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Original article

Body mass index and outcome in patients with COVID-19: A dose–response meta-analysis



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ARTICLE INFO

Article history:

Received 10 June 2020

Received in revised form 4 July 2020

Accepted 12 July 2020

Available online 29 July 2020

Keywords:

Body mass index

Coronavirus

Obesity

SARS-CoV-2

Weight

ABSTRACT

Background. – There is mounting evidence related to the association between obesity and severity of COVID-19. However, the direct relationship of the increase in the severe COVID-19 risk factors, with an increase in body mass index (BMI), has not yet been evaluated.

Aim. – This meta-analysis aims to evaluate the dose–response relationship between body mass index (BMI) and poor outcome in patients with COVID-19.

Methods. – A systematic literature search was conducted using PubMed, Europe PMC, ProQuest, and the Cochrane Central Database. The primary outcome was composite poor outcome composed of mortality and severity. The secondary outcomes were mortality and severity.

Results. – A total of 34,390 patients from 12 studies were included in this meta-analysis. The meta-analysis demonstrated that obesity was associated with composite poor outcome (OR 1.73 [1.40, 2.14], $P < 0.001$; I^2 : 55.6%), mortality (OR 1.55 [1.16, 2.06], $P = 0.003$; I^2 : 74.4%), and severity (OR 1.90 [1.45, 2.48], $P < 0.001$; I^2 : 5.2%) in patients with COVID-19. A pooled analysis of highest BMI versus reference BMI indicate that a higher BMI in the patients was associated with composite poor outcome (aOR 3.02 [1.82, 5.00], $P < 0.001$; I^2 : 59.8%), mortality (aOR 2.85 [1.17, 6.92], $P = 0.002$; I^2 : 79.7%), and severity (aOR 3.08 [1.78, 5.33], $P < 0.001$; I^2 : 11.7%). The dose–response meta-analysis showed an increased risk of composite poor outcome by aOR of 1.052 [1.028, 1.077], $P < 0.001$ for every 5 kg/m² increase in BMI ($P_{\text{non-linearity}} < 0.001$). The curve became steeper with increasing BMI.

Conclusion. – Dose–response meta-analysis demonstrated that increased BMI was associated with increased poor outcome in patients with COVID-19.

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Introduction

As of 2nd July 2020, the coronavirus disease (COVID-19) has infected 10,533,779 people worldwide, with a death toll of 512,842 [1]. Although a majority of the patients are either asymptomatic or only have a mild, influenza-like illness, a significant proportion develop severe symptoms. However, the factors leading to critical illness in some patients, but not in others, remain unclear. Hence, a

detailed investigation of the factors linked to severe COVID-19 is needed, in order to facilitate appropriate resource allocation [2].

There is mounting evidence of a strong association between obesity and severity of COVID-19 [3–5]. However, the direct relationship of the increase in the risk factor of severe COVID-19, with an increase in body mass index (BMI), has not yet been evaluated. In this systematic review and meta-analysis, we aim to evaluate the association between obesity and poor outcome (mortality and severity) in patients with COVID-19 and explore the dose–response relationship between BMI and poor outcome in these patients by pooling data from observational studies. We hypothesize that obesity and increase in BMI increases mortality and severity of patients with COVID-19 in a dose–response fashion.

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Material and methods

This systematic review and meta-analysis follows the Meta-analysis of Observational Studies in Epidemiology (MOOSE) reporting guidelines.

Eligibility criteria

The following types of articles were included: research articles on adults with COVID-19 with information available regarding obesity (categorical) or BMI, and the clinically validated definition of death, severe illness (WHO-China joint commission), the need for intubation, or a referral to the intensive care unit (ICU). Only published studies have been included in this systematic review and meta-analysis. We have excluded preprints, abstract-only publications, review articles, letters without primary data, commentaries, case reports/case series <20 patients, non-English

language articles and studies that did not report key exposures or outcomes of interest.

Search strategy and study selection

A systematic literature search was conducted using PubMed, Europe PMC, ProQuest, and the Cochrane Central Database with keywords (“SARS-CoV-2” OR “COVID-19” OR “Coronavirus”) AND (“Obesity” OR “Overweight” OR “Body Mass Index”) for records published from 1 January 2020 up until 28 May 2020. The PubMed (MEDLINE) search strategy was (“SARS-CoV-2”[All Fields] OR “COVID-19”[All Fields] OR “Coronavirus” [All Fields]) AND (“Obesity”[All Fields] OR “Overweight”[All Fields] OR “body mass index” [All Fields]) 2020/01:2020/05/29 [edat]. Hand-searching for related articles were also performed. Full search strategies can be accessed in Table S1 (see supplementary materials associated with this article on line). Duplicates were removed, and the titles and

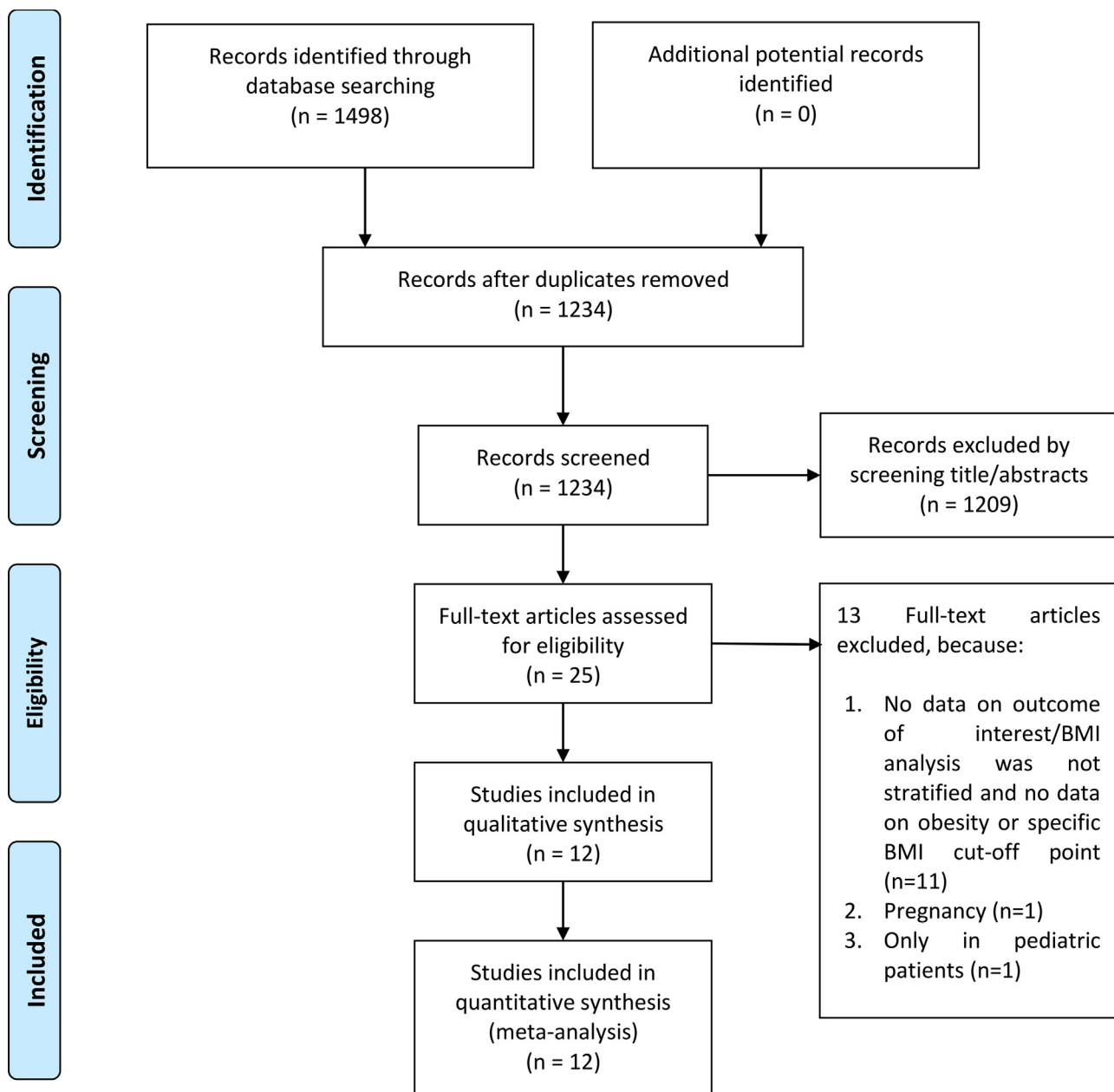


Fig. 1. Study flow diagram.

abstracts of the remaining articles were independently assessed by two authors using the inclusion and exclusion criteria. Both literature searchers are medical doctors with experience in performing systematic reviews and meta-analyses.

Data extraction

Two independent authors abstracted data using standardized forms and obtained information on first author, year, study design, age, gender, diabetes mellitus, hypertension, cardiovascular diseases, mortality, severe COVID-19, the need for intubation, and a need for referral to the ICU. Selection of data was based on potential variables that may affect the relationship between obesity and the outcome.

Exposure in this study was obesity was defined as BMI ≥ 30 kg/m², BMI ≥ 28 kg/m² is acceptable for Asian studies. The primary outcome was composite poor outcome composed of mortality and severity. Secondary outcomes were mortality and severity. Severity was defined as severe COVID-19 as per the WHO-China Joint Mission on COVID-19, the need for intubation, or referral to the ICU [6]. To reduce the influence of confounders, adjusted odds ratios (ORs) were used for effect estimate obtained with the pooling method, whenever possible. Risk of bias/quality of studies were assessed using the Newcastle-Ottawa Scale (NOS) by two independent authors and discrepancies were resolved through discussion.

Statistical analysis

We used STATA 16.0 (StataCorp LLC, Texas, US) to perform meta-analysis. The prevalence of obesity across the studies were pooled using random-effects meta-analysis of proportion. ORs were reported for the effect estimate, along with its 95% confidence intervals (CIs). Adjusted ORs (aORs) were pooled for meta-analysis of obesity and poor outcome; if only dichotomous variables were present, we converted them into OR. The aORs were pooled for analysis stratified by BMI and the adjusted hazard ratios (HRs) were converted into adjusted ORs for the analysis. The unadjusted outcomes were excluded. Random-effects model was used for the analyses, regardless of heterogeneity. Two-tailed *P*-values were used, with the statistical significance set at <0.05 . Inter-study heterogeneity was assessed using Cochran's *Q* test and *I*² statistic; *I*² values $> 50\%$ and *P*-value <0.10 indicated statistically significant heterogeneity. A dose response meta-analysis was then performed for studies that have at least three

quantitative classifications. A two-stage random-effects dose-response meta-analysis was performed using generalized least-squares regression trend estimation based on logaORs across BMI intervals. The potential for a non-linear relationship based on aORs of each quantitative BMI was examined using restricted cubic splines with three-knots model. The restricted maximum likelihood method in a multivariate random-effects meta-analysis was used to combine the effect estimates. Wald-type test was used to assess non-linearity by testing regression coefficient of the second spline. A subgroup analysis was performed for individual components of the composite poor outcome (mortality and severity). The sensitivity analysis was performed by excluding studies with a BMI cut-off other than >30 kg/m² for obesity analysis. A leave-one-out sensitivity analysis was performed to test the statistical robustness of the analysis. Random effects meta-regression was conducted using a restricted-maximum likelihood method for gender, hypertension, diabetes, and the continent in which the study was conducted. To assess the risk of publication bias, funnel-plot analysis and Begg's test were performed.

Results

Baseline characteristics

Our initial search yielded 1498 records, of which 1234 remained after the removal of duplicates. After a screening of the titles and abstracts of these records, 25 potential articles were found. Their full-texts were assessed and 13 were excluded due to the following reasons: (1) no data on outcome of interest/BMI analysis was not stratified, no data on obesity or specific BMI cut-off point ($n = 11$), (2) pregnancy ($n = 1$), and (3) only in pediatric patients ($n = 1$). The remaining 12 studies were included in the systematic review and meta-analysis [Fig. 1] [3–5,7–15]. There were a total of 34,390 patients from these 12 studies. The baseline characteristics of the included studies is given in Tables 1 and 2. The mean NOS was 8.3 ± 1.1 (Table S2; see supplementary materials associated with this article on line), indicating a low risk of bias.

Prevalence of obesity

The prevalence of obesity in this meta-analysis was 31% (21–42%), with the values being 42% (38–45%) for North America, 24% (9–39%) for Europe, and 6% (4–8%) for Asia.

Table 1
Characteristics of the included studies.

Author	Design	Center	Location	Sample (n)	Obesity Cut-off Used for Analysis (kg/m ²)	Prevalence of Obesity (%)	Outcome of Interest	NOS
Klang E 2020	Restrospective Cohort	Single-Center	New York, USA	3406 (1136 vs. 2270)	>30	36.1	Mortality	9
Palaiodimos 2020	Retrospective cohort	Single-Center	New York, USA	200	>35	23	Mortality	9
Petrilli 2020	Prospective Cohort	Multi-center	New York, USA	5279	>30	35.3	Mortality	9
Docherty AB 2020*	Prospective Cohort	Multi-center	UK	20133	>30	10.5	Mortality	8
Giacomelli A 2020	Prospective Cohort	Single-Center	Milan, Europe	233 (48 vs. 185)	>30	16.3	Mortality	9
Cai Q 2020	Restrospective Cohort	Single-Center	Shenzen, China	383 (91 vs. 292)	>28	10.7	Severity	9
Buckner FS 2020	Restrospective Cohort	Multi-center	Seattle, USA	105 (51 vs. 51)	>30	47	Severity	7
Hu L 2020	Restrospective Cohort	Single-Center	Wuhan, China	323 (172 vs. 151)	>30	4	Severity	7
Simonnet A 2020	Restrospective Cohort	Single-Center	Lille, France	124 (85 vs. 39)	>30	47.5	Intubation	9
Hur K 2020	Restrospective Cohort	Multi-center	Chicago, USA	486 (138 vs. 348)	>30	53.3	Intubation	9
Lighter J 2020	Restrospective Cohort	Single-Center	New York, USA	3615	>30	37.8	ICU	6
Kalligeros 2020	Restrospective Cohort	Multi-center	Rhode Island, USA	103 (44 vs. 59)	>30	47.5	ICU	9

* Information on characteristics were dichotomized by gender or BMI.

Information is presented as poor outcome (+) vs. poor outcome (-). If there is no information based on such grouping, data for overall sample is presented instead. UK: United Kingdom; USA: United States of America; N/A: Not Available/Applicable; NOS: Newcastle-Ottawa Scale.

Table 2
Characteristics of patients in the included studies.

Author	Age (mean \pm SD or median (IQR))	Male (%)	Hypertension (%)	Diabetes (%)	Cardiovascular disease (%)
Klang E 2020	74.4 \pm 12.89 vs. 61.68 \pm 15.84	58 vs. 57	78 vs. 62	56 vs. 43	32 vs. 17 (CAD)
Palaiodimos 2020	64 (50–73.5)	49	76	39.5	16.5 (CAD)
Petrilli 2020	Stratified	Stratified	Stratified	Stratified	Stratified
Docherty AB 2020*	72.9 (58.0–82.0)	60	N/A	20.7 (uncomplicated) 7.4 (complicated)	30.9 (Chronic Cardiac Disease)
Giacomelli A 2020	Stratified	81 vs. 66	58 vs. 31 (based on antihypertensive medications use)	17 vs. 11 (based on antidiabetic medications use)	N/A
Cai Q 2020	61 (52–65) vs. 44.5 (34–57)	64 vs. 43	23 vs. 13	13 vs. 3	19 vs. 6 (CVD)
Buckner FS 2020	70 (23–97) vs. 67 (25–96)	59 vs. 43	59 vs. 59	35 vs. 31	35 vs. 42 (CVD)
Hu L 2020	64 (23–87) and 70 (44–91) vs. 56 (23–89)	53 vs. 50	38 vs. 26	19 vs. 9	19 vs. 5 (CAD mix CVD)
Simonnet A 2020	60 (51–69) vs. 60 (50–72)	75 vs. 67	56 vs. 31	27 vs. 13	NA
Hur K 2020	Dichotomized at 60 y.o	64 vs. 53	59 vs. 53	41 vs. 30	29 vs. 20 (CVD)
Lighter J 2020	N/A	N/A	N/A	N/A	N/A
Kalligeros 2020	61.5 (54.5–72.5) vs. 57 (48–72)	66 vs. 58	70 vs. 59	48 vs. 29	32 vs. 19 (Heart Disease)

* Information on characteristics were dichotomized by gender or BMI.

Information is presented as poor outcome (+) vs. poor outcome (-). If there is no information based on such grouping, data for overall sample is presented instead. CAD: Coronary Artery Disease; CVD: Cardiovascular Diseases; IQR: Interquartile Range; N/A: Not Available/Applicable; SD: Standard Deviation

Obesity and composite poor outcome

This meta-analysis demonstrated that obesity was associated with composite poor outcome (OR 1.73 [1.40, 2.14], $P < 0.001$; I^2 : 55.6%, $P_{\text{heterogeneity}} = 0.003$) [Fig. 2A]. The subgroup analysis showed that obesity increased mortality (OR 1.55 [1.16, 2.06], $P = 0.003$; I^2 : 74.4%, $P_{\text{heterogeneity}} = 0.002$) [Fig. 2B] and severity (OR 1.90 [1.45, 2.48], $P < 0.001$; I^2 : 5.2%, $P_{\text{heterogeneity}} = 0.394$) [Fig. 2C] in patients with COVID-19. A sensitivity analysis was performed to remove studies with a BMI cut-off of $>28 \text{ kg/m}^2$, which showed an OR of 1.66 [1.35, 2.05], $P < 0.001$; I^2 : 53.2%, $P_{\text{heterogeneity}} = 0.006$ for composite poor outcome and an OR of 1.77 [1.35, 2.31], $P < 0.001$; I^2 : 0%, $P_{\text{heterogeneity}} = 0.472$ for severity. Upon removal of Klang et al. study on leave-one-out sensitivity analysis, the effect estimate for composite poor outcome was OR of 1.60 [1.31, 1.94], $P < 0.001$; I^2 : 44.1%, $P_{\text{heterogeneity}} = 0.034$ and for mortality was OR of 1.35 [1.08, 1.68], $P < 0.001$; I^2 : 62.1%, $P_{\text{heterogeneity}} = 0.048$.

BMI and composite poor outcome

The pooled analysis of highest BMI versus reference BMI of each of the studies showed that a higher BMI was associated with composite poor outcome (aOR 3.02 [1.82, 5.00], $P < 0.001$; I^2 : 59.8%, $P_{\text{heterogeneity}} = 0.021$) [Fig. 3A]. The subgroup analysis showed that a higher BMI was associated with mortality (aOR 2.85 [1.17, 6.92], $P = 0.002$; I^2 : 79.7%, $P_{\text{heterogeneity}} = 0.021$) [Fig. 3B] and severity (aOR 3.08 [1.78, 5.33], $P < 0.001$; I^2 : 11.7%, $P_{\text{heterogeneity}} = 0.334$) in patients with COVID-19 [Fig. 3C]. Upon removal of Petrilli et al. study on leave-one-out sensitivity analysis, the effect estimate for composite poor outcome was OR of 3.53 [2.39, 5.19], $P < 0.001$; I^2 : 0%, $P_{\text{heterogeneity}} = 0.453$ and for mortality was OR of 4.52 [2.46, 8.30], $P < 0.001$; I^2 : 0%, $P_{\text{heterogeneity}} = 0.636$.

Dose-response meta-analysis

A total of 7 studies were included in the dose-response meta-analysis. Linear association analysis demonstrated an increased risk of composite poor outcome by aOR of 1.052 (1.028, 1.077),

$P < 0.001$ for every 5 kg/m^2 increase in BMI. A non-linear relationship ($P_{\text{non-linearity}} < 0.001$) was observed between BMI and composite poor outcome in patients with COVID-19, depart from linearity occurs at BMI of $30\text{--}35 \text{ kg/m}^2$ and the curves became steeper. Using BMI of 20 kg/m^2 as the reference, the ORs for patients with BMI of 25, 30, 35, and 40 kg/m^2 were 1.02 (0.99, 1.05), 1.09 (1.04, 1.15), 1.28 (1.17, 1.41), and 1.61 (1.31, 1.97), respectively [Fig. 4].

Meta-regression analysis

Meta-regression analysis showed that the association between obesity and composite poor outcome did not vary with the proportion of male ($P = 0.250$), hypertension ($P = 0.669$), diabetes ($P = 0.599$), and the continent in which the study was conducted ($P = 0.919$).

Publication bias

The funnel-plot analysis qualitatively showed an asymmetrical shape [Fig. 5], indicating the possibility of publication bias for the association between obesity and composite poor outcome. Begg's test for small-study effects showed no indication of small-study effects ($P = 0.053$). Funnel-plot analysis and begg's test was not performed for body mass index and composite poor outcome because the number of studies were <10 .

Discussion

Our meta-analysis showed that obesity was associated with composite poor outcome, mortality, and severity of COVID-19. The dose-response meta-analysis showed that the risk for composite poor outcome increased by OR of 5% for every 5 kg/mg^2 increase in BMI; the relationship departed from linearity and became steeper from $30\text{--}35 \text{ kg/mg}^2$ onwards. To the best of the authors' knowledge, this is the first meta-analysis to evaluate the dose-response relationship of BMI and its' effect on COVID-19 prognosis.

The association between obesity and composite poor outcome has a moderate-high heterogeneity, this heterogeneity persists

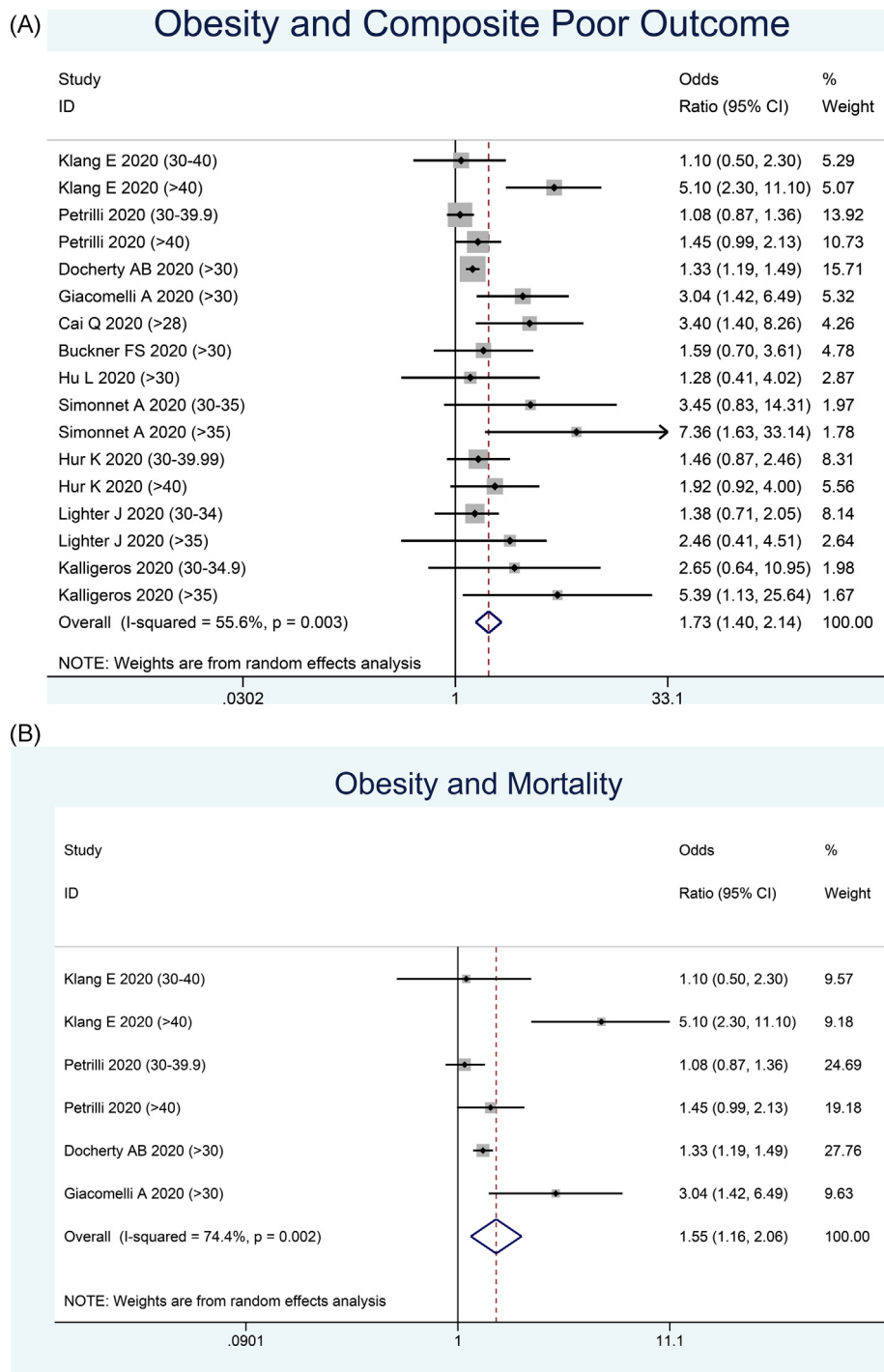


Fig. 2. Obesity and poor outcome. Forest-plot showing the association between obesity and composite poor outcome (A), mortality (B), and severity (C). 95% CI: 95% confidence interval, I-squared: I^2 .

despite the removal of studies without BMI cut-off of $>30 \text{ kg/m}^2$ for obesity. The asymmetrical funnel plot and a nearly significant Begg's test indicate possible publication bias/small-study effects. The funnel plot was skewed toward right indicating possible overestimation of the effect estimate. The heterogeneity can be reduced by a leave-one-out sensitivity analysis, removal of Klang et al. study results in the greatest reduction in heterogeneity. The effect estimate remains in the same direction (obesity increases the risk of composite poor outcome) which indicates statistical robustness. Klang et al. study have a higher prevalence of hypertension and diabetes, however, meta-regression analysis

showed that the relationship between obesity and composite poor outcome did not vary with hypertension and diabetes. Nevertheless, it should be noted that meta-regression has low power to detect genuine relationships especially with the limited number of studies eligible for meta-regression in this meta-analysis (9 studies for gender and hypertension; 8 studies for diabetes). Obesity Surgery Mortality Risk Score (OS-MRS) for patients undergoing bariatric surgery suggest that gender and hypertension were predictive of mortality [16–18]. More studies are needed before concluding the result of meta-regression, patient-level subgroup analysis may provide a stronger conclusion.

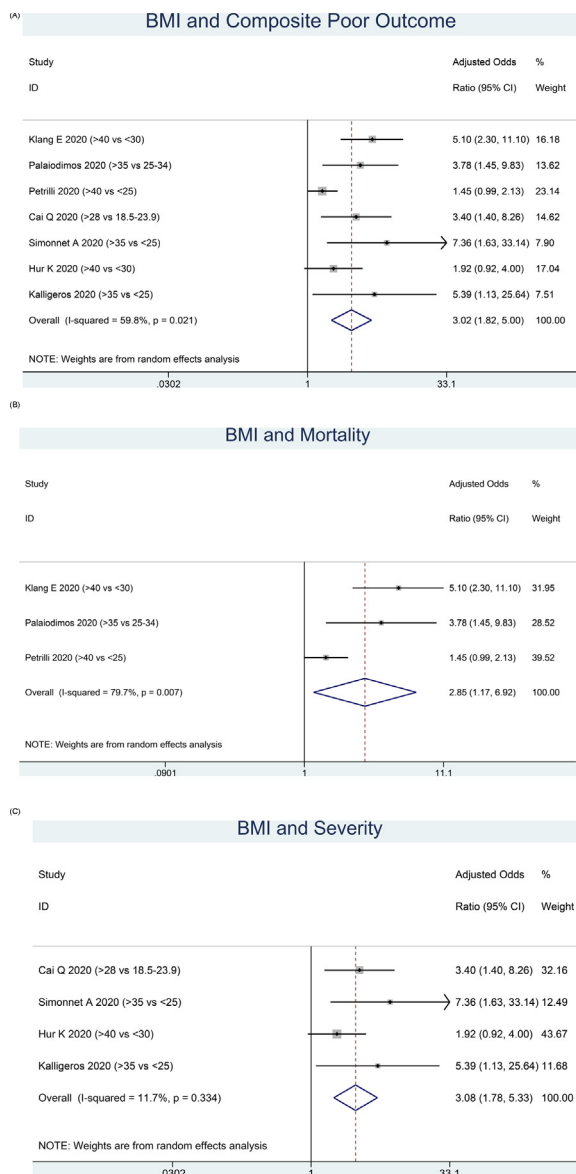


Fig. 3. Body mass index and poor outcome. Forest-plot showing the association between body mass index and composite poor outcome (A), mortality (B), and severity (C). 95% CI: 95% confidence interval, I-squared: I^2 .

For the pooled analysis BMI and composite poor outcome, the removal of Petrilli et al. study reduces heterogeneity to 0%. Unfortunately, the patient characteristics were presented in a different format by Petrilli et al. study, thus, cannot be compared to the other included studies. These analyses showed that the highest BMI in the studies was consistently associated with increased mortality and severity compared to the reference BMI. The dose-response meta-analysis showed that the association became stronger in higher BMI, this explains that the pooled analysis of highest BMI versus reference BMI demonstrated a stronger association compared to obesity with a cut-off of $>30 \text{ kg/m}^2$.

According to the Centers for Disease Control and Prevention (CDC), people with a BMI of 25 to <30 are classified as overweight, while those with a BMI of 30 or higher are categorized as obese. Obesity is often classified into three classes: (1) BMI of 30 to <35 , (2) BMI of 35 to <40 , and (3) BMI of 40 or higher [19]. Class 3 obesity is frequently called “severe” or “extreme” obesity and it

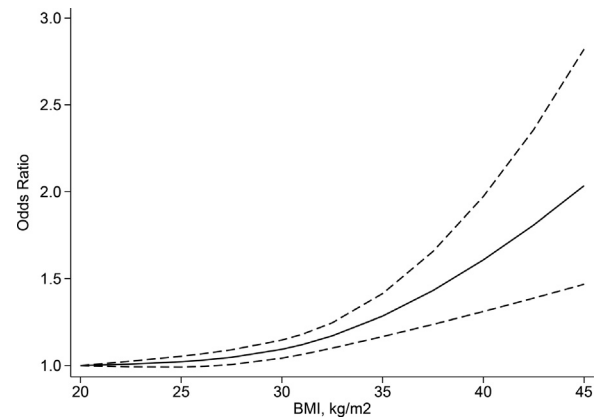


Fig. 4. Dose response meta-analysis between body mass index and composite poor outcome in patients with COVID-19 with restricted cubic splines in a multivariate random-effects dose-response model. Adjusted odds ratio (solid line) with 95% confidence interval (long dashed lines) for the association of the body mass index level with the risk of composite poor outcome.

may, along with several other medical conditions, increase the risk of severe COVID-19 [20–24].

When compared to individuals with normal BMI, subjects with obesity have a greater risk of hypertension, dyslipidemia, insulin resistance, type 2 diabetes mellitus (T2DM), cardiovascular disease and cerebrovascular disease, all of which are recognized as comorbidities for poor outcomes in COVID-19 patients [21,22,24,25]. Excess BMI has been shown to increase susceptibility to infections, and obesity itself is an independent risk factor for severe COVID-19 [26,27]. In fact, individuals with obesity are found to have reduced protection from influenza vaccination and are at risk of contracting infections, respiratory infections in particular [26,28]. People with excessive BMI and/or having comorbid conditions generally have low-grade chronic inflammation that makes them susceptible to infections with poorer outcomes [29–31]. Obesity causes systemic inflammation and adversely affects innate and adaptive immunity in a manner similar to immunosenescence or immune system aging [32].

Low-grade inflammation in overweight and individuals with obesity is characterized by the dysfunction and hypoxia of adipocyte, which leads to an increased release of pro-inflammatory cytokines such as interleukin (IL)- 1β , IL-6, IL-8, C-reactive protein (CRP), and tumor necrosis factor- α (TNF- α), and the recruitment of immune cells including macrophages, B-cells, and T-cells. This results in a cycle of auto-regenerating inflammation leading to a cytokine storm, which is one of the fundamental pathomechanisms of severe COVID-19 and can lead to acute respiratory distress syndrome or even multi-organ failure (MOF), affecting kidney and liver. It exhibits a phenomenon of immune hyperactivation very similar to cytokine-release syndrome [31].

In COVID-19 patients, the virus may either invade organs directly or enter the cells through angiotensin-converting enzyme 2 (ACE2) receptor [33]. In addition, viral invasion may generate huge amounts of cytokines, which is also thought to be involved in the pathophysiology of MOF [34]. The combination of virus-induced and obesity-driven hyperinflammation could further exacerbate the inflammation in COVID-19 patients and lead to worse prognosis, including mortality [21–24].

Individuals with obesity generally have low adiponectin (an anti-inflammatory adipokine) and high leptin (a pro-inflammatory adipokine) concentrations. This unfavorable hormonal state negatively influences immune function and may play a role in the development of obesity-related complications [29]. Another concern among subjects with obesity is the lack of physical

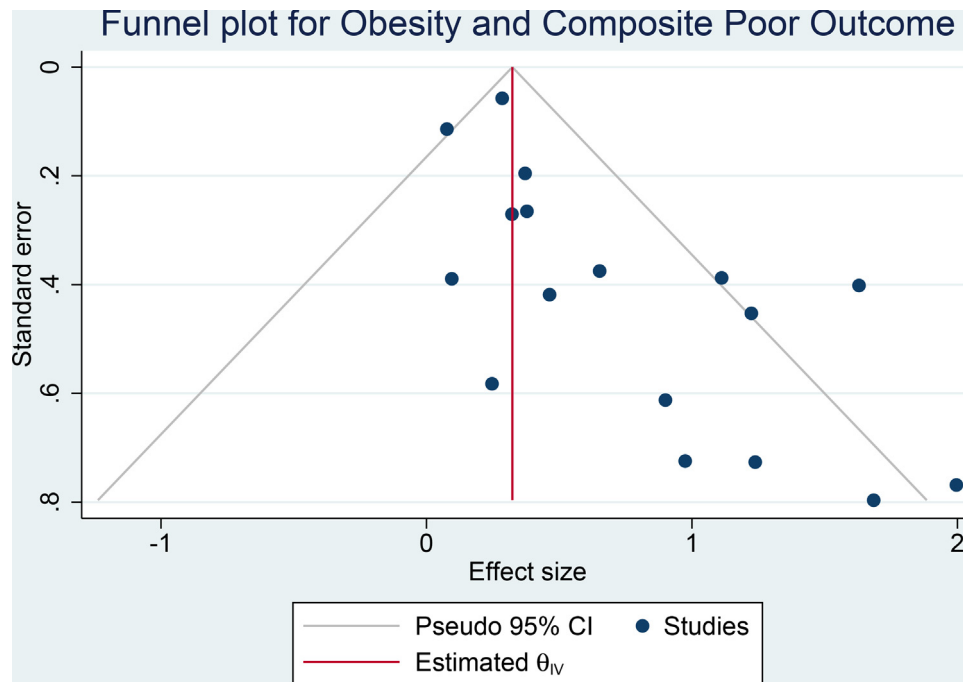


Fig. 5. Funnel-plot analysis for obesity and composite poor outcome.

activity. Aging, physical inactivity, obesity and metabolic syndrome are shown to contribute to weakened immune and viral defense systems [32].

Reduced physical activity, irrespective of insulin resistance, disrupts the immune response against pathogenic agents. The presence of antigen may not be adequately managed due to diminished macrophage activation and the inhibition of release of pro-inflammatory cytokines upon its stimulation. These defects in the immune response cause prolonged shedding of the virus, which increases the possibility of its transmission to others. Furthermore, the obese microenvironment leads to diminished production of interferons, which enables greater viral RNA replication. This may eventually result in the emergence of novel more virulent virus strains. In addition, BMI correlates positively with infectious virus in exhaled breath [29].

A higher BMI is associated with poor pulmonary function, including lower respiratory reserve volume, functional capacity, and respiratory system compliance. In patients with metabolic syndrome or those who have increased abdominal circumference, decreased lung function is further compromised in supine position due to reduced diaphragmatic excursion, causing additional difficulties in ventilation [35]. Patients with severe obesity and full expression of the obstructive sleep apnea phenotype receive less benefit from non-invasive positive pressure ventilation, and require medical management of its comorbid conditions. These patients have increased risk of cardiovascular diseases, cancer, and all-cause mortality and frequently present with exaggerated pro-inflammatory profile [26]. In addition, chronic low-grade inflammation and impaired fibrinolysis put subjects with obesity at the risk of thrombosis, which appears to be a causative factor of worsening lung damage and death in COVID-19 patients. This is in agreement with several current protocols and recommendations that endorse the use of heparin, an anticoagulant, for the treatment for COVID-19 patients [31,36].

Another medical condition commonly presented in subjects with obesity is metabolic associated fatty liver disease (MAFLD), defined by the presence of hepatic steatosis in addition to one of the following conditions- overweight/obesity, T2DM, or metabolic

dysregulation. In such patients, IL-6 concentration independently predicted liver inflammation, which could synergistically promote more severe COVID-19. Moreover, gut dysbiosis in obesity is another significant factor potentially linked with the development of severe forms of COVID-19 [31]. Furthermore, vitamin D deficiency or insufficiency is another common finding in obesity which can disrupt immune function and increase the risk of systemic infections [37].

Individuals with obesity are generally a high-risk and complicated group of patients to treat for COVID-19, often requiring longer hospitalization and comprehensive management of its comorbidities and complications [31]. Because of prolonged viral shedding, subjects with obesity are also required to be quarantined longer than those who have normal BMI [29]. It is clear that an increase in BMI is significantly correlated with composite poor outcome in COVID-19, however, the impact of body composition (fat/fat-free muscle) on the outcome for COVID-19 patients needs to be investigated further. Table 3 summarizes the possible mechanisms of the association between obesity and poor prognosis in patients with COVID-19. The perception of weight gain during lockdown was observed in half of the respondents in an Italian survey [38], although it was not an objective measurement, it may indicate a potential rise for obesity. These may increase the number of individuals at risk for developing severe COVID-19. An increase in the obesity prevalence along with other diseases may also lead to a surge in non-communicable diseases post pandemic [39]. Hence, physical activity and healthy eating habits should be encouraged during the pandemic [40–42].

This meta-analysis has several limitations. Firstly, although the analysis for BMI only pooled adjusted OR/HR, there might be other confounders that might not be accounted for in their study. Secondly, the majority of the studies were retrospective which is less reliable compared to prospective studies. Thirdly, we did not include articles published in foreign languages, which may limit epidemiological data from non-English speaking countries.

In conclusion, obesity was associated with an increase in poor outcome for COVID-19 patients. The dose-response meta-analysis

Table 3
Mechanisms of association between obesity and poor prognosis in patients with COVID-19.

Mechanism	Explanation
A higher risk of developing comorbidities	A greater risk of hypertension, dyslipidemia, insulin resistance, T2DM, cardiovascular disease and cerebrovascular disease, all of which are known as comorbidities for poor outcomes in COVID-19
Impaired immunity	Dysfunction in innate and adaptive immunity increases the susceptibility to contract infections, particularly respiratory infections.
Proinflammation state	Low-grade, systemic, chronic inflammation that is characterized by adipocyte dysfunction and hypoxia, which leads to an increased release of pro-inflammatory cytokines such as IL-1 β , IL-6, IL-8, CRP, and TNF- α , and the recruitment of immune cells including macrophages, B-cells, and T-cells. This results in a cycle of auto-regenerating inflammation leading to a cytokine storm, which is one of the main pathomechanisms of severe COVID-19 and serious complications.
Virus-induced hyperinflammation	SARS-CoV-2 may enter human cells or organs through ACE2 receptor and consequently generate huge amount of cytokines. The combination of virus-induced and obesity-driven hyperinflammation could further exacerbate the inflammation in COVID-19 and lead to worse prognosis, including mortality.
Unfavorable hormonal state	Low adiponectin (an anti-inflammatory adipokine) and high leptin (a pro-inflammatory adipokine) concentrations negatively affects immune function.
Reduced physical activity	The lack of physical activity disrupts the immune response against pathogenic agents, while aging, obesity, and metabolic syndrome are shown to contribute to weakened immune and viral defense systems.
Prolonged viral shedding	The defects in the immune response cause prolonged shedding of the virus, which delays recovery from COVID-19 (a longer period of hospitalization or quarantine) while increasing the possibility of its transmission to others.
Obese microenvironment	Obese microenvironment leads to diminished production of interferons, which enables greater viral RNA replication. This may eventually result in the emergence of novel more virulent virus strains.
Poor lung function	Lower respiratory reserve volume, functional capacity, and respiratory system compliance, coupled with reduced diaphragmatic excursion (in individuals with metabolic syndrome or increased abdominal circumference) when lying supine contributes to decreased lung function and cause additional difficulties in ventilation.
OSA	Interference in ventilation occurs in OSA, which is also a major source of cardiovascular morbidity and mortality. Individuals with full expression of the OSA phenotype receive less benefit from non-invasive positive pressure ventilation, and require medical management of its comorbid conditions.
Thrombosis	Impaired fibrinolysis, complemented by low-grade inflammation, put obese individuals at the risk of thrombosis, which appears to be a causative factor of worsening lung damage and death in COVID-19.
MAFLD	It is defined by the presence of hepatic steatosis in addition to one of the following conditions: overweight/obesity, T2DM, or metabolic dysregulation. In this condition, IL-6 concentration independently predicted liver inflammation, which could synergistically promote more severe COVID-19.
Gut dysbiosis	Imbalance of bacteria in the gastrointestinal tract is a significant factor potentially linked with the development of severe forms of COVID-19.
Vitamin D deficiency	Insufficient levels of vitamin D can disrupt immune function and increase the risk of systemic infections.

COVID-19: Coronavirus Disease 2019; SARS-CoV-2: Severe acute Respiratory Syndrome Coronavirus 2; T2DM: Type 2 diabetes mellitus; IL: Interleukin; TNF: Tumor necrosis factor; ACE2: Angiotensin-converting enzyme 2; OSA: Obstructive sleep apnea; MAFLD: Metabolic associated fatty liver disease.

demonstrated that increased BMI was associated with increased poor outcome in patients with COVID-19 and the curve became steeper with increasing BMI. More prospective studies are encouraged, especially from countries in South America, Africa, and Asia-Pacific regions.

Ethics approval

Not applicable.

Consent to participate

Not applicable.

Consent for publication

All authors consent to the publication of this manuscript.

Declaration of conflicting interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Author contributions

RP developed the concept and drafted the manuscript. EY, MAL, RV, and RP performed data acquisition, and data analysis. AAL, MM, and BBS reviewed, performed extensive research on the topic, and provided critical revision to the manuscript. All authors approved the final form of this manuscript. RP performed the statistical analysis.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <https://doi.org/10.1016/j.diabet.2020.07.005>.

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