The Negative Impact of Obesity on the Occurrence and Prognosis of the 2019 Novel Coronavirus (COVID-19) Disease: A Systematic Review and Meta-Analysis

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Research

Keywords: Obesity, COVID-19, Hospitalization, Intensive care unit, Mechanical ventilation, Death

Posted Date: October 8th, 2020

DOI: <https://doi.org/10.21203/rs.3.rs-86237/v1>

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Abstract

Background: the 2019 novel coronavirus (COVID-19) is an emerging pandemic, with a disease course varying from asymptomatic infection to critical disease resulting to death. Recognition of prognostic factors is essential because of its growing prevalence and high clinical costs. This meta-analysis aimed to evaluate the global prevalence of obesity in COVID-19 patients and to investigate whether obesity is a risk factor for the COVID-19, COVID-19 severity, and its poor clinical outcomes including hospitalization, intensive care unit (ICU) admission, need for mechanical ventilation, and mortality.

Methods: The study protocol was registered on to PROSPERO (CRD42020203386). A systematic search of Scopus, Medline, and Web of Sciences was conducted on June 2020, to find pertinent studies. After selection, 54 studies from 10 different countries were included in the quantitative analyses. Pooled odds ratios (OR) with 95% confidence intervals (CIs) were calculated to assess the associations.

Results: The prevalence of obesity was 33% (95% CI, 30.0%–35.0%) among patients with COVID-19. Obesity was significantly associated with susceptibility to COVID-19 (OR=2.42, 95% CI: 1.58 to 3.70; moderate certainty) and COVID-19 severity (OR=1.62, 95% CI: 1.48 to 1.76; low certainty). Furthermore, obesity was a significant risk factor for hospitalization (OR=1.75, 95% CI: 1.47 to 2.09; very low certainty), mechanical ventilation (OR=2.24, 95% CI: 1.70 to 2.94; low certainty), intensive care unit (ICU) admission (OR=1.75, 95% CI: 1.38 to 2.22; low certainty), and death (OR=1.23, 95% CI: 1.06 to 1.41; low certainty) in COVID-19 patients. In the subgroup analyses, these associations were supported by the majority of subgroups.

Conclusions: Obesity is associated with COVID-19 and its poor clinical outcomes. Thus, it is highly recommended to consider obesity status in prognostic scores and improvement of guidelines for the clinical care of patients with COVID-19.

Background

The 2019 novel coronavirus (COVID-19), caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), is a viral disease which first diagnosed in late 2019 in Wuhan City of Hubei Province of China, and it is spreading rapidly (1). Currently, the prevalence of COVID-19 has turned into one of the most critical public health concerns (2). Recent evidence suggests that the severity of clinical manifestations and mortality rate of the disease varies from person to person and depends on a variety of factors (3). Given this, the identification of prognostic factors related to COVID-19 and its poor clinical outcomes is urgent to distinguish populations at higher risk for the disease and to better prevention and early treatment of the disease. Since obesity is associated with a mild chronic inflammatory condition (4) and immune dysfunction (5), evidence suggests that obesity may be a risk factor (6), but the findings are still insufficient in this regard. In a single center in France, 75% of individuals with SARS-CoV-2 infections admitted to the intensive care unit (ICU) had a body mass index (BMI) > 30 kg/m². This study showed that with increasing BMI, the severity of the disease, and the proportion of patients who need mechanical

ventilation increases but no difference in mortality rates was observed between obese and non-obese patients (7). Findings in Italy revealed that the need for intensive care and the use of a ventilator in overweight and obese patients, despite their younger age, is higher than in normal weight patients (8). A cross-sectional study in Mexico demonstrated that obesity is one of the most critical risk factors for coronavirus respiratory infection (9). In contrast, Wu J et al. did not consider a statistically significant relationship between obesity and the severity of COVID-19 (10).

Heterogeneous findings may be due to low statistical power, small sample size, unified ethnicity, and differences in age and adjustment level for covariates in individual studies. To date, some meta-analyses (11–14) have attempted to summarize available evidence regarding the relation of obesity to Covid-19 outcomes. Nevertheless, the preliminary meta-analyses included small number of studies, did not comprehensively assess related clinical outcomes, did not assess the influence of potential effect modifiers such as confounder factors, age, ethnicity and study design, or were conducted on Chinese populations, and thus, were not generalizable to other populations. The current systematic review and meta-analysis study aimed to comprehensively investigate the global prevalence of obesity in patients with COVID-19 and the relation of obesity to COVID-19, COVID-19 severity, and its poor clinical outcomes including hospitalization, ICU admission, need for mechanical ventilation, and mortality.

Methods

This study was performed in a stepwise process in accordance with the guidelines of the Preferred reporting items for systematic reviews and meta-analyses (PRISMA)(15). The protocol of this study is registered in PROSPERO (ID: CRD42020203386). This article does not contain any studies with human participants performed by any of the authors.

Search strategy

An exhaustive systematic search was conducted by multiple researchers through electronic databases (Scopus, Medline, Web of Sciences) retrieving all potential publication, published up to June 2020, investigating the prevalence of obesity among COVID-19 patients or the association of obesity with the risk of COVID-19, COVID-19 severity, death, ICU admission, need for mechanical ventilation, and hospitalization due to COVID-19. The combination of key words was as follow: (“obese” OR “obesity” OR “overweight” OR “body mass index” OR “BMI” OR “adiposity” OR “adipose” OR “body size” OR “weight”) AND (“COVID-19” OR “2019 novel Coronavirus” OR “2019-nCoV” OR “SARS-CoV-2” OR “coronavirus 2019”). No restriction filter was applied for primary search and if required, Google translate was used to translate the data into English. Moreover, cross references within both eligible and review articles was carried out for feasible additional publications.

Inclusion and exclusion criteria

The retrieval publications were screened and abstracted if they met the following inclusion criteria: a) Observational studies (cohort, case-control, cross-sectional, case series); b) Studies providing sufficient

information for the calculation of relative risk (RR) and / or odds ratio (OR), in cases which critical data were not reported in the eligible articles, we contacted authors; c) Studies reporting the prevalence of obesity in COVID-19 patients (primary outcome) and/or data on the association between obesity and following secondary outcomes: COVID-19 and COVID-19 severity (severe COVID-19 was defined based on international guidelines or hospitalization, ICU (Intensive Care Unit) admission, need for mechanical ventilator, mortality due to COVID-19 or a combination of these) (16–25). Duplicates, case reports, reviews, studies with insufficient data after contacting with authors, and abstracts were all excluded, but letters were included. It is worth mentioning that all process of data extraction was performed by two independent investigators, they verified the validity of extracted data any potential disagreements were resolved by discussion or, where necessary, by a third investigator.

Data Extraction and quality assessment

All required data were extracted conforming to the standardized extraction checklist for the following data: the first author's name, journal and year of publication, variables adjusted for, country of origin, ethnicity, mean, median or range of age, and odds ratio (OR) and corresponding confidence interval (CI) for outcomes. Moreover, Grading of Recommendations Assessment, Development and Evaluation (GRADE) was applied to assess the overall quality of the evidence in each pooled analysis (26).

Statistical analysis

In the current study, odds ratios (ORs) were used to estimate the association of obesity with outcomes. The potential between study heterogeneity was estimated by Cochran's Q-statistic (P value < 0.10 was considered as statistically significant) and I-squared (I^2) tests. Because of a remarkable evidence for heterogeneity, the random-effected model was applied (27, 28). In order to assessed the predefined sources of heterogeneity among included studies, subgroup analysis based on obesity severity, study design (cohort vs. non-cohort), ethnicity (Caucasian vs. East-Asian), age category (≥ 50 years vs. < 50 years), and adjustment for covariates (Adjusted vs. Non-adjusted effect size) and univariate random effects meta-regressions based on sex and age of participants were used. Additionally, in sensitivity analysis, we evaluate the conclusiveness and robustness of results by excluding each of the studies from the pooled estimate and analyzing the rest of them. This method enables the assessment of whether the pooled estimates were affected by any individual studies. To discover the risk of publication bias and the small-study effect, Begg's funnel plots and Egger's regression test were estimated (P value < 0.05 was considered as statistically significant) (29, 30). The funnel plot asymmetry was interpreted as follow: in case of no evidence of publication bias, studies with high precision (large study effects) will be located near the average line, and studies with low precision (small study effects) will be spread equally on both sides of the average line; any deviation from this shape can indicate publication bias. In the forest plot figures, the area of the squares for individual studies or diamond-shaped for overall results are inversely proportional to the variances of the log odds ratio estimates, and horizontal lines display CIs. The data analyses were carried out using STATA (version 14.0; Stata Corporation, College Station, TX) and SPSS (version 23.0; SPSS, Inc. Chicago, IL) software.

Results

We identified 956 studies from our preliminary systematic search and 4 additional records through reference list searching. Of the 960 studies, 54 studies (8, 9, 16–25, 31–72) were eventually eligible to be included in the meta-analysis (Fig. 1); some studies reported data on > 1 pertinent outcome. Of these, there were 52 studies reporting results on obesity prevalence among patients with COVID-19 involving a total of 504,556 cases (8, 9, 16–25, 31–70) and data regarding the secondary outcomes was reported in 43 studies (8, 9, 16–25, 31, 32, 34–38, 42, 43, 45–55, 57–61, 64, 67, 68, 70–72). A study by Chao et al. (73) was exclusively performed on children and thus was not included in the meta-analysis. Included publications were all observational in nature, published in 2020. The number of COVID-19 participants varied between 16 and 387,109 cases. Participants were from two ethnicities (Caucasian and East-Asian) from 10 different countries, including Mexico, United Kingdom (UK), Italy, United States of America (USA), France, China, Bolivia, Spain, Germany, and Singapore. Further characteristic of included studies are presented in Table 1.

Quantitative synthesis of data

Main pooled estimates are summarized in Table 2, and corresponding plots are provided in the Additional file 1. Meta-analysis indicated that the prevalence of obesity was 33% among individuals with COVID-19 (prevalence estimate: 33.0%; 95% CI, 30.0–35.0%). Moreover, not only obesity was associated with increased risk of COVID-19 (OR = 2.42, 95% CI: 1.58 to 3.70), but it also was associated with greater risk for disease severity (OR = 1.62, 95% CI: 1.48 to 1.76) and poor clinical outcomes of COVID-19 such as, hospitalization (OR = 1.75, 95% CI: 1.47 to 2.09), need for mechanical ventilation (OR = 2.24, 95% CI: 1.70 to 2.94), ICU admission (OR = 1.75, 95% CI: 1.38 to 2.22), and death (OR = 1.23, 95% CI: 1.06 to 1.41) (Table 2). There was significant evidence for heterogeneity across studies in all analyzes (Table 2). Meta-regression showed that the relationships between obesity and all outcomes were not affected by sex and age.

Main findings of subgroup analysis

Subgroup analyses have been provided in the Additional file 1. Findings showed the relationship between obesity and the occurrence COVID-19 was independent of study design, age category of participants, and the level of adjustment for covariates. Nevertheless, this association was not supported in different categories of obesity severity due to the small number analyzed studies for each category. Notably, the association of obesity with COVID-19 severity and hospitalization was supported by all subgroups. For mechanical ventilation, the relationship was significant in all subgroups except for patients with Class I/Sever obesity (2 studies), East-Asians (1 study), and patients with age ≥ 50 years (3 studies). For ICU admission, the relationship was significant in all subgroups except for patients with Class I obesity (3 studies) and East-Asians (1 study). Moreover, for death, the findings were supported in cohort studies, patients with Caucasian ethnicity, patients with age ≥ 50 years, and in studies with adjusted effect sizes.

Sensitivity analysis

In the sensitivity analysis of studies on the relation of obesity to COVID-19 susceptibility and COVID-19 severity, no individual study significantly affected the pooled effect size, showing the reliability of the results. The pooled effect size ranged from 1.83 (95% CI: 1.44–2.33) to 2.61 (95% CI: 1.64 to 4.14) for studies on COVID-19 (Additional file 1) and ranged from 1.83 (95% CI: 1.44–2.33) to 2.61 (95% CI: 1.64 to 4.14) for COVID-19 severity (Additional file 1).

Publication bias

Egger test revealed no evidence of publication bias for any of the outcomes except COVID-19 severity ($t = 2.12$, $p = 0.04$), hospitalization ($t = 2.48$, $p = 0.04$), and need for mechanical ventilation ($t = 6.50$, $p = 0.001$) (Additional file 1).

Evaluation of quality of evidence according to the GRADE

The quality of evidence for each of the outcomes is as follow: very low (COVID-19 hospitalization), low (COVID-19 severity, death, ICU admission, and need for mechanical ventilation), moderate (the risk of susceptibility to COVID-19) (Additional file 1).

Discussion

The current meta-analysis showed that the prevalence of obesity was 33% among individuals with COVID-19. Not only was obesity associated with increased occurrence of COVID-19; but it was also associated with greater odds of developing critical conditions (e.g. hospitalization, mechanical ventilation, ICU admission), and mortality. Notably, these associations were consistently observed among Caucasians. To the best of our knowledge, this is the first study that has provided a comprehensive evaluation of both occurrence and prognosis of COVID-19 in relation to obesity.

The 33% prevalence of obesity among patients with COVID-19 corroborates a recent review that has shown obesity is the most prevalent comorbidity among patients with severe or fatal COVID-19 (42%) (12). Similar observations have been reported in other respiratory-related outbreaks including MERS-CoV (74), influenza (75), and SARSCoV (76). Moreover, the positive association of obesity with the occurrence and severity of COVID-19 is in line with similar reviews that only included initial studies from China (14).

In the current study obesity was associated with poor prognosis of COVID-19 by increasing the need for hospitalization, mechanical ventilation, ICU admission, and even mortality. This finding was in the line with a current systematic review that included mostly case-report, case-series, letter to editor, and comments (77). That review found that obesity was associated with the increasing prevalence of hospitalization (average of 20.4%) and greater lethality (average of 20.4%) in the patient with COVID-19 (77). The contribution of obesity to diseases severity and the requirement of advanced medical care in COVID-19 has been also stated in another initial review that only included 3 studies (78). Our study also further added to a meta-analysis that showed obesity is a risk factor for both ICU admission and

mechanical ventilation requirement in COVID-19 patients (11). This is of particular importance since restricted IUC capacity has created great concern across the world. So, knowledge of relevant risk factors can help clinicians better identify and guide the high-risk populations for making the most use of available facilities to reduce morbidity and mortality outcomes of COVID-19 infection.

Although the underlying mechanism linking obesity to COVID-19 has remained to be elucidated, several potential pathways may justify this association through chronic inflammation, higher Angiotensin-Converting Enzyme-2 (ACE-2) concentration, and functional restrictive capacity of the lung. Chronic inflammation is accompanied by the increased level of *C-reactive protein*, interleukin 6, and adipokines, all of which can suppress the immune system and put the body at greater risk for the COVID-19 infection (67, 79). Moreover, ACE-2 receptors -responsible for facilitating COVID-19 entry into cells- can be expressed in different parts of the body including adipose tissue (80). That is, greater adiposity is equal to having more ACE-2 receptors and subsequently be more susceptible to catch COVID-19. Finally, individuals with obesity have physiological respiratory dysfunction which can increase the risk for hypoventilation (81), and thus may contribute to a worse prognosis of COVID-19.

The limitations of this study should be reported. Studies used different criteria to define obesity such that some studies define obesity based on national cut-points ($\text{BMI} > 25 \text{ kg/m}^2$), while others used the WHO definition of obesity ($\text{BMI} > 30 \text{ kg/m}^2$). Also, the included studies did not mention the detailed comorbidities of obese patients, such as diabetes and hypertension. Additionally, although we divided disease severity based on clinical symptoms, ICU care and death, the included studies still varied in their differentiation of patients' disease severity in clinical definition, with classifications of "mild, moderate, severe, and critical", "ordinary and severe/critical", "common and severe", and "non-severe and severe" disease. A high heterogeneity existed between studies; however, subgroup analyses were conducted to trace potential sources. Nonetheless, this is the first study that provided an extensive evaluation of health literature to assess the association of obesity with odds of occurrence and prognosis of COVID-19. This study brings attention to obesity as an important risk factor for COVID-19, which has dire consequences in relation to morbidity, mortality and the financial burden generated by the current pandemic. We followed a rigorous methodology as all stages were conducted by two reviewers independently including study selection, data extraction, and quality appraisal. The large sample size and extensive coverage of different regions around the world will increase the power and representativeness of the results to the whole patient population worldwide.

Conclusions

In conclusion, obesity was associated with the occurrence and poor prognosis of COVID-19. Patients with obesity need closer monitoring and earlier escalation of specific treatments to prevent severe or fatal outcomes. As waves of the pandemic are recurring, improvement of guidelines tailored to individuals with obesity is highly recommended. To provide a solid foundation for prevention and control, further investigations are required to identify the pathological mechanism underlying the association observed in our study.

Abbreviations

COVID-19: The 2019 novel coronavirus disease; ICU: intensive care unit; OR: odds ratio; CI: confidence interval; SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2; BMI: body mass index; PRISMA: Preferred reporting items for systematic reviews and meta-analyses; RR: relative risk; GRADE: Grading of Recommendations Assessment, Development and Evaluation; ACE-2: Angiotensin-Converting Enzyme-2

Declarations

Acknowledgements

Each author acknowledges he/she has participated in the work in a substantive way and is prepared to take full responsibility for the work.

Authors' contributions

SA designed the study. MA, HM and TR searched, screened and selected the articles. NS, MD, BR and SH extracted the data from the articles. SA and HM performed data analysis and interpretation. TR drafted the manuscript. All authors contributed in writing and editing of the manuscript. SA supervised the study.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Availability of data and materials

Data can be reached by contacting the corresponding author.

Ethics approval and consent to participate

Not applicable

Consent for publication

This is formally to submit the article entitled "The negative impact of obesity on the occurrence and prognosis of the 2019 novel coronavirus (COVID-19) disease: a systematic review and meta-analysis" prepared by the Tehran University of Medical Sciences for review and, hopefully, publication in your prestigious journal. The authors would like to advise that all authors listed have contributed to the work. All authors have agreed to submit the manuscript to Critical Care. No part of the work has been published before. There is no conflict of interest in this paper.

Competing interests

All authors declared that they have no competing interests.

Financial Disclosure

All authors have no financial relationships relevant to this article to disclose.

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Tables

Due to technical limitations, table 1 & 2 is only available as a download in the Supplemental Files section.

Figures

Figure 1

Flow diagram of the study

Supplementary Files

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