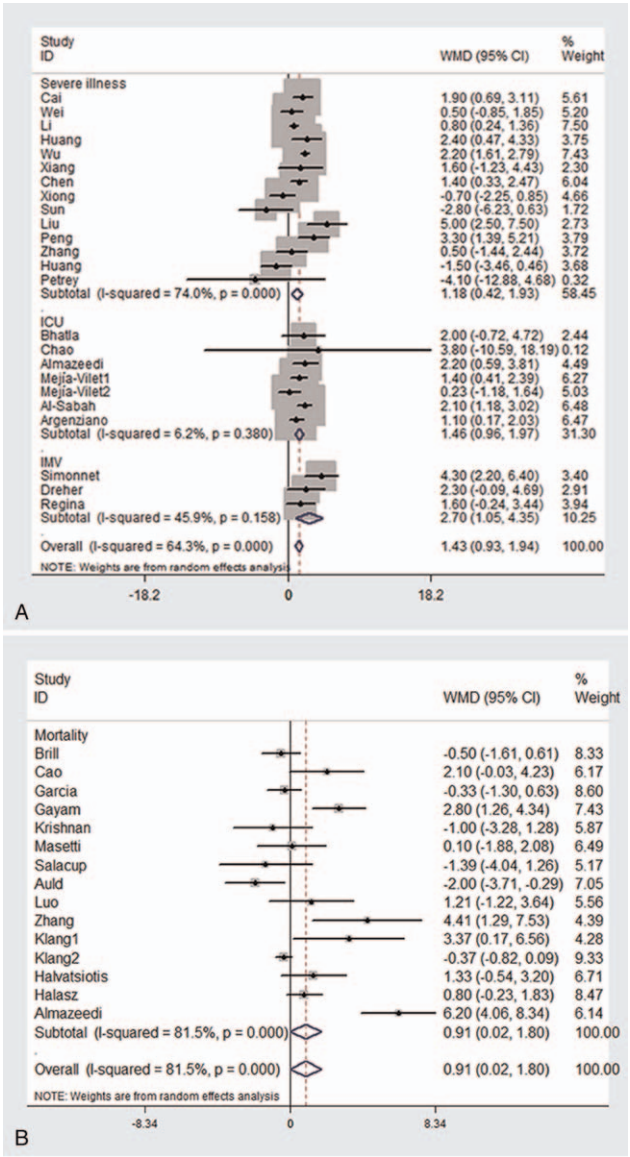

Figure 2. Forest plots of the weighted mean difference of elevated BMI and different clinical outcomes. (A) Severe illness; admission to an ICU; need for IMV; (B) mortality. ICU = intensive care unit; IMV = invasive mechanical ventilation.

3.5. Associations between obesity and different clinical outcomes

A total of 29 studies[13,24,31–34,36,47–67] were included in this meta-analysis of association between different clinical outcomes and obesity in patients with COVID-19. In 2 of these studies,[13,24] the obesity standard was a BMI of ≥28 kg/m^2, and the clinical outcomes described in these 2 studies were severe illness. In the remaining 27 studies,[31–34,36,47–67] the obesity criteria was a BMI of ≥30 kg/m^2. Among them, there were 3 studies[50,51] on hospitalization, 9[31–33,52–57] on admission to an ICU, 6[34,36,53,58–60] on need for IMV, and 11 on mortality.[47–50,61–67] These studies all directly provided the total number of patients with relevant clinical outcome events and those without relevant outcome events and the number of patients with obesity who showed relevant outcome events and those who did not. The random-effects model was used to calculate the OR values and 95% CIs for different clinical outcomes in Western patients with obesity, while in the Asian population, the fixed-effects model was used.

As shown in Figure 3A, in Western countries, obesity (BMI of ≥30 kg/m^2) not only increased the risk of hospitalization (OR: 2.08, 95% CI: 1.22–3.54), but also increased the risk of ICU admission and need for IMV in patients with COVID-19 (OR: 1.54, 95% CI: 1.29–1.84 and OR: 1.73, 95% CI: 1.38–2.17). Obesity (BMI of ≥30 kg/m^2) also increased the risk of mortality in patients with COVID-19 (OR: 1.43, 95% CI: 1.17–1.74) (Figure 3B). Figure 3C showed that in the Asian population, obesity (BMI of ≥28 kg/m^2) increased the risk of severe illness (OR: 3.14, 95% CI: 1.83–5.38).

3.6. Associations between different BMI classes and adverse clinical outcomes in patients with COVID-19

In our study, BMI was divided into 3 classes: <25 kg/m^2, 25–30 kg/m^2, and ≥30 kg/m^2. A total of 9 relevant studies[23,32–34,49,55,57,60,67] were included in this analysis. Of these studies, 3[32,55,57] reported on ICU admission, 2[34,60] on need for IMV, and 2[49,67] on mortality. For the outcome event of hospitalization,[33] severe illness,[23] and critical illness,[33] there was only 1 study each. Therefore, we did not perform a meta-analysis on these 3 outcomes. The relevant data were extracted and pairwise comparisons were made according to different BMI classes (BMI: 25–30 kg/m^2 vs <25 kg/m^2, ≥30 kg/m^2 vs <25 kg/m^2, ≥30 kg/m^2 vs 25–30 kg/m^2), and OR values and 95% CI for different clinical outcomes were calculated.

As shown in Table 3, compared with patients with COVID-19 and a BMI of <25 kg/m^2, those with a BMI of 25–30 kg/m^2 had an increased risk of need for IMV (OR: 2.19, 95% CI: 1.30–3.69). Meanwhile, compared with patients with COVID-19 and a BMI of <25 kg/m^2, those with a BMI of ≥30 kg/m^2 had an increased risk of ICU admission and need for IMV (OR: 2.32, 95% CI: 1.20–4.47; OR: 3.04, 95% CI: 1.76–5.28).

At the same time, patients with COVID-19 and a BMI of ≥30 kg/m^2 had an increased risk of ICU admission compared with those with a BMI of 25–30 kg/m^2 (OR: 1.49, 95% CI: 1.00–2.21).

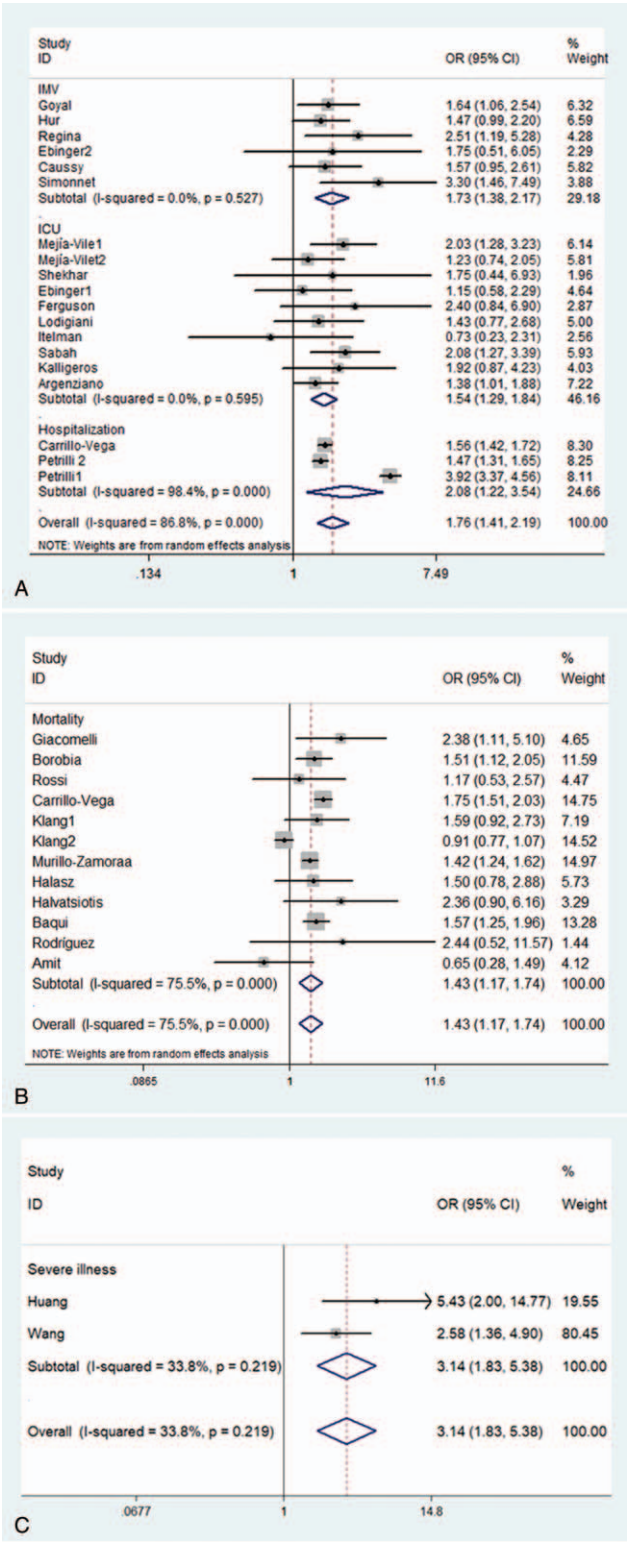

Figure 3. Forest plots of the odds ratios of obesity and different clinical outcomes. Need for IMV; admission to an ICU; hospitalization (Western population). Mortality (Western population). (C) Severe illness (Asian population). ICU = intensive care unit; IMV = invasive mechanical ventilation.

4. Discussion

In this study, we used 3 different methods from 3 different perspectives to explore the effects of BMI and obesity on the clinical outcomes of patients with COVID-19. First, we found that patients with COVID-19 who had severe illness, were admitted to an ICU, and needed IMV had higher BMI than that of patients without these clinical outcome events. Second, patients with COVID-19 and obesity had an increased risk of hospitalization, admission to an ICU, need for IMV, and mortality compared to their counterparts. Finally, we found that compared with that in the normal BMI group, there was an increased risk of hospitalization and need for IMV in the overweight group. Meanwhile, the obesity group was associated with an increased risk of hospitalization, ICU admission, and need for IMV compared with the normal BMI group.

Previous studies have shown that BMI is an independent risk factor for influenza, and obesity increases the severity of influenza and other respiratory infectious diseases.[70] Some researchers have also reported that obesity is associated with an increased risk of ICU admission, need for IMV, and death.[71] Another study found that half of the patients over the age of 20 years in California who were infected with H1N1 were obese.[72] Similarly, it was found that COVID-19 patients with obesity have a poor prognosis, with a significant proportion of patients in the ICU being overweight.[73]

However, there is still no clear explanation of why obesity increases the risk of adverse outcome events in patients with COVID-19. The possible reasons are as follows.

Patients with obesity, especially those with abdominal obesity, are likely to have limited diaphragm and chest wall movement, which reduces respiratory compliance. Moreover, they often have narrow airways in the nose and pharynx, which further increases respiratory resistance and aggravates the symptoms of dyspnea in patients with COVID-19.

Patients with obesity are likely to develop obstructive sleep apnea hypoventilation syndrome, wherein the body is in a state of chronic hypoxia for a long time, which can cause a series of target organ function damage, making patients in a state of long-term cardiopulmonary impairment, causing coronary heart disease, pulmonary hypertension and cerebral stroke and other diseases. When these patients are infected with SARS-CoV-2, they are likely to develop heart and respiratory failure, which can lead to worsening of the illness and even death. Similarly, obesity is a risk factor for diabetes mellitus, which is reportedly associated with an increased risk of adverse outcome events in patients with COVID-19.

Adipose tissue not only stores energy but also has endocrine functions. It can secrete a variety of inflammatory factors, participate in inflammatory responses, and regulate immunity. Obesity is a chronic metabolic disease that is associated with chronic inflammation, oxidative stress, and changes in hormone levels in the body. Inflammatory factors produced by adipose tissue include leptin, adiponectin, resistin, and visfatin. Individuals with obesity tend to have higher leptin levels[74] and lower adiponectin levels[75] compared to those with normal BMI. Studies have shown that leptin level can affect the proliferation of effector T cells, thereby influencing the function of immune system.[76] Adiponectin is an inflammatory factor secreted by bronchial epithelial cells; it plays an important role in preventing airway smooth muscle thickening, airway hyper reactivity, and bronchial inflammation.[77] At the same time, macrophages, as a component of adipose tissue, can secrete a variety of cytokines and chemokines, such as tumor necrosis factor (TNF)-alpha, interleukin (IL)-6, and monocyte chemotactic protein-1. These factors can damage the patient's immune system, and immune

Table 3

Associations between different BMI levels and adverse clinical outcomes in patients with COVID-19.

BMI (kg/m^2)	ICU	IMV	Death
BMI 25–30 vs BMI <25	1.55 (0.75,3.17)	2.19 (1.30, 3.69)	0.50 (0.09, 2.65)
BMI >30 vs BMI <25	2.32 (1.20,4.47)	3.04 (1.76, 5.28)	0.63 (0.09, 4.53)
BMI >30 vs BMI 25–30	1.49 (1.00,2.21)	1.69 (0.69, 4.15)	1.30 (0.75, 2.28)

BMI = body mass index, ICU = intensive care unit, and IMV = invasive mechanical ventilation.

dysfunction and excessive immune system activation can cause cytokine storms, further aggravating the disease and even leading to life-threatening events.[78] Many patients with severe COVID-19 have significantly increased serum levels of inflammatory factors, especially TNF-alpha, IL-6, IL-8, and IL-17.[79] Moreover, studies have found that in the treatment of COVID-19, cytoinflammatory factor antagonists, particularly anti-interleukin-6 drugs, can effectively improve the prognosis of patients with severe COVID-19,[80] suggesting that chronic inflammation may play an important role in the progression of COVID-19.

SARS-CoV-2 is a virus that uses angiotensin-converting enzyme 2 (ACE2) as an invasion receptor. SARS-CoV-2 spike protein receptor binding domain interacts with ACE2 to invade cells.[81] ACE2 is highly expressed in adipose tissue, and patients with obesity tend to have more adipose tissue than that observed in the general population. This may explain why patients with COVID-19 and obesity are more likely to have serious clinical outcomes than are patients with a normal BMI. ACE2 plays an extremely important regulatory role in the renin-angiotensin-aldosterone system, and infection with SARS-CoV-2 reduces the activity of ACE 2, leading to increased levels of angiotensin II, further causing lung damage.[82]

Previous studies have shown that compared with normal weight mice, obese mice are more prone to lung injury, pulmonary edema, and inflammatory reactions, and obese mice require a longer recovery period during the process of tissue repair.[83] Additionally, studies have shown that obesity prolongs the time required for virus shedding from the body.[84] This may explain the increased severity of the COVID-19 in patients with obesity.

Patients with obesity usually present with impaired T or B cell immunity. Previous studies on obese mice have found that the cytotoxicity and levels of influenza-specific CD8+ memory T cells in obese mice are significantly reduced, while neutrophil counts increase, which usually indicates severe disease status and poor prognosis.[85]

Finally, studies have confirmed that moderate aerobic exercise has a certain anti-inflammatory effect.[86] Patients with obesity often have a sedentary lifestyle, which increases their chance of being infected with SARS-CoV-2.

5. Limitation

Most of the studies included in this meta-analysis were single-center retrospective studies, while multi-center and large-sample studies were rarely included. This study only used BMI as a single indicator to define obesity and lacked data on multi-dimensional indicators such as waist circumference, waist-to-hip ratio, and the distribution of visceral fat.

In this meta-analysis, the heterogeneity of the research results may be related to race, comorbidities, age, and gender distribution of the patients. The lack of subgroup analyses is another limitation of this study.

6. Conclusions

This meta-analysis suggests that BMI is closely related to COVID-19 severity. As BMI increases, especially in COVID-19 patients with obesity, the risks of hospitalization, ICU admission, and need for IMV increase. Therefore, during the COVID-19 epidemic, the protection of people with obesity should be strengthened. Clinicians should take into consideration the impact of BMI when assessing the risks of COVID-19 in patients and determining the next treatment steps.

Author contributions

Conceptualization: Jingfang Liu.
Data curation: Yaxian Yang, Liting Wang, Songbo Fu.
Methodology: Yaxian Yang, Jingfang Liu, Songbo Fu.
Resources: Jingfang Liu, Songbo Fu, Liyuan Zhou.
Software: Liting Wang.
Writing – original draft: Yaxian Yang.
Writing – review & editing: Yaxian Yang, Jingfang Liu, Songbo Fu, Liyuan Zhou, Yan Wang.

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