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Obesity is Associated with Poor Covid-19 Outcomes: A Systematic Review and Meta-Analysis

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ABSTRACT

Our aim was to assess the association between obesity and the risk of unfavourable outcomes (composite of severe disease and mortality) in inpatients with COVID-19. We conducted a systematic search of databases between December 2019 and 28th June 2020. Studies were included if they reported or allowed estimation of an odds ratio (OR) for unfavourable outcome in obese compared to non-obese patients hospitalised for COVID-19. Twenty cohort studies of 28 355 hospitalised patients with COVID-19 infection were included. Meta-analysis estimated a pooled OR of 2.02 (1.41–2.89, $p < 0.001$) for an unfavourable outcome in obese versus non-obese patients when adjusted for age, sex and co-morbidities. When unadjusted for confounders, the OR for unfavourable outcomes was 1.25 (CI 1.07–1.45, $p = 0.005$). An increased adjusted OR was also seen for death (OR 1.51; CI 1.13–2.21, $p = 0.006$) and severe illness (OR 2.26; CI 1.47–3.48, $p < 0.001$). Compared to a normal BMI, the risk of an unfavourable outcome was increased even in overweight patients, with severe obesity having an escalated risk. Obesity is independently associated with an unfavourable outcome of COVID-19 illness, with obese patients having twice the risk of a composite outcome of severe disease or mortality, and a 50 % increased risk of death.

Introduction

Since the discovery in December 2019, the novel Coronavirus Disease 2019 (COVID-19) has taken the world by storm with the declaration of a global health emergency on 30th January 2020 by the World Health Organization (WHO) [1]. At the latest count among 213 countries in early July 2020, 11 600 000 infections and more than 537 000 deaths have been reported worldwide with many countries still struggling to control the spread of this contagion [2].

The clinical course of COVID-19 ranges from asymptomatic or mild infection to severe, life-threatening pneumonia with multi-organ failure. With no definitive curative treatment found as yet, public health systems have sought to risk stratify and protect the more vulnerable groups in the population. Several early studies have identified some host-related risk factors, which may predispose to severe illness, such as older age and underlying comorbidities such as chronic respiratory illness, cardiovascular disease (CVD), diabetes mellitus and hypertension [3–6]. This has led to the international health authorities promoting shielding strategies of vulnerable groups of individuals above 60–70 years, the immunocompromised, or those with chronic comorbidities [7–10]. Although not studied during the initial period of COVID-19, increased body-mass index (BMI) has been increasingly reported to carry an independent risk for severe COVID-19 infection [11–14].

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Studies before the COVID-19 pandemic have been conflicting in terms of the association of obesity with poorer outcomes for acute respiratory illnesses. For severe outcomes of influenza pneumonia including hospitalisation, ICU admissions and death, results have been mixed regarding obesity as a risk factor [15–19]. However, a systematic review and meta-analysis of 234 studies and 610 782 participants found that obesity is an independent significant risk factor for severe outcomes in both the seasonal influenza as well as the pandemic H1N1 influenza [20].

With respect to the COVID-19 infection, we seek to elucidate whether obesity confers a poorer prognosis as observed in previous pandemic pneumonias. Hence, we undertook a systematic review and meta-analysis to assess the impact of obesity on unfavourable outcomes of COVID-19 disease in hospitalised adult patients, as compared to non-obese patients.

Materials and Methods

This systematic review was performed in accordance with the Cochrane Collaboration guidelines [21]. The study followed the guidelines from the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and the Meta-analyses of Observational Studies in Epidemiology (MOOSE) [22, 23].

Literature search

Three authors (CWSH, HK, and JHXL) undertook independent comprehensive search for published articles from the MEDLINE, EMBASE, Web of Science, and Cochrane databases. The articles were searched from 1st December 2019 until 28th June 2020. The search terms included 'COVID-19, 'SARS-CoV2', 'coronavirus disease 2019', 'novel coronavirus', 'outcomes', 'obesity', 'body mass index', and 'BMI'. The titles and abstracts of studies were screened, and only studies which appeared to match the pre-determined inclusion and exclusion criteria were extracted. The full texts of the extracted studies were read to determine relevance to the current study. To supplement the electronic searches, we also examined the reference list of included studies.

Selection of studies

Two authors (KH and JHXL) selected the studies, and differences were resolved by discussion. The inclusion criteria were: (1) studies which identified adult patients diagnosed with COVID-19 based on a real-time reverse transcription PCR method who were hospitalised in an acute hospital, (2) studies which clearly defined the obese and non-obese populations based on BMI, (3) studies which appropriately defined obesity as BMI > 30 or > 28, in non-Asians and Asians, respectively, (4) studies which used pre-specified criteria for outcomes of severe COVID-19 illness or mortality, (5) cohort studies which may be prospective or retrospective in nature, and (6) studies with an appropriate control group allowing estimation of odds ratio of unfavourable COVID-19 outcomes between the obese and non-obese groups. If there was suggestion of multiple publications from the same or overlapping group of patients (e. g., studies arising from the same hospital database), we decided to include the data only from the most comprehensive study.

We used the following exclusion criteria: (1) studies which were not in English, (2) studies which focused only on a specific cohort of patients (e. g., only patients in ICU, only patients with diabetes, only geriatric patients), (3) studies which included < 10 patients, (4) studies whose population are not an inpatient cohort, or (5) studies which focused on a paediatric or pregnant population.

Extraction of data

The data from the included studies were independently extracted and collated on a standardised form by three authors (CWSH, HK, and JHXL). CWSH examined the data for any error. The following data were collated from each study: the first author, the country and city, type of study, time period, location, definitions of obese and non-obese categories, criteria for defining severe COVID-19 illness, clinical and demographic characteristics, and outcomes of patients. Any reported results of univariate or multivariate analysis of outcomes in obese versus non-obese group, as well as the confounders adjusted for, were also collected.

Assessment of quality of the included studies

Two authors (JHXL and IH) were blinded to the study results and independently assessed the quality of studies using the Newcastle-Ottawa scale [24]. Differences were resolved through discussion. This well-established scale assesses each study across three categories: selection (4 items, maximum 4 stars), comparability (1 item, maximum 2 stars) and exposure (3 items, maximum 3 stars). Each study receives a total score ranging between 0 and 9. Scores of ≥ 7, 5–6, and ≤ 4 translate into 'high', 'medium', and 'low' quality scores respectively.

Aim of study

The primary outcome of interest was the pooled odds ratio (OR) in obese compared to non-obese hospitalised patients with COVID-19, for the composite outcome of an unfavourable clinical outcome, defined by mortality and, or severe disease, inclusive of:

1) Requiring intensive (ICU) or high-dependency care, or
2) Requiring mechanical ventilation,
3) Categorised as suffering severe pneumonia or acute respiratory distress syndrome (ARDS) as defined by either the WHO, American Thoracic Society (ATS), or National Health Commission of the People's Republic of China criteria [25–27], or
4) Clinician-defined severe disease.

The secondary outcomes of interest were mortality, and severe disease. Among studies which reported outcomes for normal BMI (defined as BMI < 25 or < 23.5 in non-Asian and Asian studies, respectively), overweight and obese categories, we examined the effect of increasing BMI categories on developing an unfavourable outcome, as well as the OR of severe obesity, defined by BMI > 35 or > 40 on an unfavourable outcome.

Subgroup analyses were done to identify study characteristics that significantly influenced the pooled OR estimate of unfavourable outcome and contributed to heterogeneity between studies. Our pre-determined subgroup analyses of study characteristics compared unfavourable outcomes in studies by:

1) Study region (Asian vs. non-Asian),
2) Quality of study (high, medium or low),
3) Type of study (prospective vs retrospective),
4) Multi-centre versus single-centre,

5) Sample size of obese population (above vs. below 100 participants), and
6) Prevalence * of possible confounding patient demographics and comorbidities including:
   a) Population mean age above versus below 60 years,
   b) Prevalence of diabetes mellitus above versus below 30 %,
   c) Prevalence of hypertension above versus below 60 %,
   d) Prevalence of CVD above versus below 20 %,
   e) Prevalence of chronic kidney disease (CKD) above versus below 15 %, and
   f) Prevalence of chronic pulmonary disease above versus below 20 %

* These cut-offs were chosen based on the median of the prevalence reported in all the studies.

Statistical analysis

For each study, the data for the unfavourable COVID-19 outcomes was reported as the Odds Ratio. Given the expected heterogeneity in the effect sizes, we decided to perform the meta-analysis using a random-effects model [28] based upon the method described by DerSimonian and Laird [29]. The heterogeneity among the studies was assessed using two methods [30]: (a) Cochran's Q statistic which takes into account the overall variance of effect sizes, with subsequent assessment of statistical significance of such heterogeneity (as the tests for heterogeneity have low power, a p-value of < 0.10 was taken as suggestive of significant heterogeneity); (b) the inconsistency index (I^2) which depicts the proportion of true heterogeneity among studies from the overall heterogeneity (conventionally, the I^2 values of < 30 %, 30–59 %, 60–75 % and > 75 % are considered to represent low, moderate, substantial and considerable heterogeneity, respectively). Using the Remove-One index, sensitivity analysis was performed to examine any disproportionate effect of a particular study on the overall estimate of the pooled estimate. Publication bias was ascertained quantitatively using Egger's regression test and qualitatively using funnel plots [31, 32]. If publication bias was found, impact of publication bias was assessed using Duval and Tweedie's "Trim and Fill" method while the 'fail-safe N' test was utilised to estimate the number of unpublished studies with non-significant results that would be required to make the publication bias non-significant [33, 34]. All analyses were performed using Comprehensive Meta-analysis (CMA) software, version 3 (Biostat Inc., Englewood, NJ, USA).

Results

Results of literature search

Initial search yielded 999 articles, and 997 articles remained after removal of duplicates. A total of 819 articles were removed after screening the title and abstract for relevance. A sum of 178 full-text articles were selected and evaluated in detail for potential inclusion, with a further 158 excluded for reasons specified in ▶ **Fig. 1**. The remaining 20 studies were used in the qualitative and quantitative meta-analysis.

Characteristics of included studies

This meta-analysis included 20 studies consisting of a total of 28 355 patients who were hospitalised with COVID-19 illness. The period of hospitalisation was between January and May 2020 (▶ **Table 1**). All included studies were observational cohort studies, of which 15 were retrospective and 5 were prospective studies. Most studies (n = 11) were from the United States, while 5 were from Europe, 3 from Asia (China), and 1 from South America (Mexico). Majority of studies (n = 12) were based on single centre while 8 were multicentre. Besides two studies which defined obesity as BMI > 28 kg/m^2, all other studies used the criteria established by the WHO with respect to BMI.

Quality of studies

As assessed with the Newcastle Ottawa scale, overall quality of studies was moderate to high. Six studies were of high quality, twelve were of moderate quality, while only two were of low quality. Majority of the studies scored low in the 'comparability' domain of the scale (**Supplementary Table 1S**).

Population characteristics

All studies were conducted in adults. The patient characteristics in each study are summarised in **Supplementary Table 2S**. The mean age of participants was 66.4 (SD 19.5) years, with a predominance of male patients (59.5 %). A total of 6361 (22.4 %) of patients were obese, defined as a BMI above 30 (or above 28 in Asians). Overall, 8097 (28.4 %) patients had an unfavourable outcome. 30.6 % of obese patients had an unfavourable outcome, compared with 28.0 % of non-obese patients.

Risk of unfavourable outcome in obese patients

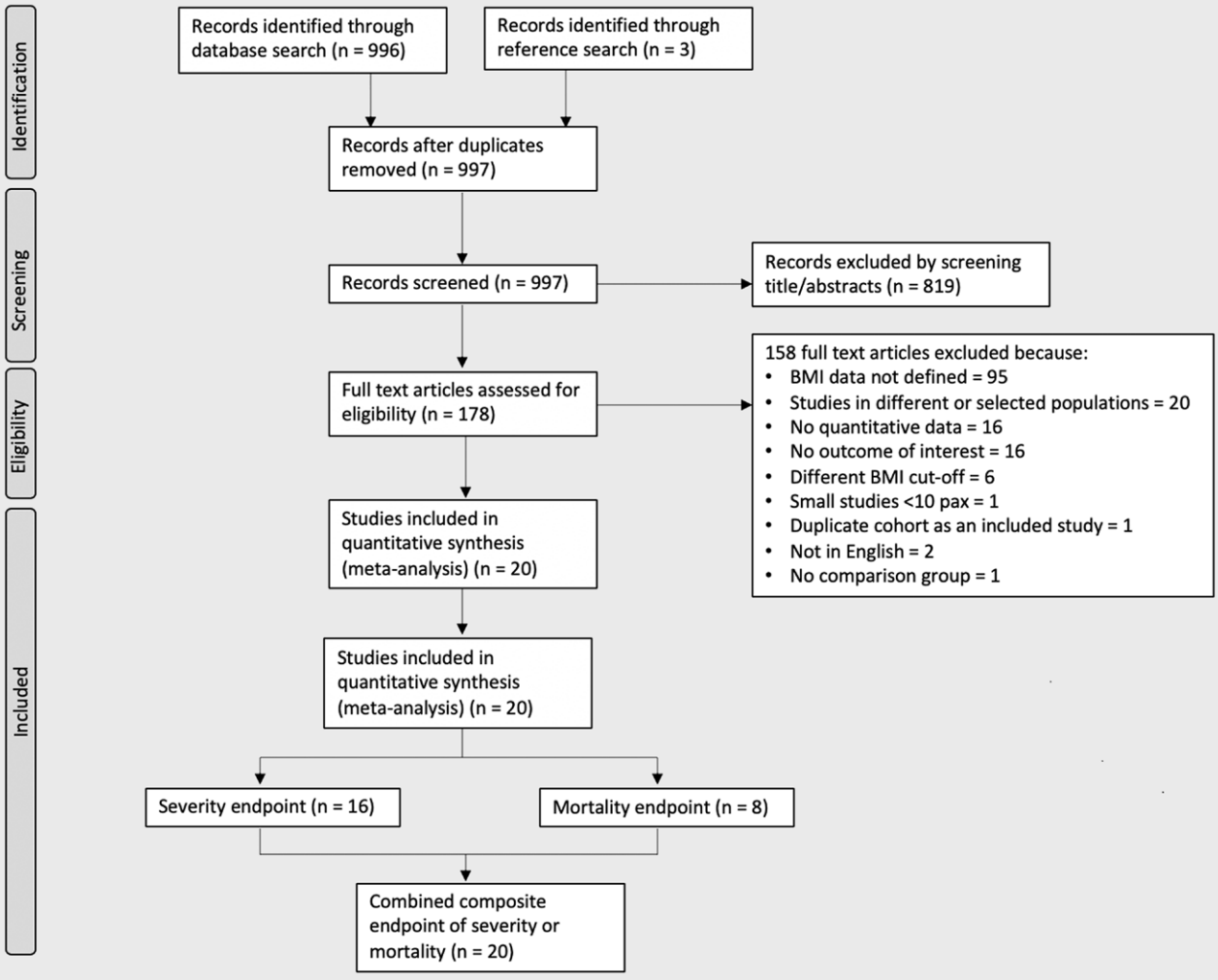
As the primary outcome of this study, OR of unfavourable outcome was estimated for obese patients as compared to non-obese patients who were hospitalised with COVID-19 illness. The unadjusted pooled OR 1.25 (n = 28 355 patients in 9 studies, 95 % CI 1.07–1.45, p = 0.005; I^2 = 65.8 %) for an unfavourable outcome (▶ **Fig. 2**). When adjusted for potential confounders, the pooled OR was 2.02 (n = 17 861 patients in 6 studies, 95 % CI 1.41–2.89, p < 0.001; I^2 = 73.5 %). For both ORs, there were significant and substantial heterogeneity among the studies (discussed later).

Risk of mortality in obese patients

In the four studies (n = 17 322 patients), the adjusted pooled OR for mortality was significantly higher in the obese cohort (OR 1.51, 95 % CI 1.13–2.21, p = 0.006, I^2 = 46.2 %) (**Supplementary Fig. 1S**). The heterogeneity among studies (Cochran's Q 5.48, p = 0.134) and publication bias (Egger's test, p = 0.362) were non-significant for this outcome.

Risk of severe COVID-19 illness in obese patients

Four studies consisting of 1547 patients reported severity outcomes with adjustment for age, sex and other comorbidities. The pooled adjusted OR for risk of severe disease in obese versus non-obese patients was 2.26 (95 % CI 1.47–3.48, p < 0.001; I^2 = 67.2 %) (**Supplementary Fig. 1S**). Publication bias was non-significant on Egger's test (p = 0.053).



▶ **Fig. 1** PRISMA flow chart of study selection.

Graded analysis between increasing BMI groups and risk of unfavourable outcome, compared to a normal BMI

Nine studies of 3255 patients reported unfavourable outcomes in patients with normal BMI, overweight and obese groups. Normal weight was defined as BMI < 25 kg/m^2, overweight was defined as BMI 25–29.9 kg/m^2 and obese was defined as BMI > 30 kg/m^2. One study [11] defined normal weight as BMI 18.5–23.9 kg/m^2, overweight as BMI 24–27.9 kg/m^2 and obese as BMI > 28 kg/m^2. The pooled unadjusted OR comparing overweight and obese groups to normal weight group was 1.81 (95 % CI 1.10–2.98, p = 0.019; I^2 = 75 %), and 2.11 (95 % CI 1.17–3.82, p = 0.014; I^2 = 78.5 %), respectively (▶ **Fig. 3**).

In patients with severe obesity (class II obesity, BMI > 35) compared to a normal BMI, the pooled unadjusted OR from 3 studies for an unfavourable outcome was significantly increased at 2.54 (95 % CI 1.20–5.37, p = 0.015; I^2 = 0 %). The adjusted OR for an unfavourable outcome was similarly increased in 4 studies of severely and morbidly obese patients, as compared to patients with a normal BMI (**Supplementary Table 3S**).

Subgroup analysis

As mentioned earlier, significant and substantial heterogeneity were noted for the primary outcomes of interest (ORs of unfavourable outcomes in obese hospitalised patients with COVID-19 illness). For the unadjusted OR of unfavourable outcomes, pre-specified subgroup analysis was performed to explore study-related cofactors which could have influenced the outcomes (**Supplementary Table 4S**).

Reduction in the heterogeneity was noted when studies were separately analysed according to whether they had large or small numbers of obese patients, with smaller studies (< 100 obese patients) reporting a significantly greater risk of unfavourable outcome with obesity and larger studies (> 100 obese patients) reporting no significant difference in unfavourable outcomes between obese and non-obese participants. There was no difference observed between subgroups when studies were separated into

▶ **Table 1** Characteristics of included studies.

Author, Year, [Ref]	Country, City	Study design	Setting	Number of participants	Time of study	Outcome studied	Participants with endpoint (%)	Quality
Docherty AB et al. 2020 [35]	UK	Prospective cohort	Multicentre, hospitalised patients	16 081	6 Feb–10 Apr 2020	Mortality	4185 (26)	High
Giacomelli A et al. 2020 [36]	Italy, Milan	Prospective cohort	Single centre, hospitalised patients	233	21 Feb–19 Mar 2020	Mortality	48 (21)	Moderate
Petrilli CM et al. 2020 [37]	US, New York and Long Island	Prospective cohort	Single centre, hospitalised patients	2661	1 Mar–8 Apr 2020	Composite = ICU, IMV, hospice, or death	964 (36)	Moderate
Klang E et al. 2020 [38]	US, New York	Retrospective cohort	Multicentre, hospitalised patients	3406	1 Mar–17 May 2020	Mortality	1136 (33)	High
Buckner FS et al. 2020 [39]	US Seattle	Retrospective cohort	Multicentre, hospitalised patients	93	2 Mar–8 May 2020	Composite = ICU or death	43 (46)	Low
Hajifathalian K et al. 2020 [14]	US, New York	Retrospective cohort	Two centres, hospitalised patients	770	4 Mar–16 Apr 2020	Severe = ICU Mortality Composite = ICU or death	196 (25) 88 (11) 241 (31)	Moderate
Hur K et al. 2020 [40]	US, Chicago	Retrospective cohort	Multicentre, hospitalised patients	486	1 Mar–18 Apr 2020	Severe = IMV	138 (28)	Moderate
Hu L et al. 2020 [41]	China, Wuhan	Retrospective cohort	Single centre, hospitalised patients	294	8 Jan–10 Mar 2020	Severe = defined by WHO	164 (56)	Low
Dreher M et al. 2020 [42]	Germany, Heinsberg	Retrospective cohort	Single centre, hospitalised patients	50	1 Mar–31 Apr 2020	Severe = ARDS	24 (48)	Moderate
Kalligeros M et al. 2020 [43]	US, Rhode Island	Retrospective cohort	Muticentre, hospitalised patients	103	17 Feb–5 Apr 2020	Severe = ICU	44 (43)	High
Cai Q et al. 2020 [11]	China, Shenzhen	Prospective cohort	Single centre, hospitalised patients	383	11 Jan–16 Feb 2020	Severe = Any of 1) RR > 30, 2) Resting SpO2 < 93%, 3) PaO2 < FiO2 < 300mmHg	91 (24)	High
Huang R et al. 2020 [3]	China, Jiangsu province	Retrospective cohort	Multicentre, hospitalised patients	202	22 Jan–10 Feb 2020	Severe = Any of 1) RR > 30, 2) Resting SpO2 < 93%, 3) PaO2 < FiO2 < 300mmHg	18 (8.9)	Moderate
Busetto L et al. 2020 [12]	Italy, Veneto	Retrospective cohort	Single centre, hospitalised patients	92	23 Mar–11 Apr 2020	Severe = ICU + semi-intensive respiratory unit Mortality	35 (38) 12 (13)	High
Lighter J et al. 2020 [13]	US, New York	Retrospective cohort	Single centre, hospitalised patients	1762	4 Mar–4 Apr 2020	Severe = ICU	431 (24)	Moderate
Argenziano MG et al. 2020 [44]	US, New York	Retrospective cohort	Single centre, hospitalised patients	781	1 Mar–5 Apr 2020	Severe = ICU	234 (30)	Moderate

▲ **Table 1** Continued.

Author, Year, [Ref]	Country, City	Study design	Setting	Number of participants	Time of study	Outcome studied	Participants with endpoint (%)	Quality
Mani VR et al. 2020 [45]	US, New York	Retrospective cohort	Single centre, hospitalised patients	171	Mar–Apr 2020	Severe = ICU Mortality Composite = ICU or death	29 (17) 31 (18) 48 (28)	Moderate
Moriconi D et al. 2020 [46]	Italy, Pisa	Retrospective cohort	Single centre, hospitalised patients	100	16 Mar–15 Apr 2020	Mortality	18 (18)	Moderate
Ortiz-Brizuela E et al. 2020 [47]	Mexico, Mexico City	Prospective cohort	Single centre, hospitalised patients	140	26 Feb–11 Apr 2020	Severe = ICU	29 (21)	Moderate
Pettit N et al. 2020 [48]	US, Chicago	Retrospective cohort	Single centre, hospitalised patients	238	1 Mar–18 Apr 2020	Severe = hypoxaemia Mortality	140 (59) 24 (10)	High
Suleyman G et al. 2020 [49]	US, Michigan	Retrospective cohort	Multicentre, hospitalised patients	355	9 Mar–27 Mar 2020	Severe = ICU	141 (40)	Moderate

ICU: Intensive care unit; IMV: Invasive mechanical ventilation; RR: Respiratory rate; UK: United Kingdom; US: United States.

location, multi-centre versus single centre studies, prospective versus retrospective studies, or study quality. Among patient characteristics, a lower prevalence of CVD < 20 % and CKD < 15 % in studies were associated with a higher pooled OR for unfavourable outcome in obese versus non-obese patients.

Sensitivity analysis and publication bias for primary outcomes

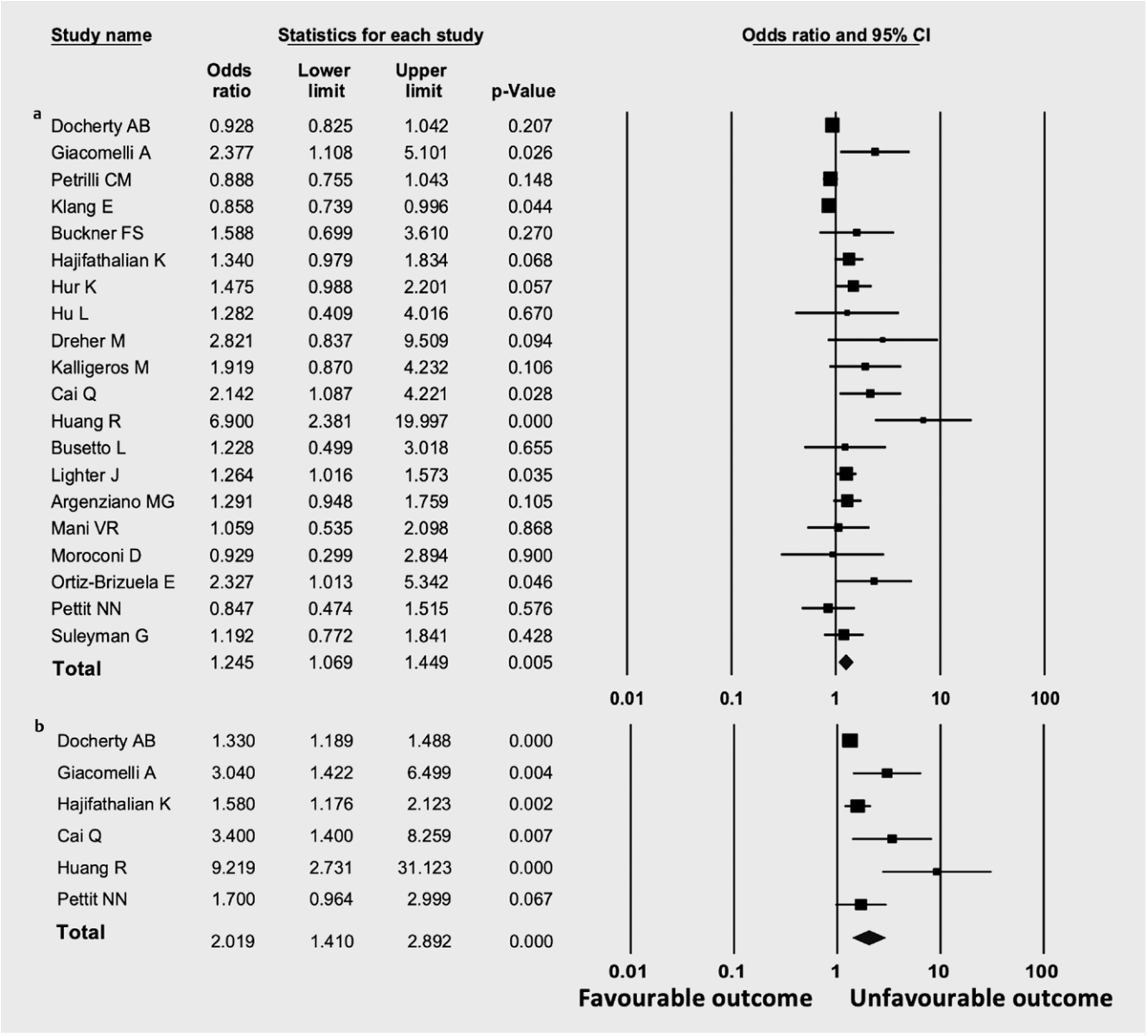
Using Remove-one index for sensitivity analysis, the pooled ORs were re-evaluated after excluding one study at a time. However, no significant change in the heterogeneity or pooled OR was noted, suggesting that our eligibility criteria for inclusion or exclusion of studies did not have an inherent deficiency. Based on the visual inspection of the funnel plot and Egger's test, significant publication bias was found (**Supplementary Fig. 2S**). For the primary outcome of unfavourable unadjusted OR, the publication bias was re-assessed using the 'Trim and Fill' method of Duvel and Tweedie [33]. Despite trimming five of 20 studies (on the left of the mean), publication bias still remained significant.

Discussion

To the best of our knowledge, this is the first systematic review and meta-analysis studying an association between obesity and unfavourable outcomes in patients who are hospitalised with COVID-19 illness. In this meta-analysis of more than 28 000 adult COVID-19 infected patients, the risk of an unfavourable outcome (of developing severe disease or dying from COVID-19) was estimated to be approximately twice as compared to the non-obese patients even after adjustment for other potential confounders. Also, obese patients also had 50 % greater odds of mortality compared to non-obese patients. The association of an unfavourable outcome were seen even in patients with BMI in the overweight category, as opposed to a normal BMI, and this was further increased in the severely obese group. This strengthens the relationship between increasing BMI and COVID-19 outcomes observed.

These findings are consistent with the increased risk observed in obese patients for developing critical disease in acute respiratory and non-respiratory illnesses [20, 50, 51]. Increased adiposity has been proposed to exacerbate a proinflammatory phenotype by increasing proinflammatory adipokines and reducing anti-inflammatory adipokines [52], resulting in a chronic inflammatory process that involves tonic activation of the innate immune system [53]. Obesity also results in mechanical compression of the thorax, including the chest walls, lungs, and diaphragm [54], and has been shown to have detrimental effects to respiratory function in all age groups [55].

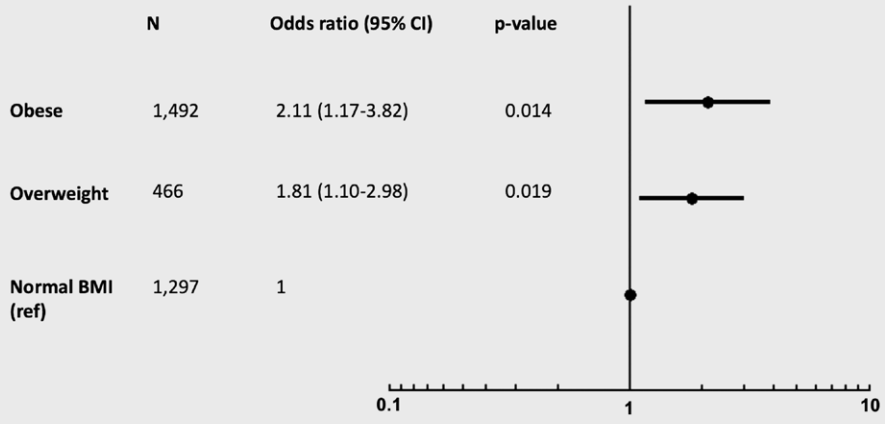
As a known risk factor for diabetes and cardiovascular disease which are independently associated with morbidity and mortality [56, 57], obesity may also be associated with poorer overall health outcomes. However, studies have not been consistent. The obesity paradox has been described in which obesity seems to be a protective factor in patients with established CV disease and advanced CKD [58, 59]. This appears to be consistent with our subgroup analysis showing a lower OR of obesity for an unfavourable outcome in populations with a higher prevalence of CV disease and CKD.



▶ **Fig. 2** Forrest plot showing a significantly increased pooled odds ratio for obese compared to non-obese patients for an unfavourable outcome, including studies reporting severity and mortality. **a** Unadjusted odds ratio. **b** Adjusted odds ratio for age, sex and major co-morbidities.

There are several mentionable strengths in our study: systematic strategy for search of the literature with well-defined criteria for inclusion and exclusion; appropriate exclusion of redundant and non-informative studies, meticulous extraction of data (both explicit as well as deduced from the studies), careful evaluation for quality of studies, and appropriate quantitative statistical assessment. Based on the large sample size in the included studies from different geographical locations of the globe, our estimate appears to have enough power (i. e., low risk for type II error) for a comfortable acceptance. Moreover, our estimates were carefully calculated with and without adjustment for potential confounders, thereby providing a better understanding of the impact of obesity on the unfavourable outcomes in patients with COVID-19 illness.

We also acknowledge several limitations in our study. First, majority of the studies were retrospective in nature which might have introduced intrinsic biases (e. g., recall bias, reporting bias, etc.). Secondly, our population for the systematic review was only hospitalised patients with COVID-19 illness. As the criteria for hospitalisation may differ between hospitals, the population of included studies might not have been uniform. To explore it further, we carefully performed a subgroup analysis for a variety of study and patient related factors. The only partial explanation for heterogeneity was that there was a significant difference in estimates in studies with larger and smaller samples. Moreover, the sensitivity analysis did not alter the estimate of pooled OR thereby providing weight to the robustness of our eligibility criteria. We believe that most of the heterogeneity could have arisen from having different types of hospitalisations (such as varying criteria for hospitalisation, escalation of treatment or definition of severity).



▶ **Fig. 3** Pooled unadjusted OR of 9 studies reporting unfavourable outcome in overweight and obese COVID-19 patients, as compared to normal weight patients. N = total number of participants.

Conclusion

Based on a large sample, our systematic review demonstrates that obesity significantly and independently increases the odds of an unfavourable outcome in hospitalised patients with COVID-19 illness. In addition, obesity is associated with increased mortality and severe course of illness. Risk stratification and a review of resource allocation for the obese patient with COVID-19 is pivotal to providing optimal care in this population. Given the growing epidemic of COVID-19 and the high prevalence of obesity globally, there is a pressing need for population strategies aimed to prevent and manage obesity, and it remains to be seen if these can be helpful in reducing overall morbidity and mortality in COVID-19.

Conflict of Interest

The authors declare that they have no conflict of interest.

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