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REVIEW

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Obesity aggravates COVID-19: An updated systematic review and meta-analysis

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Abstract

This review aimed to evaluate the impact of obesity on the onset, exacerbation, and mortality of coronavirus disease 2019 (COVID-19); and compare the effects of different degrees of obesity. PubMed, EMBASE, and Web of Science were searched to find articles published between December 1, 2019, and July 27, 2020. Only observational studies with specific obesity definition were included. Literature screening and data extraction were conducted simultaneously by two researchers. A random-effects model was used to merge the effect quantity. Sensitivity analysis, subgroup analysis, and meta-regression analysis were used to deal with the heterogeneity among studies. Forty-one studies with 219,543 subjects and 115,635 COVID-19 patients were included. Subjects with obesity were more likely to have positive SARS-CoV-2 test results (OR = 1.50; 95% CI: 1.37–1.63, I^2 = 69.2%); COVID-19 patients with obesity had a higher incidence of hospitalization (OR = 1.54, 95% CI: 1.33–1.78, I^2 = 60.9%); hospitalized COVID-19 patients with obesity had a higher incidence of intensive care unit admission (OR = 1.48, 95% CI: 1.24–1.77, I^2 = 67.5%), invasive mechanical ventilation (OR = 1.47, 95% CI: 1.31–1.65, I^2 = 18.8%), and in-hospital mortality (OR = 1.14, 95% CI: 1.04–1.26, I^2 = 74.4%). A higher degree of obesity also indicated a higher risk of almost all of the above events. The region may be one of the causes of heterogeneity. Obesity could promote the occurrence of the whole course of COVID-19. A higher degree of obesity may predict a higher risk. Further basic and clinical therapeutic research needs to be strengthened.

KEYWORDS

COVID-19, hospitalization, ICU admission, in-hospital mortality, invasive mechanical ventilation, obesity, positive SARA-CoV-2 test result

1 | INTRODUCTION

The coronavirus disease 2019 (COVID-19) first appeared in December 2019 and has been confirmed to be caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[1] COVID-19 is an infectious disease that could involve almost all the vital organs of the body. As of September 16, 2020, there have been more than 32 million COVID-19 patients and 940,000 related deaths worldwide.[2]

Studies have shown that obesity, as a worldwide epidemic, is associated with the severity and prognosis of COVID-19.[3,4] If the effects mentioned above do exist, they would hinder the prevention and control of COVID-19, cause more harm to COVID-19 patients, and deserve health policymakers' attention in various countries.

Some studies have systematically evaluated the impact of obesity on the whole process of COVID-19.[5,6] However, whether the influences of various degrees of obesity are different, especially for the positive diagnosis of COVID-19 and hospitalization, have not been involved in current systematic reviews.

The aim of this systematic review and meta-analysis of observational studies is to evaluate the impact of obesity on the positive SARS-CoV-2 test result of subjects, hospitalization of COVID-19 patients, and intensive care unit (ICU) admission, invasive mechanical ventilation (IMV), and in-hospital mortality of hospitalized COVID-19 patients, and to compare the effects of different body mass index (BMI) ranges.

2 | MATERIALS AND METHODS

We reported this systematic review and meta-analysis based on the PRISMA statement and the MOOSE checklist.[7,8] Our research protocol has been registered in PROSPERO—the international prospective register of systematic reviews (CRD42020203399). We carried out the project according to the research protocol.

2.1 | Search strategy

Two authors with medical doctorates (Jun Yang and Ying Chen) conducted a systemic literature search on July 27, 2020. PubMed, EMBASE, and Web of Science databases were searched to find all the publications between December 1, 2019, and July 27, 2020, in English. The following keywords were used without other restrictions: ("overweight" OR "obesity" OR "obese" OR "BMI" OR "body mass index") AND ("COVID-19" OR "coronavirus disease 2019" OR "2019-nCoV" OR "SARS-CoV-2" OR "2019 novel coronavirus"). We also searched the reference lists of included articles to find missing literature (Jun Yang and Ying Chen). The positive SARS-CoV-2 test result refers to a positive SARS-CoV-2 nucleic acid test result in nasopharyngeal swabs. COVID-19 patients refer to subjects with positive SARS-CoV-2 test results.

2.2 | Study selection

After importing the downloaded titles and abstracts into EndnoteX9 software, the duplicate documents were removed using the software's de-duplication function and manual reading of the authors, titles, and journals (Jun Yang and Ying Chen). Clinical studies concerning COVID-19 were screened out by two authors with medical postgraduate education background through reading the titles and abstracts. Those studies concerning the relationship between obesity and COVID-19(both positive and negative) were selected by further reading the full text (Hongyu Chi and Ying Chen). If the screening results of the two researchers were inconsistent, it would be solved through negotiation.

The final included studies should be observational ones with targeted outcome indicators, including positive SARS-CoV-2 test results, hospitalization, ICU admission, invasive mechanical ventilation, and in-hospital mortality. These papers should also include the odds ratio (OR) and 95% confidence intervals (CIs) of outcome indicators of obesity compared to those without. For in-hospital mortality, the value could be OR, risk ratio (RR), or hazard ratio (HR). Those studies with the following characteristics would be excluded: cases overlap with other larger ones, have less than 20 cases, or without a clear definition of obesity (for non-Asian: BMI ≥ 30 kg/m^2; for Asian: BMI ≥ 28 kg/m^2) or overweight (for non-Asian: 30 kg/m^2>BMI ≥ 25 kg/m^2; for Asian: 28 kg/m^2>BMI ≥ 24 kg/m^2). In this process, if two studies overlap in both source hospital and collection time, we consider the overlap of cases. In this case, we would include the larger one.

We have contacted 11 authors by E-mail who had not mentioned the exact definition of obesity in their papers. Six of them have responded with the detailed diagnostic criteria for obesity. One has provided data that were not published in the original article. The other five studies were not included in the final analysis.

2.3 | Data extraction

We established an information extraction table. Two researchers with medical postgraduate education background (Jun Yang and Congmin Tian) independently extracted the literature information. If there were any differences, it would be solved through negotiation and discussion.

Information extracted from each of the included studies included: (1) basic information of the article (the first author and title); (2) characteristics of the survey (country, the period of participation, the cut-off point of BMI, outcome indicators, study type); (3) characteristics of subjects (source of subjects, caseload, number of males, age); (4) summary measures: OR, RR, or HR as mentioned above. We would prioritize the adjusted values provided in the original text rather than the unadjusted ones calculated based on binary variables.

2.4 | Statistical analysis

Stata16.0 software was used to merge effect indicators and calculate other related values. I^2 was used to calculate the heterogeneity among studies. It would be considered low, medium, high, and very high in the range of ≤25%, 25%–50%, 50%–75%, and ≥75%.[9] The advantage of this approach relies on its independence of the number of studies included. When the heterogeneity was high or very high, we would find possible sources by sensitivity analysis, subgroup analysis, and meta-regression analysis. These potential sources include region, caseload, age, study type, and type of value. When the heterogeneity was very high, we would not carry out a meta-analysis but just conduct a systematic review. As the heterogeneity among studies could not be entirely measured by I^2, we used the random-effects model to merge the effect indicators. This method would take into account both intra-study and inter-study variation.

2.5 | Risk of bias assessment

To assess the risk of bias in the included literature, two researchers (Jun Yang and Congmin Tian) independently used the Newcastle-Ottawa Quality Assessment Scale (NOS) to score the quality of each research.[10] Most of the included studies scored 7 or above, indicating that the overall quality was high. The inconsistency was solved through negotiation and discussion.

We drew a funnel plot and made a preliminary judgment from the visual symmetry to assess the risk of bias among the included articles. Also, Egger's test was conducted, and $p < .05$ indicated that the existence of publication bias could not be rejected.

3 | RESULTS

3.1 | General study characteristics

The PubMed, EMBASE, and Web of Science databases were searched for a total of 1913 records. The included literature references were explored in the later stage, and two pieces of literature were further included. A total of 917 articles remained after de-duplication, 696 of which were not clinical observational studies and were further removed. Full-text browsing led to the elimination of 180 pieces, and 41 papers were finally included in the systematic review (Figure 1). Two pairs of studies with overlapping cases were included in the meta-analysis but belonged to different outcome indicators.[3,13,11,12]

The included studies were mainly conducted in the USA and Europe, including 23, 5, 3, 2, 2, 2, 1, 1, 1, and 1 from the USA, Italy, France, Spain, the UK, China, Mexico, Greece, Brazil, and international cooperation among the USA, Italy, and Spain. The 41 studies included 219,543 subjects receiving the SARS-CoV-2 test and 115,635 confirmed COVID-19 patients. The number of patients included in a single survey ranged from 46 to 51,633. Most studies included more male patients, and those older than 60 years are also in the majority. All the studies were conducted and published in 2020. The detailed information of each paper is shown in Table 1. The research quality scores based on the NOS are shown in Table S1.

3.2 | Positive SARS-CoV-2 test result

This section included three studies, which were from the USA,[11] Mexico,[14] and the UK,[15] respectively. A total of 164,622 subjects were tested for SARS-CoV-2 nucleic acid, and 57499 were positive. The positive rate ranged from 15.4% to 49.7% among included studies.

Pooled analysis showed that subjects with obesity had a higher incidence of positive test results than those without (OR = 1.50, 95% CI: 1.37–1.63, I^2 = 69.2%, Figure 2A). The trend of the pooled results did not change after each study was removed (Figure S1). Due to the small number of included studies, no subsequent subgroup analysis, meta-regression, or funnel plot were conducted.

We further compared the possibility of positive test results among subjects receiving the SARS-CoV-2 test with different BMI ranges. The results showed that a higher BMI indicates a higher possibility of positive test result (25 ≤ BMI < 30 vs. BMI < 25: OR = 1.58, 95% CI: 1.44–1.72, I^2 = 0.0%; 30 ≤ BMI < 40 vs. BMI < 25: OR = 1.86, 95% CI: 1.69–2.04, I^2 = 0.0%; BMI ≥ 40 vs. BMI < 25: OR = 1.85, 95% CI: 1.28–2.66, I^2 = 58.6%; Figure S2).

3.3 | Hospitalization

A total of 11 studies were included in this section, including eight from the USA[11,13,16–21] and the remaining three from Brazil,[22] Mexico,[14] and Spain.[23] Of the 70795 confirmed patients included, 25,403 were hospitalized. The hospitalization rate ranged from 10.8% to 85.0% among included studies. All the research studies were case-control studies.

Pooled analysis showed that COVID-19 patients with obesity had a higher incidence of hospitalization than those without (OR = 1.54, 95% CI: 1.33–1.78, I^2 = 60.9%, Figure 2B). The trend of this result did not change after each study was excluded (Figure S3). We conducted subgroup analysis and meta-regression analysis on all included studies. We found no confounding factors causing heterogeneity among studies (Tables S2 and S5).

We further compared the possibility of hospitalization among COVID-19 patients with different BMI ranges. The results showed that a higher BMI would predict higher possibility of hospitalization (25 ≤ BMI < 30 vs. BMI < 25: OR = 1.30, 95% CI: 1.09–1.57, I^2 = 0.0%; 30 ≤ BMI < 40 vs. BMI < 25: OR = 2.09, 95% CI: 1.34–3.26, I^2 = 51.5%; BMI ≥ 40 vs BMI < 25: OR = 2.76, 95% CI: 1.76–4.32, I^2 = 25.8%; Figure S4).

3.4 | ICU admission

A total of 15 studies were included, 10 from the USA,[3,13,16,19,24–29] two from Italy,[30,31] and the remaining three from China,[32] Mexico,[14] and Spain,[33] respectively. Of all the 30,268 inpatients from 15 studies, 4086 in 29905 from 14 studies involving the exact number of patients requiring ICU admission, with the remaining one just provide OR value. The ICU admission rate of inpatients ranged from 9.1% to 44.3% among the 14 studies.

Pooled analysis showed that hospitalized COVID-19 patients with obesity had a higher incidence of ICU admission than those without (OR = 1.48, 95% CI: 1.24–1.77, I^2 = 67.5%, Figure 2C). The trend of this result did not change after each study was excluded (Figure S5). We conducted subgroup analysis and meta-regression analysis on all included studies and found region to be the possible confounding factor causing heterogeneity among studies (Tables S3 and S6).

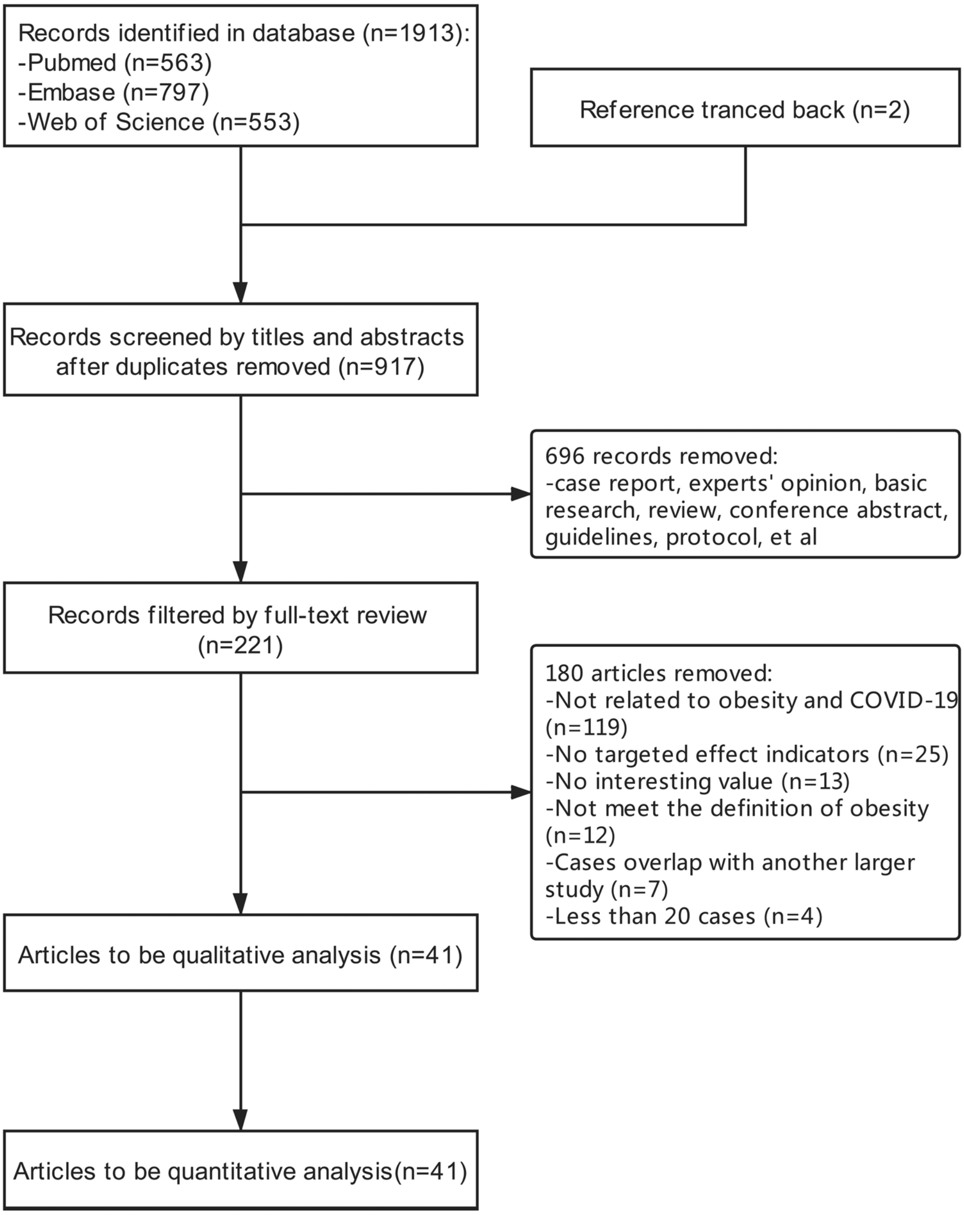

FIGURE 1 Flow chart of literature screening

We further compared the possibility of ICU admission among hospitalized patients with different BMI ranges. The results showed that patients with a higher BMI may have a higher trend of ICU admission, though they were not significant ($25 \le BMI < 30$ vs. $BMI < 25$: OR = 1.90, 95% CI: 0.89–4.07, $I^2 = 0.0\%$; $30 \le BMI < 40$ vs. $BMI < 25$: OR = 1.44, 95% CI: 0.67–3.09, $I^2 = 0.0\%$; $BMI \ge 40$ vs. $BMI < 25$: OR = 2.19, 95% CI: 0.51–9.35, $I^2 = 63.8\%$; Figure S6).

3.5 | Invasive mechanical ventilation

A total of 14 studies were included, including nine from the USA,[19,25–27,29,34–37] two from France,[4,38] and the remaining three from China,[32] Mexico[14] and Italy,[30] respectively. Of all the 25,945 hospitalized patients from 14 studies, 2789 in 22,176 patients from 12 papers had received IMV with a detailed description. The remaining two just provide OR values. The IMV rate of inpatients ranged from 9.1% to 68.5% among the 12 studies.

Pooled analysis showed that hospitalized COVID-19 patients with obesity had a higher incidence of receiving IMV than those without (OR = 1.47, 95% CI: 1.31–1.65, $I^2 = 18.8\%$, Figure 2D).

We further compared the possibility of IMV among hospitalized patients with different BMI ranges. The results showed that a higher BMI may indicate a higher possibility of IMV ($25 \le BMI < 30$ vs. $BMI < 25$: OR = 1.60, 95% CI: 0.97–2.65, $I^2 = 0.0\%$; $30 \le BMI < 40$ vs. $BMI < 25$: OR = 2.02, 95% CI: 1.23–3.30, $I^2 = 0.0\%$; $BMI \ge 40$ vs. $BMI < 25$: OR = 3.73, 95% CI: 1.86–7.50, $I^2 = 30.9\%$; Figure S7).

TABLE 1 Characteristics of included studies

First author	Region	Patient source and period	N (M)	Age (average/median)	Outcome	Studytype-1	Studytype-2
Argenziano MG	USA	Presbyterian/Columbia University Irving Medical Center Mar 1st–Apr 5th, 2020	1000 (596)	63	Hospitalization ICU admission	Retrospective	Case-control study
Argyropoulos KV	USA	Emergency department in Manhattan, New York Mar 12th–18th, 2020	205 (108)	Nonhospitalized: 45 Hospitalized: 60	Hospitalization	Retrospective	Case-control study
Barbero P	Spain	Hospital Universitario 12 de Octubre, Madrid Mar 3rd–May 31st, 2020	91 (0)	-	Hospitalization	Retrospective	Case-control study
Bello-Chavolla OY	Mexico	The General Directorate of Epidemiology of Mexican Ministry of Health As to May 18th, 2020	Positive: 51,633 (29,803) Negative: 98,567 (47,177)	Positive: 46.65 Negative: 42.25	Positive test Hospitalization ICU admission IMV In-hospital mortality	Retrospective	Case-control study
Busetto L	Italy	Padova University Hospital Mar 23rd–Apr 11th, 2020	92 (57)	70.5	ICU admission IMV In-hospital mortality	Prospective	Cohort study
Cai QX	China	The Third People's Hospital of Shenzhen Jan 11th–Feb 16th, 2020 followed until Mar 26th, 2020	383 (184)	Normal: 50 Underweight: 35.5 Overweight: 50 Obesity: 48	ICU admission IMV	Prospective	Cohort study
Cariou B	France	53 French centers Mar 10th–31st, 2020	1317 (855)	69.8	In-hospital mortality	Prospective	Case-control study
Caussy C	France	Lyon University Hospital Feb 27th–Apr 8th, 2020	291	-	IMV	Prospective	Cohort study
Chao JY	USA	The Children's Hospital at Montefiore in New York City Mar 15th–Apr 13th, 2020	46 (31)	Non-ICU: 3.6 ICU: 14.8	ICU admission	Retrospective	Case-control study
Ciceri F	Italy	San Raffaele Hospital in Milano Feb 25th–Mar 24th	410 (299)	65	In-hospital mortality	Prospective	Case-control study
Cravedi P	USA Italy Spain	12 centers in the international TANGO consortium Mar 2nd–May 15th, 2020	144 (94)	62	In-hospital mortality	Retrospective	Case-control study
de Lusignan S	UK	Oxford RCGP Research and Surveillance Center network Jan 28th–April 4th, 2020	3802 (1612)	Men: 58.0 Women: 51.5	Positive test	Retrospective	Case-control study

TABLE 1 (Continued)

First author	Region	Patient source and period	N (M)	Age (average/median)	Outcome	Studytype-1	Studytype-2
Docherty AB	UK	208 acute care hospitals in England, Wales, and Scotland Feb 6th–Apr 19th, 2020	20,133 (12,068)	72.9	In-hospital mortality	Prospective	Case-control study
Duanmu Y	USA	Stanford Health Care in Santa Clara County Mar 4th–23rd, 2020	100 (56)	45	Hospitalization	Prospective	Case-control study
Ebinger JE	USA	Cedars-Sinai Health System in Los Angeles, California Mar 8th–21st, 2020	442 (256)	52.72	Hospitalization ICU admission IMV	Retrospective	Case-control study
Giacomelli A	Italy	Luigi Sacco Hospital in Milan Feb 21st–Mar 19th, 2020	233 (161)	61	In-hospital mortality	Prospective	Case-control study
Goyal P	USA	Weill Cornell Medicine in Manhattan, New York Mar 5th–27th, 2020	1687 (1004)	66.5	In-hospital mortality	Retrospective	Cohort study
Gupta S	USA	ICUs at 65 hospitals across the US Mar 4th–Apr 4th, 2020	2215 (1436)	60.5	In-hospital mortality	Prospective	Case-control study
Hajifathalian K	USA	New York - Presbyterian Hospital and Weill Cornell Medical Center in New York Mar 4th–Apr 9th, 2020	770 (468)	64	ICU admission IMV In-hospital mortality	Retrospective	Cohort study
Halasz G	Italy	Guglielmo da Saliceto Hospital in Piacenza February–April 2020	242 (194)	64	In-hospital mortality	Retrospective	Case-control study
Halvatsiotis P	Greece	8 hospitals in Greece Mar 10th–Apr 13th, 2020	90 (72)	65.5	In-hospital mortality	Retrospective	Case-control study
Hashemi N	USA	Single healthcare system in Massachusetts Mar 11th–Apr 2nd, 2020	363 (201)	63.4	ICU admission IMV In-hospital mortality	Retrospective	Case-control study
Hur K	USA	Northwestern-affiliated healthcare centers in Chicago, Illinois Mar 1st–Apr 8th, 2020	486 (271)	59	IMV	Retrospective	Case-control study
Kalligeros M	USA	Rhode Island Hospital, The Miriam Hospital, or Newport Hospital in Rhode Island Feb 17th–April 5th, 2020	103 (63)	60	ICU admission	Retrospective	Case-control study
Killerby ME	USA	Hospitalized in Metropolitan Atlanta, Georgia Mar 1st–30th, 2020	531 (228)	Nonhospitalized: 45 Hospitalized: 61	Hospitalization	Retrospective	Case-control study
Kim L	USA	154 acute care hospitals in 74 counties in 13 states Mar 1st–May 2nd, 2020	2491 (1326)	62	ICU admission	Retrospective	Case-control study

(Continues)

TABLE 1 (Continued)

First author	Region	Patient source and period	N (M)	Age (average/median)	Outcome	Studytype-1	Studytype-2
Klang E	USA	5 hospital campuses in Mount Sinai, New York Mar 1st–May 17th, 2020	3406 (1961)	Age ≤ 50: Survivors 40.0 Non-survivors 46.5 Age > 50: Survivors 68.0 Non-survivors 76.0	IMV In-hospital mortality	Retrospective	Case-control study
Lighter J	USA	NYU Langone Health Mar 4th–Apr 4th, 2020	3615	-	Hospitalization ICU admission	Retrospective	Case-control study
Mani VR	USA	Harlem Hospital in Manhattan, New York March–April 2020	184 (111)	64.72	IMV	Retrospective	Case-control study
Nakeshbandi M	USA	SUNY Downstate Health Sciences University in New York Mar 10th–Apr 13th, 2020	504 (263)	68	Intubation In-hospital mortality	Retrospective	Cohort study
Petrilli CM	USA	NYU Langone Health Mar 1st–Apr 8th, 2020	Positive: 5279 (2615) Hospitalization: 2741 (1678)	Positive: 54	Positive test Hospitalization In-hospital mortality	Prospective	Case-control study
Pettit NN	USA	University of Chicago Medical Center Mar 1st–Apr 18th, 2020	238 (113)	58.5	ICU admission IMV In-hospital mortality	Retrospective	Cohort study
Rottoli M	Italy	Sant'Orsola Hospital Mar 1st–Apr 20th, 2020	482 (302)	66.2	ICU admission In-hospital mortality	Retrospective	Cohort study
Salacup G	USA	Henry Ford Health System in metropolitan Detroit, Michigan Mar 9th–27th, 2020	242 (123)	66	In-hospital mortality	Retrospective	Case-control study
Shah P	USA	Phoebe Putney Memorial Hospital, Albany, Georgia Mar 2nd–May 6th, 2020	522 (218)	63	In-hospital mortality	Retrospective	Case-control study
Simonnet A	France	Roger Salengro Hospital Feb 27th–Apr 5th, 2020	124 (90)	60	IMV	Retrospective	Case-control study
Soares R	Brazil	The State Health Secretariat page from Esp´ırito Santo state Last updated on June 11th, 2020	10,713 (4804)	< 60	Hospitalization In-hospital mortality	Retrospective	Case-control study
Suleyman G	USA	Henry Ford Health System in metropolitan Detroit, Michigan Mar 9th–27th, 2020	463 (204)	57.5	Hospitalization ICU admission	Retrospective	Case-control study

TABLE 1 (Continued)

First author	Region	Patient source and period	N (M)	Age (average/median)	Outcome	Studytype-1	Studytype-2
Toussie D	USA	Mount Sinai Hospital in New York city Mar 10th–26th, 2020	338 (210)	39	Hospitalization IMV	Retrospective	Case-control study
Urra JM	Spain	University Hospital of Ciudad Real Mar 1st–Apr 15th, 2020	172 (104)	-	ICU admission	Retrospective	Case-control study
Zhang F	China	Tongji Hospital and Wuhan Pulmonary Hospital Feb 7th–Mar 27th, 2020	53	-	In-hospital mortality	Retrospective	Case-control study

Abbreviations: Apr, April; Feb, February; ICU, Intensive Care Unit; IMV, invasive mechanical ventilation; Jan, January; M, male; Mar, March; N, number; Studytype-1, retrospective/prospective; Studytype-2, cohort study/case-control study; UK, United Kingdom; USA, United States of America.

3.6 | In-hospital mortality

A total of 23 studies were included in this section, including 11 from the USA,[11,12,25,26,28,29,35,37,39–41] five from Italy,[30,31,42–44] and the remaining seven from Brazil,[22] China,[45] France,[46] Greece,[47] Mexico,[14] UK,[48] and international cooperation among the USA, Italy and Spain,[49] respectively. Of all the 54938 patients from 23 studies, 8259 in 51330 inpatients from 19 studies involved a specific death toll. The remaining four just provide OR values. The in-hospital mortality rate ranged from 10.1% to 43.5% among the 19 studies.

Pooled analysis showed that hospitalized COVID-19 patients with obesity had a higher incidence of in-hospital mortality than those without (OR = 1.14, 95% CI: 1.04–1.26, I^2 = 74.4%, Figure 2E). The direction of this result did not change after each study was excluded (Figure S8). We conducted subgroup analysis and meta-regression analysis on all included studies. We found no confounding factor causing heterogeneity among the included studies (Tables S4 and S7).

We further compared the possibility of in-hospital mortality among COVID-19 patients with different BMI ranges. The results showed that patients with BMI ≥ 40 have a higher possibility of in-hospital mortality (25 ≤ BMI < 30 vs. BMI < 25: OR = 1.06, 95% CI: 0.79–1.42, I^2 = 0.0%; 30 ≤ BMI < 35 vs. BMI < 25: OR = 1.01, 95% CI: 0.74–1.39, I^2 = 0.0%; 35 ≤ BMI < 40 vs. BMI < 25: OR = 1.32, 95% CI: 0.88–1.96, I^2 = 0.0%; BMI ≥ 40 vs. BMI < 25: OR = 1.56, 95% CI: 1.07–2.26, I^2 = 0.0%; Figure S9).

3.7 | Risk of bias

We have drawn funnel charts for the effect indicators of the included literature concerning hospitalization, ICU admission, IMV, and in-hospital mortality. Preliminary judgments have shown that the figures' points are all in symmetrical distribution (Figure 3). We further conducted the Egger's test and found all the p-values were larger than 0.05, indicating no evidence of publication bias (Table S8).

4 | DISCUSSION

This systematic review and meta-analysis found that subjects with obesity were more likely to show positive results in the detection of SARS-CoV-2. Obese COVID-19 patients were more likely to be hospitalized than those without. Hospitalized COVID-19 patients with obesity were more likely to receive ICU admission, invasive mechanical ventilation, and die than those without. A higher degree of obesity also indicates a higher risk of occurrence for the above events.

Ten systematic reviews have assessed the relationship between obesity and COVID-19. Tamara et al.[50] have included three retrospective cohort studies and found that obesity could significantly increase the risk of severe conditions in COVID-19 patients. Our research team conducted the first meta-analysis on this topic at

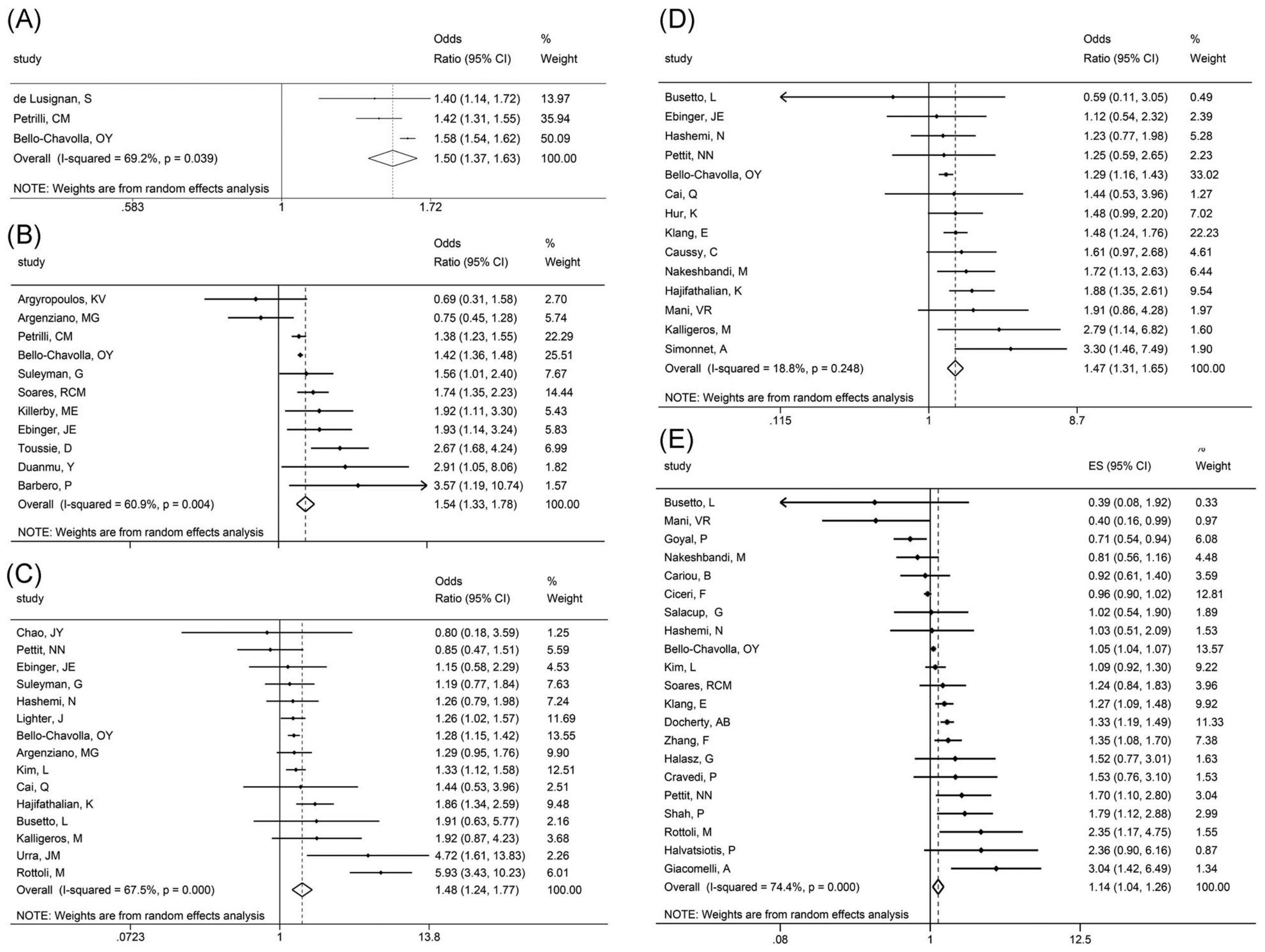

FIGURE 2 Meta-analysis of effect indicators in subjects with obesity compared to those without. A, Positive SARS-CoV-2 test result. B, Hospitalization. C, ICU admission. D, Invasive mechanical ventilation. E, In-hospital mortality

almost the same time.[51] We have found that the BMI of COVID-19 patients with severe conditions was significantly higher than those with mild conditions. The risk of developing severe conditions in COVID-19 patients with obesity was significantly higher than those without. Zhou et al.,[52] Sales-Peres et al.,[53] and Malik et al.[6] have come to almost the same conclusion as us. Pranata et al.[54] looked at the association between higher BMI and the risk of composite adverse endpoints, death, and critical illness. They found that a higher BMI was associated with increased risk of these events. However, most studies' BMI ranges were not consistent, which may lead to a decline in the reliability and extrapolation of the results. Hussain et al have found a significant correlation between BMI > 25 kg/m^2 and increased mortality, needs for respiratory support, and critical illness in COVID-19 patients.[55] Földi et al.[56] found that obesity was a risk factor for ICU admission and IMV therapy. They have also compared the risk of receiving IMV in different BMI ranges of COVID-19 patients and found that a higher BMI indicates a higher risk of receiving IMV. Malik et al.[57] have observed the prevalence of COVID-19 to be 0.60 among patients with BMI < 25 kg/m^2 compared to 0.34 among patients with BMI > 25 kg/m^2. However, as they included a small sample of retrospective case-control studies, such results' credibility needs to be further validated. Most of these studies adopt composite endpoints, which have made it difficult to assess the impact of obesity on the risk of specific single endpoint events. During this paper's writing, a meta-analysis published in the latest issue of Obesity Reviews had systematically evaluated outcome indicators of COVID-19 patients with obesity.[5] Unlike current studies, this one has set a strict definition of obesity and BMI segmentation points for comparing the risk of five outcome events in subjects with different BMI ranges. In this study, we used the index of in-hospital mortality rather than overall mortality to reduce the impact of other factors on mortality. This paper also tries to find the heterogeneity source and finds that region may be an essential factor.

Many factors may participate in the aggravation of obesity on COVID-19. Obesity could increase the expression of ACE2- and CD147-related genes in the bronchus and blood, while the latter two are receptors for SARS-CoV-2 to invade.[58] This would make obese subjects more susceptible to infection and may explain the higher positive test rate of SARS-CoV-2 to some extent. Obesity and concomitant metabolic syndrome may bring about potential damages to organ function, making lung, kidney and other organs more prone to

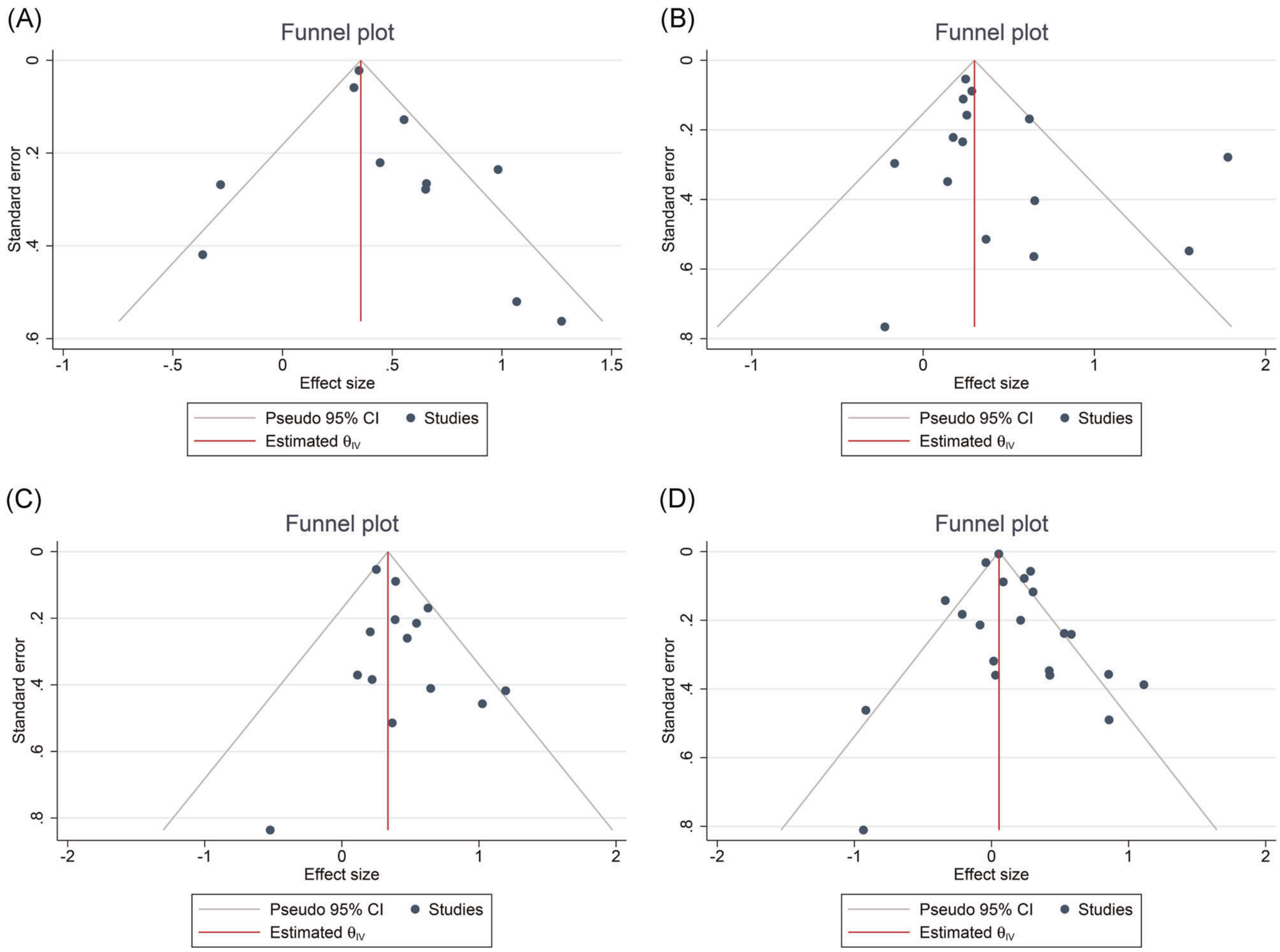

FIGURE 3 Funnel plots of the literature concerning effect indicators. A, Hospitalization. B, ICU admission. C, Invasive mechanical ventilation. D, In-hospital mortality

the state of dysfunction.[59] Adipose tissue may become the site of virus retention due to the increased expression of ACE2 in obese subjects, which could slow down virus clearance and aggravate the infection.[60] The low-level inflammation caused by obesity may also damage the immune system and make it abnormal in the infection of SARS-Cov-2. Obesity itself may lead to increased chest and abdominal pressure, limiting the expansion of the lungs.[61] In the case of COVID-19, obese patients would be more prone to acute respiratory distress. These factors could largely explain why obese patients are more likely to be infected with SARS-Cov-2 and be more severe after infection.

By integrating the results of different original studies, this study aims to avoid the limitation of the applicability of conclusions caused by the insufficient number of cases in a single research study and the single source of patients. Nevertheless, there are inevitable limitations in this study. The included studies may have different implementation standards for hospitalization, ICU admission, IMV, and other COVID-19 patients' treatments, impacting the final meta-analysis results' reliability. Second, the risk of bias in the included studies is inconsistent. The types of studies are mainly retrospective, including case-control studies and cohort studies, which may further affect the conclusions' reliability. Third, we only selected literature in English, which may lead to the omission of related non-English literature and the lack of the final conclusion's reliability.

In this systematic review and meta-analysis, we have systematically retrieved the existing literature and restricted the diagnosis of obesity and other BMI section cut-off points. The results have indicated a promoting role of obesity for subjects in COVID-19 diagnosis, for COVID-19 patients in hospitalization, and for hospitalized COVID-19 patients in ICU admission, invasive mechanical ventilation, and in-hospital mortality. Simultaneously, subjects with a higher degree of obesity may have a greater risk of developing the above adverse outcomes. These findings suggest that obesity would bring about severe challenges to the prevention and control of this epidemic. It would also cause more pain and harm to COVID-19 patients and deserves health policymakers' attention in various countries. To combat this potential impact in the context of the COVID-19, we should maintain healthy diets and exercise habits while wearing masks frequently and keeping distance from others. Obesity is a risk factor for many diseases, and eating healthily and exercising regularly should be a program to be adhered to by people worldwide. Also, the pathophysiological characteristics of obese

COVID-19 patients need further study. When writing this paper, a newly published multicenter study further suggested the relationship between obesity and mortality in COVID-19 patients, which further confirmed our conclusion.[62] This also indicates the importance of high-quality observational studies and basic research.

5 | CONCLUSIONS

Obesity could promote the occurrence of positive SARS-Cov-2 test results, hospitalization of COVID-19 patients, ICU admission, invasive mechanical ventilation therapy, and in-hospital mortality of hospitalized COVID-19 patients. Subjects with a higher degree of obesity may have a greater risk of developing the adverse outcomes mentioned above. Further basic and clinical therapeutic research concerning this aggravation needs to be strengthened.

CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

AUTHOR CONTRIBUTIONS

Jun Yang and Chunyan Zhu conceived the plan for this study. Jun Yang, Ying Chen, Congmin Tian, and Hongyu Chi conducted literature retrieval, screening, and data extraction. Jun Yang and Jiahao Li carried out statistical analysis. Congmin Tian and Jun Yang carried out the risk of bias scoring. Jun Yang and Ying Chen interpreted the findings; Jun Yang and Congmin Tian made figures. Jun Yang and Ying Chen made tables. Jun Yang wrote the first draft. Jun Yang, Ying Chen, Congmin Tian, Hongyu Chi, Jiahao Li, and Chunyan Zhu checked and revised the manuscript together. Jun Yang conducted the final examination and submission. The corresponding author (Jun Yang) gaurantees that all listed authors meet the author's criteria. No other authors who meet the criteria are omitted. We are grateful to Professor Omar Yaxmehen Bello-Chavolla for his generous contribution to the unpublished data and Professor Na Lin for her help in forming the research team. The authors, who belong to the Institute of Chinese Materia Medica, China Academy of Chinese Medical Sciences, were funded by the Special project for training outstanding young scientific and technological talents (innovative type) of necessary scientific research business expenses of the China Academy of Chinese Medical Sciences (ZZ13-YQ-051).

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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