COVID-19 in Metabolism

Association of body mass index (BMI) with critical COVID-19 and in-hospital mortality: A dose-response meta-analysis

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ABSTRACT

Background and purpose: The coronavirus disease 2019 (COVID-19) pandemic presents an unprecedented health crisis to the entire world. As reported, the body mass index (BMI) may play an important role in COVID-19; however, this still remains unclear. The aim of this study was to explore the association between BMI and COVID-19 severity and mortality.

Methods: The Medline, PubMed, Embase and Web of science were systematically searched until August 2020. Random-effects models and dose-response meta-analysis were used to synthesize the results. Combined odds ratios (ORs) with their 95% confidence intervals (CIs) were calculated, and the effect of covariates were analyzed using subgroup analysis and meta-regression analyses.

Results: A total of 16 observational studies involving 109,881 patients with COVID-19 were included in the meta-analysis. The pooled results showed that patients with a BMI ≥ 30 kg/m^2 had a 2.35-fold risk (OR = 2.35, 95%CI = 1.64–3.38, P < 0.001) for critical COVID-19 and a 2.68-fold risk for COVID-19 mortality (OR = 2.68, 95%CI = 1.65–4.37, P < 0.001) compared with patients with a BMI <30 kg/m^2. Subgroup analysis results showed that patients with obesity and age > 60 years was associated with a significantly increased risk of critical COVID-19 (OR = 3.11, 95%CI = 1.73–5.61, P < 0.001) and COVID-19 mortality (OR = 3.93, 95%CI = 2.18–7.09, P < 0.001). Meta-regression analysis results also showed that age had a significant influence on the association between BMI and COVID-19 mortality (Coef. = 0.036, P = 0.048). Random-effects dose-response meta-analysis showed a linear association between BMI and both critical COVID-19(P$_{non-linearity}$ = 0.242) and mortality (P$_{non-linearity}$ = 0.116). The risk of critical COVID-19 and mortality increased by 9%(OR = 1.09, 95%CI = 1.04–1.14, P < 0.001) and 6%(OR = 1.06, 95%CI = 1.02–1.10, P = 0.002) for each 1 kg/m^2 increase in BMI, respectively.

Conclusions: Evidence from this meta-analysis suggested that a linear dose-response association between BMI and both COVID-19 severity and mortality. Further, obesity (BMI ≥ 30 kg/m^2) was associated with a significantly increased risk of critical COVID-19 and in-hospital mortality of COVID-19.

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1. Introduction

The coronavirus disease 2019 (COVID-19) pandemic has led to worldwide research efforts to identify individuals at greatest risk of developing critical illness and dying [1]. Initial data indicated that diabetes, cardiovascular disease, and respiratory or kidney disease were associated with an increased risk of adverse outcomes in patients with COVID-19 [2–4]. Increasing numbers of reports have linked obesity to more severe COVID-19 and mortality [5–8]. However, existing studies,

including epidemiological studies and meta-analyses, reported inconsistent results on the association between BMI and COVID-19.

In a French cohort study, the risk for invasive mechanical ventilation in patients with COVID-19 infection admitted to Intensive Treatment Unit was >7-fold higher for those with a BMI >35 kg/m^2 compared with those with a BMI <25 kg/m^2 [9]. Among individuals with COVID-19 in New York, those with a BMI between 30 and 34 kg/m^2 and >35 kg/m^2 were 1.8 times and 3.6 times more likely to be admitted to critical care, respectively, than individuals with a BMI <30 kg/m^2 [10]. Besides, the meta-analysis conducted by Yang et al. [11] and Soeroto et al. [12] revealed that patients with severe COVID-19 have a higher BMI than non-severe ones. However, Cai et al. reviewed a study in the Third People's Hospital of Shenzhen, Guangdong province, China, with 298 patients (aged 33–61 years) with COVID-19 and found no significant differences between non-severe (n = 240) and severe (n = 58)

patients with the value of BMI being 22.9 kg/m^2 and 25.5 kg/m^2, respectively [13]. Thus, great differences were shown among existing studies. In addition, most conclusions were obtained from univariate estimates only and the sample size is also small. Whether obesity is an independent risk factor for COVID-19 and the dose-response association between BMI and the risk of severe COVID-19 and mortality are unclear.

Therefore, we conducted this meta-analysis to explore the association between BMI and COVID-19. Compared with the previously published meta-analyses, we herein performed a subgroup analysis based on the adjusted effect estimates to explore whether obesity is an independent risk factor for critical COVID-19 and mortality. In addition, age, sex and some comorbidities were analyzed by meta-regression analyses. More importantly, the dose-response association between BMI and the risk of critical COVID-19 and mortality were established.

2. Materials and methods

This meta-analysis was planned and conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist [14]. Additionally, because the included studies were observational in design, we also followed the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines [15].

3. Literature search strategy

A systematic search of published articles was conducted in the Medline, PubMed, Embase, Web of Science and Cochrane Library databases until August 27, 2020. Following search terms were used: ("coronavirus disease 2019" OR "COVID-19" OR "SARS-CoV-2" OR "coronavirus" OR "nCoV-2019") AND ("body mass index" OR "BMI" OR "weight" OR "overweight" OR "obesity" OR "risk factor" OR "characteristics" OR "clinical features") AND ("clinical trial" OR "observational study" OR "cohort" OR "trial" OR "case-control" OR "study"). We also reviewed the reference lists from the retrieved articles and manually searched to identify additional relevant studies that may not have been identified by our database searches.

4. Inclusion and exclusion criteria

Studies that met the following criteria were included in this meta-analysis: 1) observational studies in humans with either a cohort or case-control or cross-sectional design; 2) concerning the effects of BMI on COVID-19; 3) patients were diagnosed as COVID-19 by the laboratory test and age≥18 years old; 4) outcomes of COVID-19 infection severity reported; 5) provided data of mortality、critical or no-critical between patients with at least two BMI categories; and 6) publication in English. Conversely, studies that met the following criteria were excluded: 1)duplicate studies; 2) reviews, reports, conferences, commentaries; 3) insufficient data; and 4) sample size <10; In this study, patients with acute respiratory distress syndrome (ARDS) who required life support, mechanical ventilation, or intensive care unit (ICU) support were considered as critically illness patients. And obesity was defined as a BMI ≥30 kg/m^2. Two of the authors independently searched all references, and any discrepancy was resolved by all authors, on the basis of a vote.

5. Data extraction

Two authors (Yanbin Du and Nan Zhou) performed the data extraction, again any disagreements were discussed and resolved by consensus. For each study, the following information was collected: first author's name, publication year, country, study design, age and sex distribution, sample size, BMI category and risk estimates with 95% confidence intervals (CIs) for each exposure category, number of patients with different BMIs in the severe and non-severe COVID-19 groups, number of patients with different BMIs in the survivors and non-
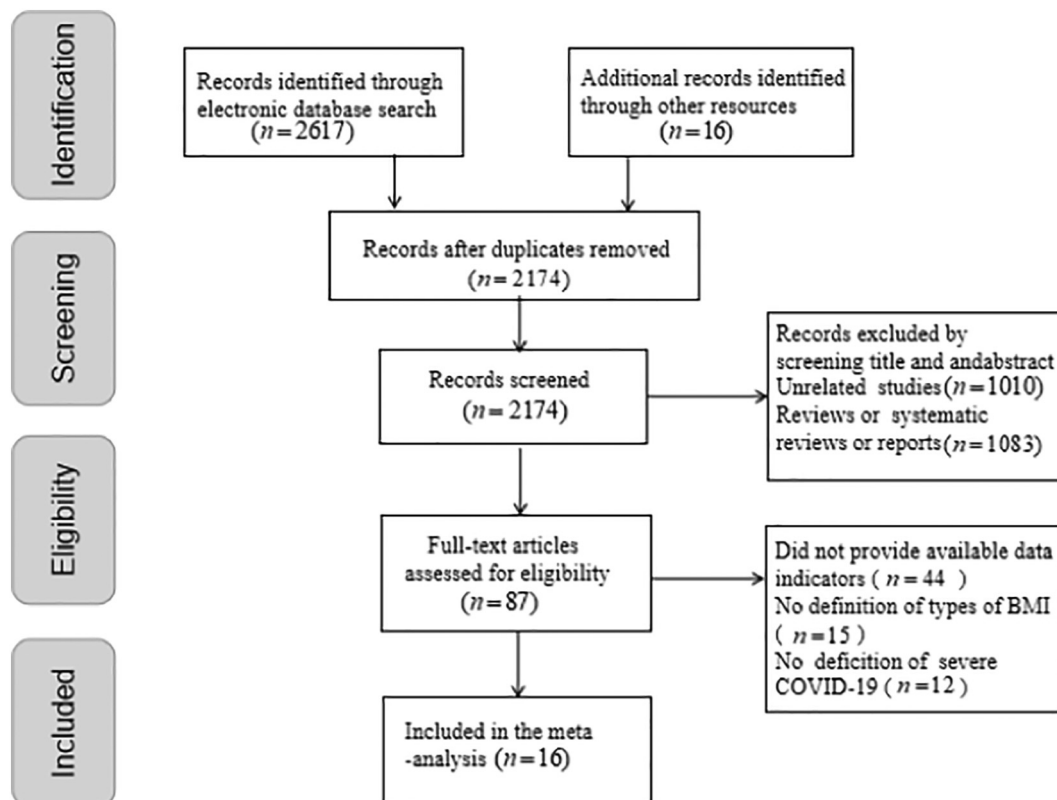

Fig. 1. Flowchart of the study procedure.

survivors groups. In addition, other data, such as the presence of diabetes, hypertension, cardiovascular disease, cancer, or other diseases and smoking, were also collected.

6. Quality assessment

Quality assessment of the eligible studies was performed by two investigators (Wenting Zha and Xiuqin Hong), using the Newcastle-Ottawa Quality Assessment Scale (NOS), which is a validated scale for non-randomized observational studies [16]. Each study was assessed on the basis of three broad perspectives: selection (0-4points), comparability (0-2 points), and exposure (0-3 points) with a score ranging from 0 to 9 points. We assigned scores of 0–3, 4–6, and 7–9 points for low, moderate, and high quality of the studies, respectively.

7. Statistical analysis

Odds ratios (ORs) and 95%CIs were considered to determine the association between BMI and the risk of critical COVID-19 and mortality. Heterogeneity among the studies was estimated using the Q and I^2 statistic. For the Q statistics, $P < 0.10$ indicated a statistically significant heterogeneity. And the I^2 values of 25%, 25–50%, 50–75%, and > 75% were classified as indicating no, small, moderate, and significant heterogeneity, respectively. Pooled ORs were obtained using the fixed-effects

Table 1
Characteristics of patients included in the severity analysis studies.

Author and publication year	Country	Study design	Age (years)	Men (%)	Sample size	BMI (kg/m²)	Critical N(%)	n(%)	Non-critical M(%)	m(%)	Multivariate analysis*
Palaiodimos et al., 2020 [8]	USA	Cohort	64(50–73.5)	49%	200	≥ 35	32 (16%)	11 (34.3%)	168 (84%)	35 (20.8%)	Yes
Kalligeros et al., 2020 [21]	USA	Cohort	60 (52–70)	61.17%	103	< 25	44 (42.7%)	5 (11.3%)	59 (57.3%)	14 (23.7%)	Yes
						25–29.9		14 (31.8%)		21 (35.5%)	
						30–34.9		11 (25%)		11 (18.6%)	
						≥ 35		14 (31.8%)		13 (22%)	
Busetto et al., 2020 [22]	Italy	Cross-sectional	70.5(55–84)	61.9%	92	≥ 30	47 (51%)	22 (46.8%)	45 (49%)	7 (15.6%)	No
Hajifathalian et al., 2020 [23]	USA	Cohort	64(47–81)	61%	434	< 18.5	241 (55.5%)	5 (2.1%)	193 (44.5%)	3 (1.6%)	Yes
						18.5–30		98 (40.6%)		91 (47.1%)	
						≥ 30		138 (57.3%)		99 (51.3%)	
Zheng et al., 2020 [24]	China	Cross-sectional	47(18–75)	25.8%	66	<25	19 (28.8%)	2 (10.5%)	47 (71.2%)	19 (40%)	No
						25–29.9		6 (31.6%)		12 (25.6%)	
						≥ 30		11 (67.3%)		16 (34.4%)	
Petrilli et al., 2020 [25]	USA	Cohort	< 60	53%	1582	<30	650 (41.1%)	359 (55.2%)	932 (58.9%)	504 (54.1%)	Yes
						30–40		210 (32.3%)		312 (33.5%)	
						>40		50 (7.7%)		66 (7.1%)	
Gao et al., 2020 [26]	China	Cohort	48(18–75)	62.7%	150	≥ 30	36 (24%)	12 (33.3%)	114 (76%)	17 (14.7%)	No
Giannouchos et al., 2020 [27]	Mexico	Cohort	44(18–75)	51%	89,756	≥ 30	11,706 (13%)	3160 (27%)	78,050 (87%)	15,220 (19.5%)	Yes
Salman et al., 2020 [28]	Kuwait	Cohort	54.0 (46.4–63.4)	63.5%	1158	<25	104 (9%)	33 (31.7%)	1054 (91%)	398 (37.8%)	Yes
						25–29.9		47 (45.2%)		523 (49.6%)	
						30–35		15 (14.4%)		83 (7.8%)	
						35–40		5 (4.8%)		35 (3.3%)	
						>40		4 (3.8%)		15 (1.4%)	
Rottoli et al., 2020 [29]	Italy	Cohort	66(49–83)	62.7%	482	<30	67 (13.9%)	31 (46.3%)	415 (86.1%)	365 (88%)	No
						30–35		28 (41.8%)		35 (8.4%)	
						>35		8 (11.9%)		15 (3.6%)	
Kaeuffer et al., 2020 [30]	France	Cohort	66(40–82)	59%	1045	≥ 30	424 (40.6%)	164 (38.7%)	621 (11.9%)	187 (30.1%)	Yes
Mendy et al., 2020 [31]	USA	Cohort	60(49–75)	53%	689	≥ 30	91 (13.2%)	24 (26.4%)	598 (86.8%)	104 (17.4%)	Yes

N: Total number of critical patients; n: Number of critical patients with each BMI category.
M: Total number of non-critical patients. m: Number of non-critical patients with each BMI category.
* The multivariate analysis was adjusted for age, sex, history of cancer, smoking, diabetes, cardiovascular diseases, hypertension, chronic kidney disease (CKD), and other chronic diseases.

model, if $I^2 < 50\%$; otherwise, the random-effects model was used [17]. In addition, we performed subgroup analyses using geography (Asian vs. non-Asian), age (≤60 years vs. >60 years), study type (cohort vs. cross-sectional), sample size (≤ 1000 vs. > 1000), BMI category (BMI >35 kg/m² vs. 30-35 kg/m²) and performance of a multivariate analysis (Yes vs. No) to explore the potential heterogeneity. We also performed meta-regression analyses to examine the effect of age, sex and comorbidities (diabetes, hypertension, and cardiovascular disease) on the association between BMI and both COVID-19 severity and mortality.

A dose-response analysis was also performed to further describe the relationship between BMI and critical COVID-19 and mortality using the method described by Orsini et al. [18]. The potential nonlinear dose-response association between BMI and risk of critical COVID-19 and mortality was examined using a restricted cubic splines regression model with three knots at the 25th, 50th and 75th percentiles of the BMI distribution. We calculated the nonlinear P-value by testing the null hypothesis that the second spline coefficient is equal to zero [19]. Considering the heterogeneity among the studies, we performed a random-effect meta-analysis to calculate the trend based on the relevant logOR estimated across BMI levels. And a generalized least squares (GLS) regression was used to estimate the dose-response coefficients and 95%CIs. The median or mean BMI level in each category was assigned to the corresponding risk estimates of each study. If the BMI level was in a range,

the midpoint of the upper and lower boundaries was considered the dose; when the highest or lowest category was open-ended, we assumed the width between boundaries to be equal to that of the adjacent category.

To assess the potential publication bias, we used funnel plots and Egger's linear regression test [20]. Sensitivity analyses were conducted by excluding each study and reanalyzing the data. All statistical analyses were performed using STATA 15.0 (Stata Corp, Texas, USA). The significance level was set at P-values <0.05, and all statistical tests were two-sided.

8. Results

8.1. Literature search

Our electronic literature search identified 2633 studies concerning effects of BMI (or obesity) on COVID-19, 2621 of which were excluded because of the following reasons. Firstly, 459 duplicated articles were excluded, then 2174 articles were screened by title and abstract, leading to exclusion of 1010 irrelevant studies and 1083 reports, reviews or meta-analysis, or letters. Thereafter, 87 articles underwent full-text review, which resulted in the exclusion of 44 articles that did not provide available data index, 15 articles that did not report the BMI category,

Table 2
Characteristics of patients included in the mortality analysis studies.

Author and publication year	Country	Study design	Age (years)	Men (%)	Sample size	BMI (kg/m²)	Non-survivors		Survivors		Multivariate analysis*
							N(%)	n(%)	M(%)	m(%)	
Klang et al., 2020 [32][a]	USA	Cohort	40(34–46)	69.4%	572	< 30	60 (10.5%)	25 (41.7%)	512 (89.5%)	272 (53.1%)	Yes
						30–40		16 (26.7%)		171 (31.4%)	
						≥ 40		19 (31.7%)		69 (13.5%)	
Klang et al., 2020 [32][b]	USA	Cohort	68(60–77)	54%	2834	< 30	1076 (38.0%)	727 (67.6%)	1758 (62%)	1151 (65.5%)	Yes
						30–40		274 (25.5%)		496 (28.2%)	
						≥ 40		75 (7%)		111 (6.3%)	
Hajifathalian et al., 2020 [23]	USA	Cohort	64(47–82)	61%	770	< 18.5	88 (31.3%)	9 (1.1%)	193 (68.7%)	3 (1.6%)	Yes
						18.5–30		22 (25%)		91 (47.1%)	
						≥ 30		57 (64.8%)		99 (51.3%)	
Palaiodimos et al., 2020 [8]	USA	Cohort	64(50–73.5)	49%	200	< 25	48 (24%)	12 (25%)	152 (76%)	26 (17.1%)	Yes
						25–34		20 (41.7%)		96 (63.2%)	
						≥ 35		16 (33.3%)		30 (19.7%)	
Pettit et al., 2020 [33]	USA	Cohort	58(41–75)	47.5%	238	<25	24 (10.1%)	3 (12.5%)	214 (89.9%)	60 (28%)	No
						25–30		7 (29.2%)		67 (31.3%)	
						30–35		5 (20.8%)		38 (17.7%)	
						35–40		4 (16.7%)		25 (11.7%)	
						>40		5 (20.8%)		24 (11.2%)	
Zhang et al., 2020 [34]	China	Cohort	32(14–45)	58.4%	53	≥ 30	13 (24.5%)	3 (23%)	40 (75.5%)	6 (15%)	No
Carrillo-Vega et al., 2020 [35]	Mexico	Cohort	60(45–73)	69%	9946	≥ 30	963 (9.8%)	289 (30%)	8983 (90.2%)	1564 (17.4%)	No

N: Total number of non-survivors; n: Number of non-survivors with each BMI category.
M: Total number of survivors. m: Number of survivors with each BMI category.
 [a] Study in patients aged <60 years.
 [b] Study in patients aged >60 years.
 * The multivariate analysis was adjusted for age, sex, history of cancer, smoking, diabetes, cardiovascular diseases, hypertension, chronic kidney disease (CKD), and other chronic diseases.
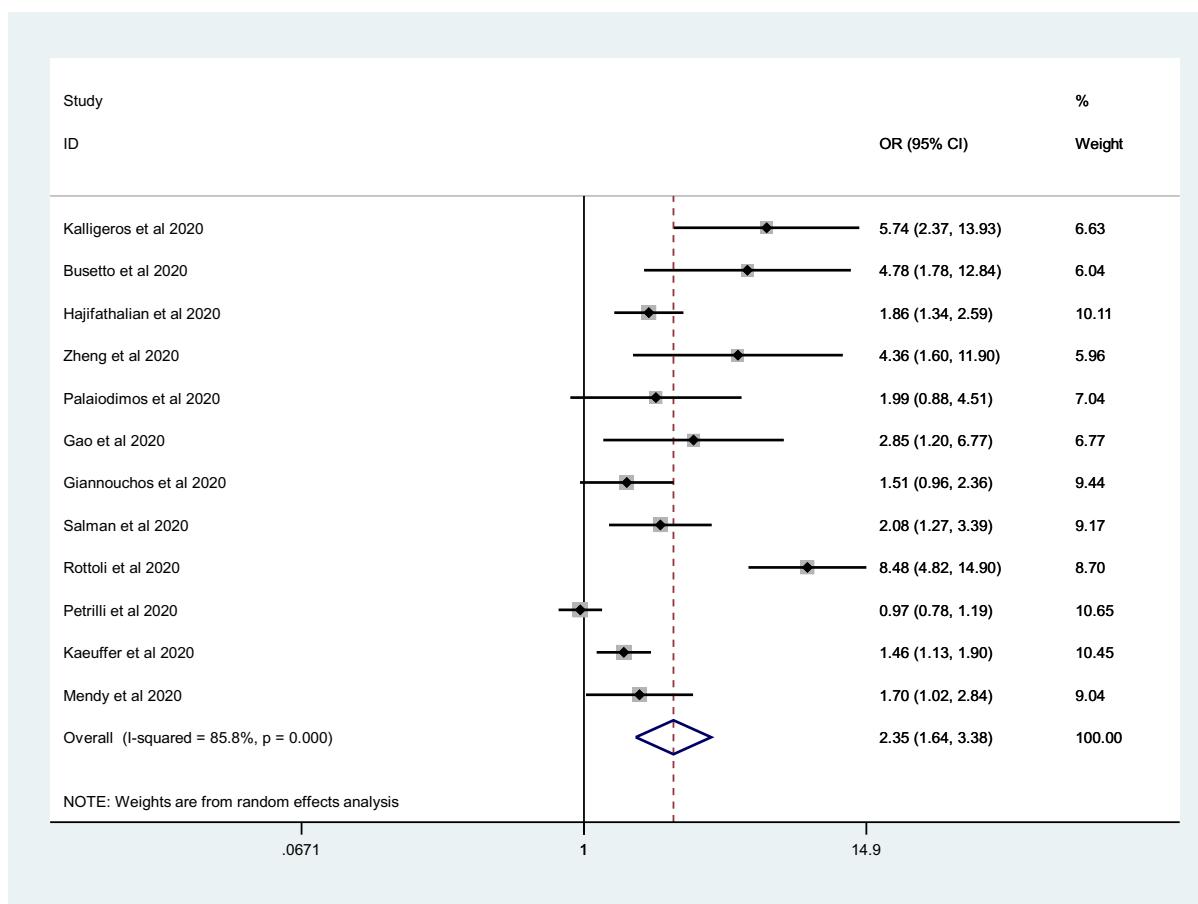
Fig. 2. Effects of BMI > 30 kg/m^2 vs. BMI < 30 kg/m^2 on COVID-19 severity.

Table 3
Subgroups analysis of association between obesity and COVID-19 severity and mortality.

COVID-19	Subgroups	Study number	OR (95%CI)	Heterogeneity test		
				Q	P-value	I^2(%)
Severity	Overall	12	2.35 (1.64–3.38)	77.24	< 0.001	85.8%
	Geography					
	Asia	3	2.49 (1.68–3.68)	1.83	0.401	0
	Non-Asia	9	2.25 (1.48–3.43)	52.83	< 0.001	79%
	Age					
	≤60 years	6	1.77 (1.17–2.69)	21.55	0.001	76.8%
	>60 years	6	3.11 (1.73–5.61)	39.09	< 0.001	87%
	Study type					
	Cohort	10	2.14 (1.47–3.12)	69.04	< 0.001	85%
	Cross-sectional	2	4.57 (2.26–9.24)	0.02	0.89	0
	Sample size					
	≤ 1000	8	2.49 (1.81–3.7)	41.9	< 0.001	75.4%
	> 1000	4	1.98 (1.12–3.52)	9.59	0.08	47.9%
	BMI (kg/m^2)					
	30–35	4	1.87 (1.19–3.35)	0.04	0.29	0
	≥ 35	7	3.64 (1.97–7.45)	52.85	< 0.001	88%
	Multivariate analysis					
	Yes	8	1.69 (1.27–2.27)	28.8	< 0.001	75.7%
	No	4	5.15 (3.06–8.69)	4.79	0.188	37.4%
Mortality	Overall	7	2.68 (1.65–4.37)	28.97	<0.001	79.3%
	Age					
	≤60 years	4	1.94 (1.41–2.67)	0.34	0.952	0
	>60 years	3	3.93 (2.18–7.09)	6.37	0.041	48.6%
	BMI (kg/m^2)					
	30–35	3	1.62 (1.15–4.28)	2.47	0.21	25%
	≥ 35	3	3.54 (1.48–8.48)	13.8	0.001	72%
	Multivariate analysis					
	Yes	4	3.34 (1.89–5.90)	13.91	0.003	78.4%
	No	3	1.83 (1.23–2.71)	0.09	0.957	0

Abbreviations: OR (95%CI): odds ratio and 95% confidence intervals; BMI: body mass index.

and 12 articles that did not describe the severity of COVID-19. Finally, a total of 16 studies were included in the meta-analysis. The details of the literature search are shown in Fig. 1.

8.2. Study characteristics and quality assessment

The characteristics of the included studies and patients are shown in Tables 1 and 2. A total of 16 observational studies (14 cohort design and 2 cross-sectional design) that met the inclusion criteria for our meta-analysis were published from January to August 2020. Twelve studies explored the association between BMI and COVID-19 severity [8,21–31] and seven studies explored the association between BMI and COVID-19 mortality [8,23,32–35]. Of these studies, four were performed in Asia [24,26,28,34], including China (n = 3) and Kuwait (n = 1); Nine in America [8,21,23,25,27,31–33,35], including USA (n = 7) and Mexico (n = 2); and three in Europe [22,29,30], including Italy (n = 2) and France (n = 1). In total, 109,881 patients with COVID-19 were included in this meta-analysis, including critical (n = 13,461), non-critical (n = 82,296), death (n = 2272), survivors (n = 11,852). Mean ages of the participants ranged from 32 to 70.5 years. Sample size ranged from 53 to 89,756, the proportion of men ranged from 49% to 69.4%. Eight studies had more than three BMI categories [8,21,23,24,28–31]; the lowest dose of BMI was <18 kg/m^2, and the highest dose of BMI was >40 kg/m^2. The NOS scores of all studies ranged from 4 to 9 points, and eight studies had a score of ≥7 points.

Table 4
Meta-regression analysis to explore the effects of confounding factors on the association between obesity and COVID-19.

Variable	P-value	
	Severity	Mortality
Age	0.054	0.048[*]
Sex	0.89	0.737
Diabetes	0.145	0.354
Hypertension	0.169	0.412
Cardiovascular diseases	0.36	0.165

[*] Indicates significance (P < 0.05).

8.3. Effect of BMI ≥ 30 kg/m^2 vs. BMI < 30 kg/m^2 on COVID-19 severity

The effect of BMI on COVID-19 severity was explored from 12 studies (13,461 cases and 82,296 controls). Heterogeneity test results revealed significant heterogeneity in these studies (Q = 77.24, P < 0.001, I^2 = 85.8%). And the random-effects model was applied, the summary OR for 12 studies showed that patients with a BMI ≥ 30 kg/m^2 was associated with a significantly increased risk (OR = 2.35, 95%CI = 1.64–3.38, P < 0.001) of developing into the critical condition compared to patients with a BMI <30 kg/m^2 (Fig. 2).

Subgroup analyses indicated that individuals in Asia (OR = 2.49, 95% CI = 1.68–3.68) had a higher risk of critical COVID-19 than those in non-Asia (OR = 2.25, 95%CI = 1.48–3.43). Older patients (aged>60 years) had a significantly higher risk of developing into the critical COVID-19
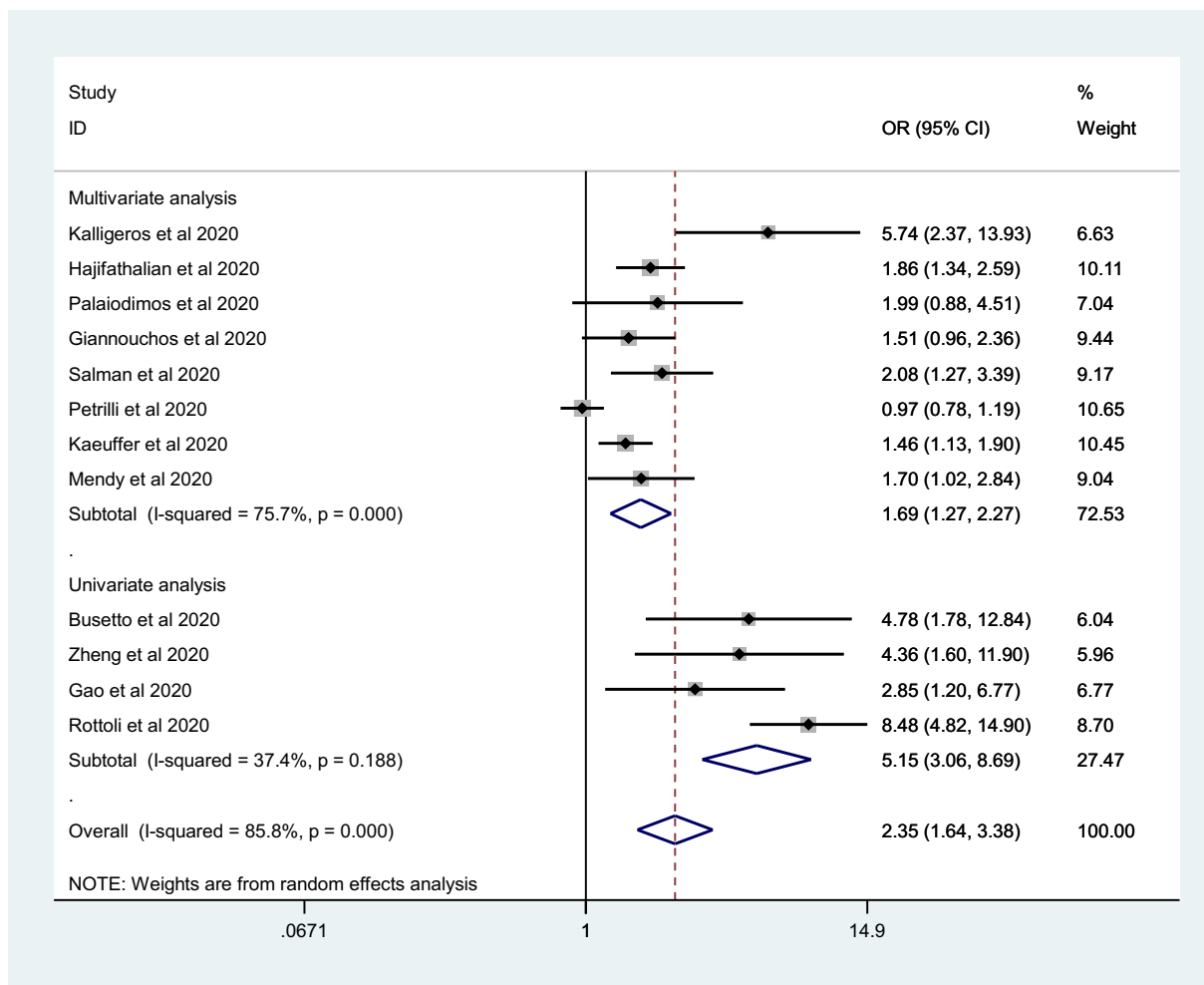

Fig. 3. Meta-analysis based on the adjusted effect estimates to explore the effect of BMI > 30 kg/m^2 vs. BMI < 30 kg/m^2 on COVID-19 severity.

(OR = 3.11, 95%CI = 1.73–5.61) than age ≤ 60 years (OR = 1.77, 95%CI = 1.17–2.69). And different types of study design showed significant difference in effect of obesity on COVID-19 severity (Cohort: OR = 2.14, 95%CI = 1.47–3.12; Cross-sectional: OR = 4.57, 95%CI = 2.26–9.24). Severe obesity (BMI >35 kg/m^2) significantly increased the risk of critical COVID-19(OR = 3.64, 95%CI = 1.97–7.45) (Table 3). In addition, the pooled results based on the adjusted OR showed significant difference in effect of obesity on COVID-19 severity (multivariate analysis: OR = 1.69, 95%CI = 1.27–2.27; univariate analysis: OR = 5.15, 95%CI = 3.06–8.69) (Fig. 3).

Meta-regression analysis results showed that age (Coef. = 0.038, P = 0.054) may have a significant influence on the association between obesity and critical COVID-19 (Fig. 6). However, sex (P = 0.89) and some comorbidities (diabetes: P = 0.145, hypertension: P = 0.169, cardiovascular diseases: P = 0.36) did not appear to exert significant effect on association between obesity and critical COVID-19 (Table 4).

8.4. Effect of BMI ≥ 30 kg/m^2 vs. BMI < 30 kg/m^2 on COVID-19 mortality

The effect of BMI on COVID-19 mortality was explored from 7 studies (2272 cases and 11,852 controls). Combined results through the random-effects model revealed that patients with a BMI ≥ 30 kg/m^2 had a significantly higher risk of COVID-19 mortality (OR = 2.68, 95%CI = 1.65–4.37, P < 0.001) with moderate heterogeneity in these studies (Q = 28.97, P < 0.001, I^2 = 79.3%) (Fig. 4).

Subgroup analyses indicated that patients with age > 60 years (OR = 3.93, 95%CI = 2.18–7.09) and severe obesity (BMI >35 kg/m^2) (OR = 3.54, 95%CI = 1.48–8.48) had a significant effect on COVID-19 mortality (Table 3). Pooled results based on the adjusted OR showed that obesity was an independent risk factor for COVID-19 mortality (OR = 3.34, 95%CI = 1.89–5.90) (Fig. 5). Meta-regression analysis results also showed that a significant influence of increasing age on the association

between BMI > 30 kg/m^2 and COVID-19 mortality (Coef. = 0.036, P = 0.048) (Fig. 6). However, sex (P = 0.737), diabetes (P = 0.354), hypertension (P = 0.412) and cardiovascular diseases (P = 0.165) did not exert significant effect on association between obesity and COVID-19 mortality (Table 4).

8.5. Dose-response association between BMI and risk of critical COVID-19

A total of six studies [21,23–25,28,29] were included in the dose-response meta-analysis of the association between BMI and critical COVID-19. It was found that there was a linear relationship (P$_{non-linearity}$ = 0.242) between BMI and the risk of critical COVID-19 (Fig. 7). And a 1.09-fold increased risk (OR = 1.09, 95%CI = 1.04–1.14, P < 0.001) of critical COVID-19 for each 1 kg/m^2 increase in BMI and a 1.19-fold increased risk (OR = 1.19, 95%CI = 1.08–1.30, P < 0.001) of critical COVID-19 for each 2 kg/m^2 increase in BMI.

8.6. Dose-response association between BMI and COVID-19 mortality

A total of four articles [8,23,30,31] were included in the dose-response meta-analysis of the association between BMI and COVID-19 mortality. A linear dose-response relationship (P$_{non-linearity}$ = 0.116) was showed in Fig. 8. The mortality of patients with COVID-19 increased by 6%(OR = 1.06, 95%CI = 1.02–1.10, P = 0.002) and 12%(OR = 1.12, 95%CI = 1.04–1.21, P = 0.002) for each 1 kg/m^2 and 2 kg/m^2 increase in BMI, respectively.

8.7. Sensitivity analysis and publication bias

Sensitivity analysis results showed that removal of each study did not significantly alter the overall effect of BMI ≥ 30 kg/m^2 on COVID-19 severity (OR altered between 1.71 and 3.59) and COVID-19 mortality
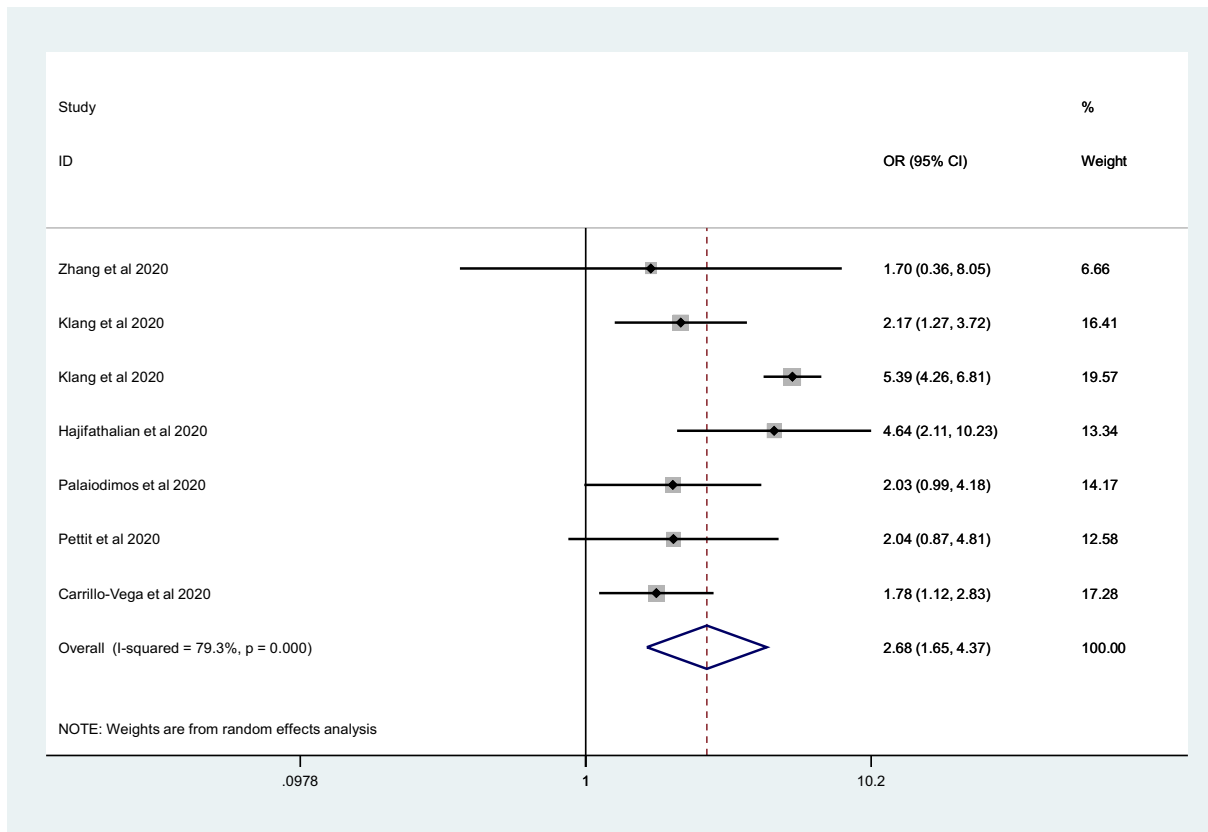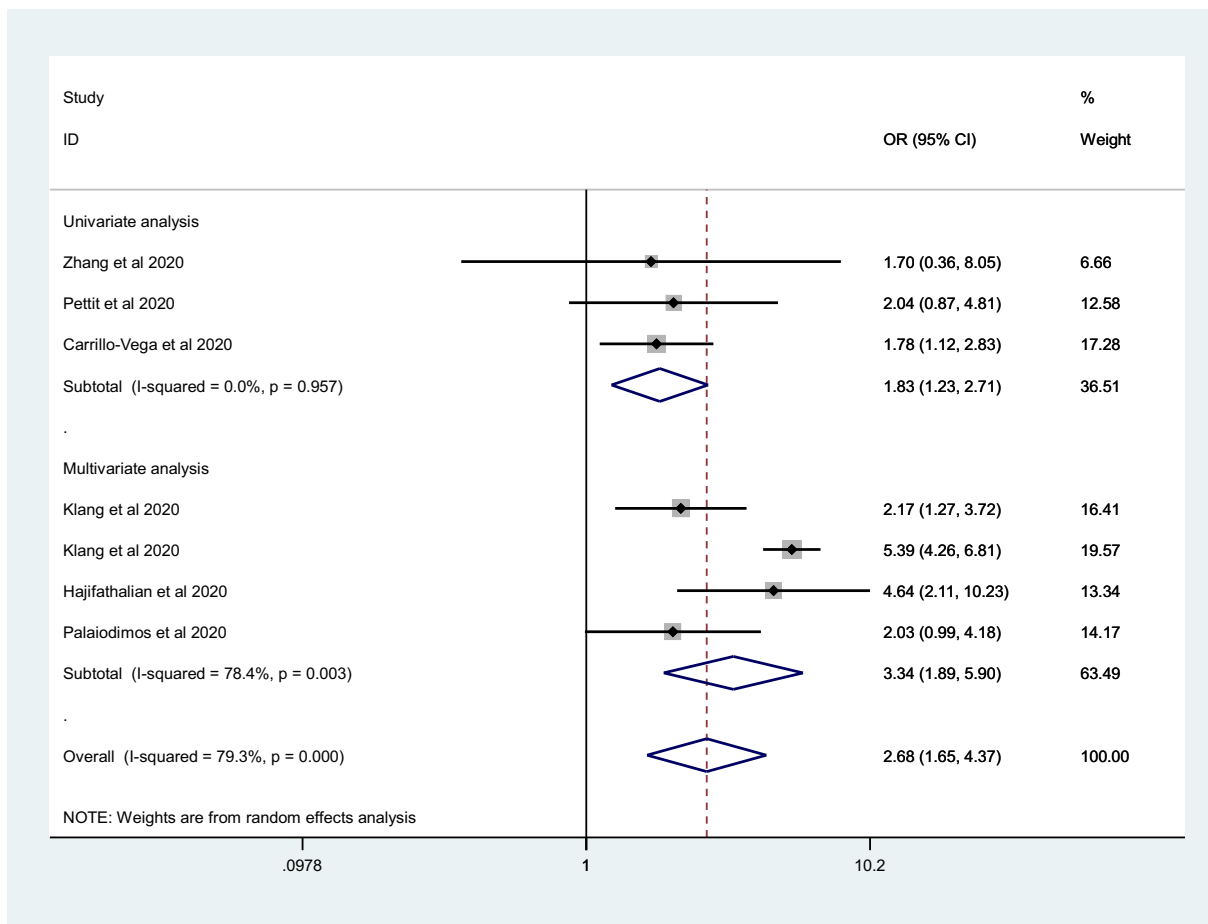

Study ID		OR (95% CI)	% Weight
Zhang et al 2020		1.70 (0.36, 8.05)	6.66
Klang et al 2020		2.17 (1.27, 3.72)	16.41
Klang et al 2020		5.39 (4.26, 6.81)	19.57
Hajifathalian et al 2020		4.64 (2.11, 10.23)	13.34
Palaiodimos et al 2020		2.03 (0.99, 4.18)	14.17
Pettit et al 2020		2.04 (0.87, 4.81)	12.58
Carrillo-Vega et al 2020		1.78 (1.12, 2.83)	17.28
Overall (I-squared = 79.3%, p = 0.000)		2.68 (1.65, 4.37)	100.00

NOTE: Weights are from random effects analysis

.0978   1   10.2

Fig. 4. Effects of BMI > 30 kg/m^2 vs. BMI < 30 kg/m^2 on COVID-19 mortality.

Study ID		OR (95% CI)	% Weight
Univariate analysis			
Zhang et al 2020		1.70 (0.36, 8.05)	6.66
Pettit et al 2020		2.04 (0.87, 4.81)	12.58
Carrillo-Vega et al 2020		1.78 (1.12, 2.83)	17.28
Subtotal (I-squared = 0.0%, p = 0.957)		1.83 (1.23, 2.71)	36.51
.			
Multivariate analysis			
Klang et al 2020		2.17 (1.27, 3.72)	16.41
Klang et al 2020		5.39 (4.26, 6.81)	19.57
Hajifathalian et al 2020		4.64 (2.11, 10.23)	13.34
Palaiodimos et al 2020		2.03 (0.99, 4.18)	14.17
Subtotal (I-squared = 78.4%, p = 0.003)		3.34 (1.89, 5.90)	63.49
.			
Overall (I-squared = 79.3%, p = 0.000)		2.68 (1.65, 4.37)	100.00

NOTE: Weights are from random effects analysis

.0978   1   10.2

Fig. 5. Meta-analysis based on the adjusted effect estimates to explore the effect of BMI > 30 kg/m^2 vs. BMI < 30 kg/m^2 on COVID-19 mortality.

(OR altered between 1.76 and 4.38). No publication bias was detected in current meta-analysis, although slight asymmetries were observed in the funnel plots, Egger's linear regression test were not statistically significant (severity: P = 0.665; mortality: P = 0.139).

9. Discussion

This meta-analysis explored the association between BMI and COVID-19 with a sample size of 109,881 individuals from 16 observational studies published in 2020. The evidence from this meta-analysis revealed that obesity (BMI ≥ 30 kg/m^2) was associated with a 2.35-fold risk of critical COVID-19 and a 2.68-fold risk of in-hospital mortality of COVID-19. This conclusions is consistent with the previous most studies, however, there are several new findings in our study, as indicated below.

Many epidemiological studies showed that obesity-related conditions seem to worsen the effect of COVID-19. However, most of these findings were obtained from univariate estimates only. Several studies have shown that the pooled effects based on adjusted effect estimates were significantly reduced or even disappeared [8,21,27]. Thus, we conducted a meta-analysis based on the adjusted OR, although the pooled OR was significantly reduced in the multivariate analysis (OR = 1.69, 95%CI = 1.27–2.27) compared with that in the univariate analysis (OR = 5.15, 95%CI = 3.06–8.69), the results also showed that obesity was an independent risk factor for critical COVID-19. Similarly, the pooled results showed that obesity was an independent risk factor for COVID-19 mortality (OR = 3.34, 95%CI = 1.89–5.9). Meta-regression analysis results also showedthat diabetes, hypertension and cardiovascular diseases did not exert significant effect on the association between obesity and COVID-19.

More interestingly, the dose-response analysis showed that with an increase in BMI, the risk of severe COVID-19 and death increased linearly. For each 1 kg/m^2 increase in BMI, the risk of critical COVID-19 and death increased by 9%(OR = 1.09, 95%CI = 1.04–1.14) and 6%(OR = 1.06, 95%CI = 1.02–1.10), respectively. Therefore, it can be inferred that severe obesity may be a strong risk factor for COVID-19. Kalligeros et al. [21] have found that severe obesity (BMI ≥35 kg/m^2) was associated with a 5.39-fold risk of ICU admission (OR = 5.39, 95%CI = 1.13–25.64). Palaiodimos et al. [8] indicted that severe obesity (BMI ≥ 35 kg/m^2) was independently associated with higher in hospital mortality (OR = 2.74, 95%CI = 1.25–5.98). They also pointed out that this association remained significant even after adjusting for several clinical entities, such as diabetes, coronary artery disease, heart failure, cancer, or chronic kidney disease, and smoking, which indicates that severe obesity may predispose to negative outcomes independently.

The initial finding suggesting that at an older ages BMI is less important in influencing COVID-19 prognosis, because obesity was defined as a state of excess fat mass. And the BMI poorly describes excess fat mass in the elderly. However, subgroup analysis and meta-regression analyses results showed that age had a significant effect on the risk of critical COVID-19 and mortality. Patients with obesity and age > 60 years had a near 4-fold higher risk of developing into the critical COVID-19 and dying. Lighter et al. [10] found that obesity (BMI ≥ 30 kg/m^2) was associated with a 1.5-fold risk of COVID-19 hospitalization in patients younger than 60 years and a 3.6-fold risk in patients older than 60 years. Moreover, a report from the USA showed that obesity was associated with a 4.5-fold risk of COVID-19 mortality in patients older than 60 years [8]. This may be because the elderly weight and muscle mass start to decline, and immune senescence. Obesity also has detrimental effects on lung function, diminishing forced expiratory volume and
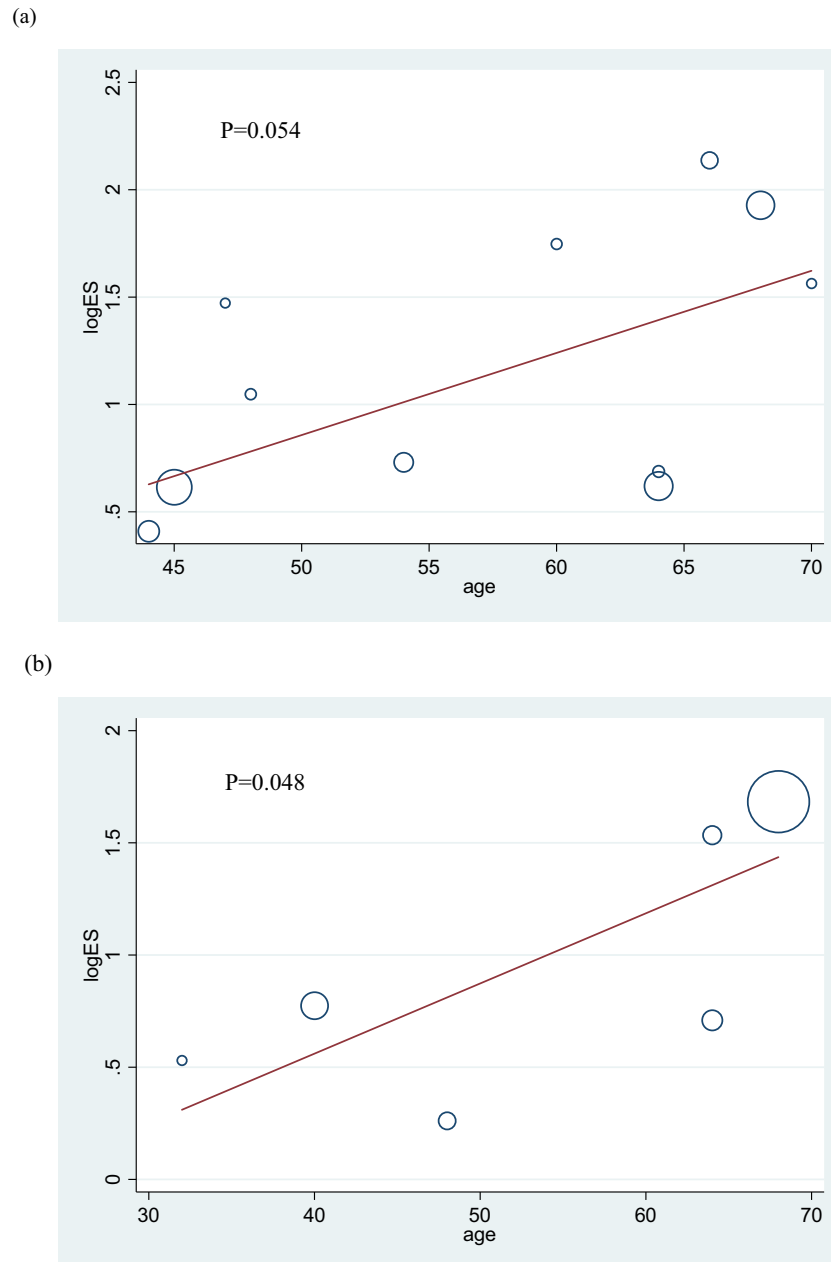
(a)

(b)

Fig. 6. Random-effects meta-regression analysis to explore the effect of age on association between BMI > 30 kg/m^2 and COVID-19 severity (a) and mortality (b).

forced vital capacity, it is more harmful to the elderly individuals [36]. In addition, older patients with obesity are more prone to develop diabetes, hypertension and cardiovascular diseases, which are reported to be associated with an increased risk of COVID-19 severity [37,38].

Our study also found that COVID-19 patients with obesity in Asian countries had a higher risk of developing into a critical or mortal condition than patients in non-Asian countries. Asians have a different BMI cutoff (28 kg/m^2) to define obesity. Thus, Asians with a BMI ≥30 kg/m^2 are actually looking at patients that are more severely obese than Caucasian ones, this is a possible explanation for Asian studies reporting more severe outcomes in these patients. Cross-sectional studies showed a significantly higher effect of obesity on COVID-19 than cohort studies, and this may be attributed to the limited research data of only two cross-sectional studies.

In addition, a study from China reported that the risk of obesity to COVID-19 severity was >6-fold greater in those with metabolic associated fatty liver disease [24]. Simultaneously, several studies indicated

that the association between obesity and COVID-19 severity may be related to smoking, but needs to be explored further [39,40]. Moreover, emerging evidence suggests that visceral fat is a strong contributor to worse COVID-19 prognosis. Visceral adipose tissue is capable of secreting Interleukin 6 (IL-6), whose levels were found to be increased in SARS-CoV-2 non-survivors [41,42].

Although the pathophysiology underlying COVID-19-infection has not been completely elucidated, but several mechanisms may exist at the same time, including: (1) SARS-CoV-2 attacks the alveolar epithelial cells via angiotensin-converting enzyme 2 (ACE2). Obesity was accompanied by increased expression of ACE2, which would bind to the virus S protein firmly and make adipose tissue a portal for virus invasion, making the lung and heart vulnerable to a virus attack [43]. (2) Obesity is in fact characterized by low-grade systemic inflammation, possibly playing a major role in the pathogenesis of respiratory conditions. Excess fat is associated with complement system overactivation, which may induce an excessive inflammatory response and immune
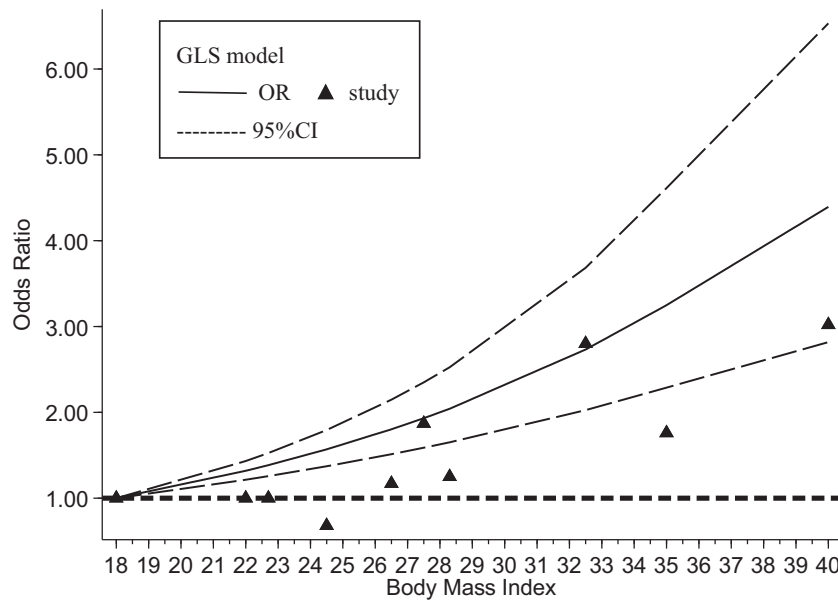
Fig. 7. Random-effects linear dose-response meta-analysis of the association between BMI and the risk of severe COVID-19($P_{non-linearity}$ = 0.242). Solid line and long dashed lines represent odds ratio and its 95% confidence interval.

exhaustion in COVID-19 [44,45]. Gralinski et al. [46] identified the complement system as an important host mediator of SARS-CoV-induced disease. (3) Related comorbidities such as diabetes, a common complication of excess body fat, are reported as risk factors for worse SARS-CoV-2 infection progression and prognosis. (4) Ultimately, excess fat could also lead to the possible presence of ectopic adipocytes within the alveolar interstitial space that may develop direct viral infection and in turn aggravate the inflammatory infiltrate, therefore contributing to the massive interstitial edema being observed [45].

This meta-analysis has several novelties. Firstly, our study showed that obesity was an independent risk factor for critical COVID-19 and mortality. Secondly, the dose-response meta-analysis showed a significant linear association between BMI and the risk of critical COVID-19 and mortality. Third, we found that patients with obesity and age > 60 years had a significantly higher COVID-19 mortality. Fourth, we

performed multivariate subgroup and meta-regression analyses to fully explore the potential effect of confounding factors on the associations between obesity and COVID-19 severity and mortality.

Meanwhile, several potential limitations of our study deserve mention. Firstly, our study is limited with the small sample size of 16 studies, although we did not restricted our searches based on language, just studies from English databases and missed non-English articles may affect the final results. Secondly, different diagnostic criteria for obesity in Asia and non-Asia, which may be one of the sources of heterogeneity. Third, the majority of patients included in the meta-analysis were of America (mostly USA population), and it was not possible to test for ethnic-specific differences in risk of critical COVID-19 and COVID-19 linked death, because of the limited studies in no-America individuals. Thus, further studies, especially on European and Asian populations, are needed to confirm these findings, and future mechanistic studies are
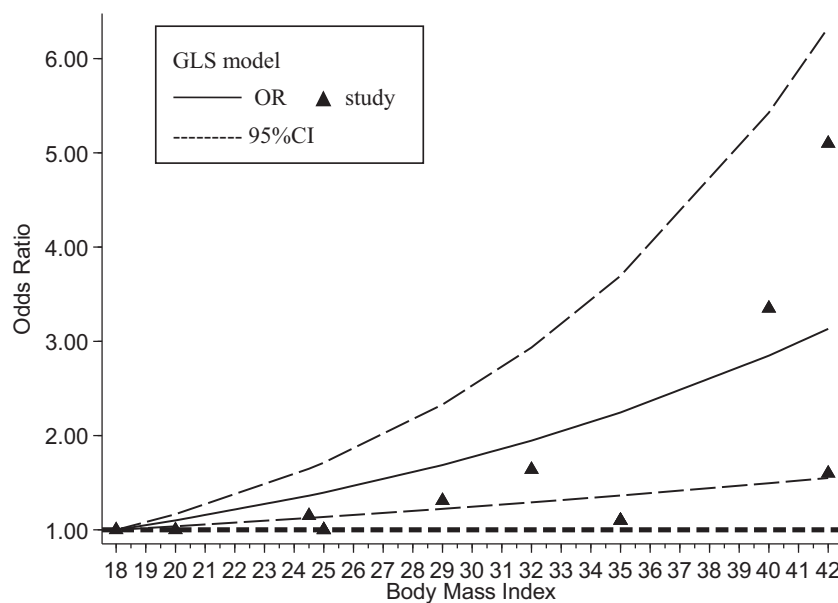

Fig. 8. Random-effects linear dose-response meta-analysis of the association between BMI and COVID-19 mortality ($P_{non-linearity}$ = 0.116). Solid line and long dashed lines represent odds ratio and its 95% confidence interval.

also required to better understand the link between BMI and the risk of severe disease and in-hospital mortality associated with COVID-19.

10. Conclusions

In conclusion, results from this meta-analysis indicate that obesity is associated with an increased risk of critical COVID-19 and mortality. Moreover, the dose-response analysis showed that with an increase in BMI, the risk of severe COVID-19 and mortality increased linearly. So, patients with both COVID-19 and obesity should be paid more attention to in hospitals, especially those with severe obesity or those older than 60 years.

CRediT authorship contribution statement

Yanbin Du: Conceptualization, Methodology, Data curation, Software, Formal analysis, Writing - original draft, Writing - review & editing. **Yuan Lv:** Validation, Resources, Supervision. **Wenting Zha:** Investigation, Methodology, Visualization, Supervision. **Nan Zhou:** Investigation, Software, Data curation. **Xiuqin Hong:** Methodology, Resources.

Declaration of competing interest

The authors declare that there are no conflicts of interest.

Acknowledgements

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