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Meta-analysis

The Association between High Body Mass Index and Mortality Risk in Hospitalized Patients Diagnosed with COVID-19: A Meta-Analysis

Yuzana Maung[1)], Eti Poncorini Pamungkasari[2)], Bhisma Murti[1)]

[1)]Masters Program in Public Health, Universitas Sebelas Maret
[2)]Faculty of Medicine, Universitas Sebelas Maret

ABSTRACT

Background: COVID-19, caused by severe acute respiratory coronavirus 2 (SARS-CoV-2), emerged as a global pandemic with confirmed death cases of more than 1.27 million worldwide. Since the past pandemic, several studies discovered the adverse effects of excess fat accumulation on the severity of viral infections. This study aimed to investigate the association between high body mass index (BMI) and mortality risk in hospitalized COVID-19 patients based on four categories of high BMI ranges.

Subjects and Method: A systematic review and Meta-Analysis was conducted using search articles from electronic databases including PubMed, Google Scholar, and Scopus, published from 2019 to 2021. The keywords used to retrieve articles were "Body Mass Index" OR BMI OR Obesity OR Overweight) AND (Mortality OR Death) AND COVID-19 OR SARS-CoV-2. The included studies were full-text articles published in the English language, reporting adjusted odds ratios from multivariate analysis. The eligibility criteria were defined using PICO model. The article selection was conducted using PRISMA flow chart. The included studies were analyzed by the Review Manager 5.3 application.

Results: A total of nine cohort studies involving 12,907 COVID-19 patients with high BMI conducted from America, Europe, and Georgia regions was included in qualitative synthesis and Meta-Analysis. The pooled estimate showed hospitalized COVID-19 patients with morbid/ class III obesity had a higher risk of mortality (aOR= 1.77; 95% CI= 1.27 to 2.47; p= 0.001) than overweight (aOR= 1.10; 95% CI= 1.00 to 1.21; p= 0.060), class I (aOR= 1.16; 95% CI= 0.87 to 1.55; p= 0.300), and class II obesity (aOR= 1.54; 95% CI= 1.11 to 2.13; p= 0.009).

Conclusion: High BMI increases the risk of mortality in hospitalized COVID-19 patients. A potential dose-response relationship may exist between different categories of high BMI range and mortality risk in COVID-19 patients.

Keywords: BMI, obesity, mortality, COVID-19, SARS-CoV-2

Correspondence:
Yuzana Maung. Masters Program in Public Health, Universitas Sebelas Maret. Jl. Ir. Sutami 36A, Surakarta 57126, Central Java. Email: yuzmg5699@gmail.com. Mobile: +6281295346614.

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BACKGROUND

COVID-19, caused by the severe acute respiratory coronavirus 2 (SARS-CoV-2), was first discovered in December 2019 in Wuhan, China (WHO, 2020). Since the first outbreak, the rapid transmission of the disease resulted in over 127 million confirmed cases of COVID-19 worldwide,

including 2,787,593 deaths in March 2021. The most death caused by COVID-19 occurred in the Americas (1,340,530), followed by Europe (961,435), South-East Asia (218,604), Eastern Mediterranean (157,852), Africa (77,688), and Western Pacific (31,471) (WHO, 2021).

The clinical spectrum of SARS-CoV-2 ranged from no symptoms to severe illness, and many may even die. The most common symptoms were fever, cough, fatigue, shortness of breath, and muscle soreness (Chen et al., 2020). In severe cases, rapid progression to acute respiratory distress syndrome (ARDS), septic shock, blood clotting dysfunction, multiple organ failure, and even death has occurred (Tsai et al., 2021).

Obesity caused by excess fat accumulation is one of the most serious diseases affecting people's health. It can cause morbidity by developing a wide range of non-communicable diseases and increasing the risk of infectious diseases (Wilding and Ralston, 2021). Several studies linked the negative impact of obesity on the severity of viral infections, including MERS, H1N1 influenza, and other seasonal influenza (Wilding and Ralston, 2021; Jain and Chaves, 2011).

Furthermore, in the case of COVID-19 infection, some studies discovered obesity as a risk factor for adverse outcome, including the need for hospitalization, invasive mechanical ventilation, intubation, and death (Docherty et al., 2020; Giacomelli et al., 2020; Hajifathalian et al., 2020; Petrilli et al., 2020). Abnormal fat accumulation is related to increased risk of thromboembolism, cytokine storm, decreased respiratory system functions, and an increased risk of acute organ injuries, leading to fatal outcomes in COVID-19 patients (Mafort et al., 2016; Mehta et al., 2020).

However, despite recent epidemiological studies discussing the impact of obesity on mortality risk in COVID-19 patients, the pooled effect from different BMI categories has not yet been evaluated to the best of the author's knowledge. Therefore, this study aimed to investigate the association between high BMI and mortality risk in hospitalized COVID-19 patients based on four categories of high BMI ranges using systematic review and Meta-Analysis.

SUBJECTS AND METHOD

1. Study Design

This was a systematic review and Meta-Analysis of observational cohort studies comparing the high BMI with normal BMI on the risk of mortality in hospitalized COVID-19 patients. A comprehensive search was conducted to collect the relevant articles from the electronic database such as PubMed, Google Scholar, and Scopus, published from 2019 to 2021. The following keywords were used to retrieve articles: "Body Mass Index" OR BMI OR Obesity OR Overweight) AND (Mortality OR Death) AND COVID-19 OR SARS-CoV-2. Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guideline was used reporting this Meta-Analysis.

2. Inclusion Criteria

The articles were included with following reasons: (1) Full-text articles with observational cohort study published in the English language; (2) Studies emphasized on mortality risk of COVID-19 patients based on four different categories of high BMI range; and (3) The reported results were from multivariate analysis with adjusted odds ratios (aOR).

3. Exclusion Criteria

The articles were excluded with following reasons: (1) Articles reported only crude odds ratio (OR) resulted from bivariate

analysis; (2) The effect measure used was aRR/ aHR, rather than aOR; (3) Reported outcomes other than mortality related to high BMI in COVID-19 patients.

4. Operational Definition of Variables

Mortality was defined by the status of death in hospitalized patients diagnosed with COVID-19. It was categorized as dead or alive. The instrument used was document confirmation of death related to COVID-19.

High Body Mass Index (BMI) means BMI above the normal or healthy weight range of 18.5-24.9 (kg/m^2). BMI was categorized into overweight (25.0-29.9 kg/m^2), class I obesity (30-34.9 kg/m^2), class II obesity (35-39.9 kg/m^2), and class III/ morbid obesity (≥40 kg/m^2). The instrument used was the body weighing scale and stadiometer.

5. Data Analysis

The data processing was carried out using the Review Manager (RevMan 5.3). The association between high BMI and mortality risk in COVID-19 patients was evaluated based on BMI categories: overweight, class I obesity, class II obesity, and morbid/ class III obesity. Odds ratios with 95% CIs were calculated from adjusted ORs. The Forest plot was drawn to present pooled estimate effect of high BMI. The heterogeneity among included studies was presented by the intuitive index (I^2). Fixed effect model Meta-Analysis was used for homogenous data and random effect model for heterogeneous data across studies. Publication bias was investigated using a funnel plot.

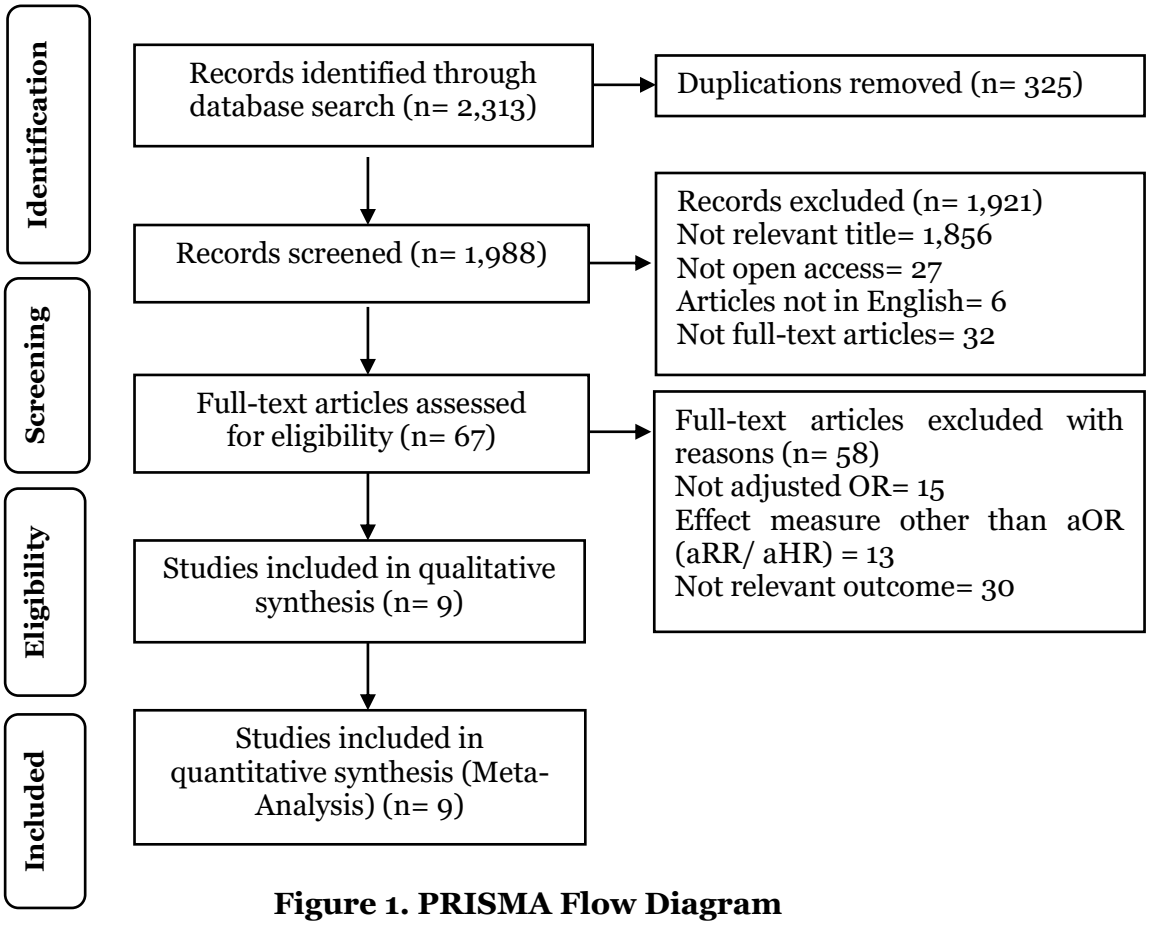

Figure 1. PRISMA Flow Diagram

RESULTS

A total of 2,313 articles were identified through electronic databases. After removed the duplications, 1,988 articles were

screened. Of these, 67 articles were assessed for eligibility criteria. A total of 9 articles that met the quality assessment were included in the quantitative synthesis using Meta-Analysis. Six of the nine included studies were conducted in the United States, two in Europe, including Italy and France, and one in Georgia. The process of selecting articles was presented in Figure 1. The studies quality assessment using the Cohort Study Checklist published by the CASP (Critical Appraisal Skills Program) was presented in Table 2.

Four forest plots were drawn to investigate the pooled effect from each BMI category on the mortality risk of COVID-19 patients. Only class III obesity was evaluated across all nine included studies, while the other categories of high BMI were evaluated across seven studies. The forest plot in Figure 2 showed that COVID-19 patients with overweight had 1.10 times as many mortality risks as patients with normal BMI (aOR= 1.10; 95% CI= 1.00 to 1.21), but it was not statistically significant (p= 0.060). The I^2 was 48%, indicating low heterogeneity in included studies; thus, a fixed-effect model was used. The funnel plot in Figure 3 showed asymmetrical distribution of plots with five plots on the left and two on the right. It indicated publication bias with the underestimated effect of overweight across studies.

The forest plot in Figure 4 showed that COVID-19 patients with class I obesity had 1.16 times as many mortality risks as patients with normal BMI (aOR= 1.16; 95% CI= 0.87 to 1.55), but it was not statistically significant (p= 0.300). The I^2 was 71%, indicating moderate heterogeneity in included studies; thus, a random-effect model was used. The funnel plot in Figure 5 showed symmetrical distribution of plots with four plots on the left and three on the right, indicating no publication bias.

The forest plot in Figure 6 showed that COVID-19 patients with class II obesity BMI range had 1.54 times as many mortality risks as normal BMI (aOR= 1.54; 95% CI= 1.11 to 2.13), and it was statistically significant (p= 0.009).

The I^2 was 65%, indicating moderate heterogeneity in included studies; thus, a random-effect model was used. The funnel plot in Figure 7 showed symmetrical distribution of plots with four plots on the left and three on the right, indicating no publication bias.

The forest plot in Figure 8 showed that COVID-19 patients with class III obesity BMI range had 1.77 times as many mortality risks as normal BMI (aOR= 1.77; 95% CI= 1.27 to 2.47), and it was statistically significant (p= 0.001). The I^2 was 86%, indicating high heterogeneity in included studies; thus, a random-effect model was used. The funnel plot in Figure 9 showed symmetrical distribution of plots with five plots on the left and four on the right, indicating no publication bias.

Table 2. Critical Appraisal Checklist for Cohort Study

No.	Critical Appraisal Checklists	Publication (Authors and Year)								
		Czernichow et al. (2020)	Guerson Gil et al. (2020)	Gupta et al. (2020)	Halasz et al. (2020)	Kim et al. (2021)	Klang et al. (2020)	Nyabera et al. (2020)	Shah et al. (2020)	Yoshida et al. (2021)
1.	Did the study address a clearly focused issue?	1	1	1	1	1	1	1	1	1
2.	Was the cohort recruited in an acceptable way?	1	1	1	1	1	1	1	1	1
3.	Was the exposure COVID-19 accurately measured to minimize bias?	1	1	1	1	1	1	1	1	1
4.	Was the outcome (status mortality) accurately measured to minimize bias?	1	1	1	1	1	1	1	1	1
5.	Have the authors identified all-important confounding factors? Have the authors took account of the confounding factors in the design and/ or analysis?	1	1	1	1	1	1	1	1	1
6.	Was the follow-up of subjects complete enough? Was the follow-up of subjects long enough?	1	1	1	1	1	1	1	1	1
7.	Was the result of this study reported in aOR?	1	1	1	1	1	1	1	1	1
8.	How precise were the results?	1	1	1	1	1	1	1	1	1
9.	Do you believe the results?	1	1	1	1	1	1	1	1	1
10.	Can the results be applied to the local population?	1	1	1	1	1	1	1	1	1
11.	Do the results of this study fit with other available evidence?	1	1	1	1	1	1	1	1	1
12.	What are the implications of this study for practice?	1	1	1	1	1	1	1	1	1
	Total	**12**	**12**	**12**	**12**	**12**	**12**	**12**	**12**	**12**

Yes = 1; No = 0

Table 1. Characteristics of included studies for Meta-Analysis

Author (Year)	Country	Study Design	Sample		P (Population)	I (Intervention)	C (Comparison)	O (Outcome)
			COVID-19	BMI Range (kg/m²)				
Halasz et al. (2020)	Italy	Retro-spective Cohort	Total = 242 Non survivor = 78	25-29.9= 104 (41%), 30-34.9= 11 (14%), 35-39.9 = 3 (3%), ≥40 = 5 (6%)	Hospitalized COVID-19 patients	COVID-19 patients with higher BMI	COVID-19 patients with normal BMI	Mortality
Gupta et al. (2020)	United States	Prospec-tive Cohort	Total = 2,215	Not stated	Hospitalized COVID-19 patients	COVID-19 patients with higher BMI	COVID-19 patients with normal BMI	Mortality
Czernichow et al. (2020)	France	Prospec-tive Cohort	Total = 4,056 Non survivor = 483	25-29.9 = 239, 30-34.9 = 145, 35-39.9 = 63, ≥40 = 36	Hospitalized COVID-19 patients	COVID-19 patients with higher BMI	COVID-19 patients with normal BMI	Mortality
Shah et al. (2020)	Georgia	Retro-spective Cohort	Total= 522 Non survivor= 92 (17.6%)	≥30= 52 (62%) ≥40= 23 (25%)	Hospitalized COVID-19 patients	COVID-19 patients with higher BMI	COVID-19 patients with normal BMI	Mortality
Guerson-Gil et al. (2021)	New York	Retro-spective Cohort	Total= 3,530	25-29.9= 700, 30-34.9= 809, ≥35-39.9= 663	Hospitalized COVID-19 patients	COVID-19 patients with higher BMI	COVID-19 patients with normal BMI	Mortality
Yoshida et al. (2021)	USA	Retro-spective Cohort	Total = 776	25-29.9=198 (25.7%), 30-34.9=157 (20.4%), 35-39.9=118 (15.3%), ≥40 = 134 (17.4%)	Hospitalized COVID-19 patients	COVID-19 patients with higher BMI	COVID-19 patients with normal BMI	Mortality
Klang et al. (2020)	New York	Retro-spective Cohort	Total= 572 Non survivor= 60 (10.5%)	≥30= 16 (26.7%) ≥40= 19 (31.7%)	Adult patients aged <50 years diagnosed with COVID-19 in hospital	COVID-19 patients with higher BMI	COVID-19 patients with normal BMI	Mortality
Nyabera et al. (2020)	New York	Retro-spective Cohort	Total= 290	25-29.9=75 (25.9%), 30-34.9=52 (17.9%), 35-39.9= 17 (5.9%), ≥40= 20 (6.9%)	Hospitalized COVID-19 patients	COVID-19 patients with higher BMI	COVID-19 patients with normal BMI	Mortality
Kim et al. (2021)	New York	Retro-spective Cohort	Total= 10,861	25-29.9= 4,021, 30-34.9= 2,345, 35-39.9= 990, ≥40= 755	Hospitalized COVID-19 patients	COVID-19 patients with higher BMI	COVID-19 patients with normal BMI	Mortality

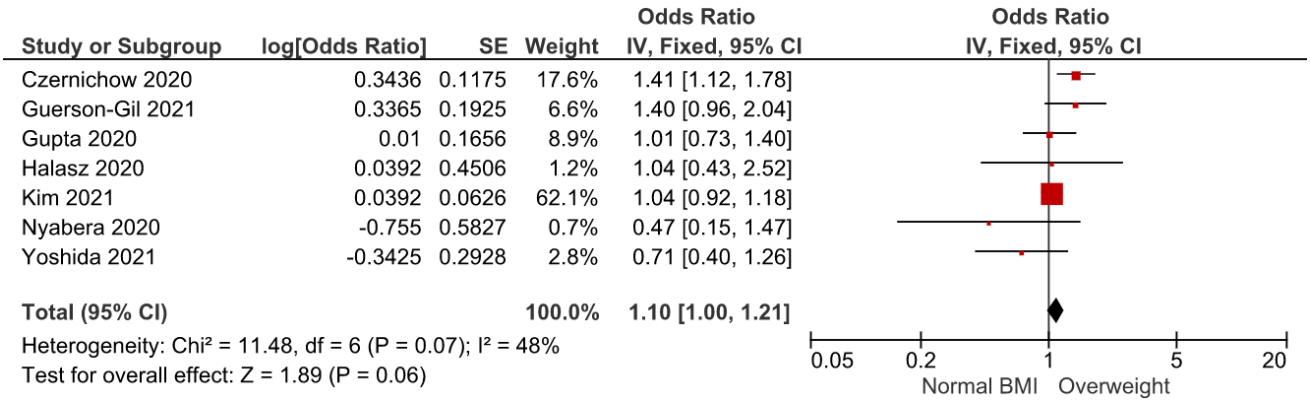

Figure 2. Forest Plot of Association between Overweight and Mortality Risk in Hospitalized COVID-19 Patients

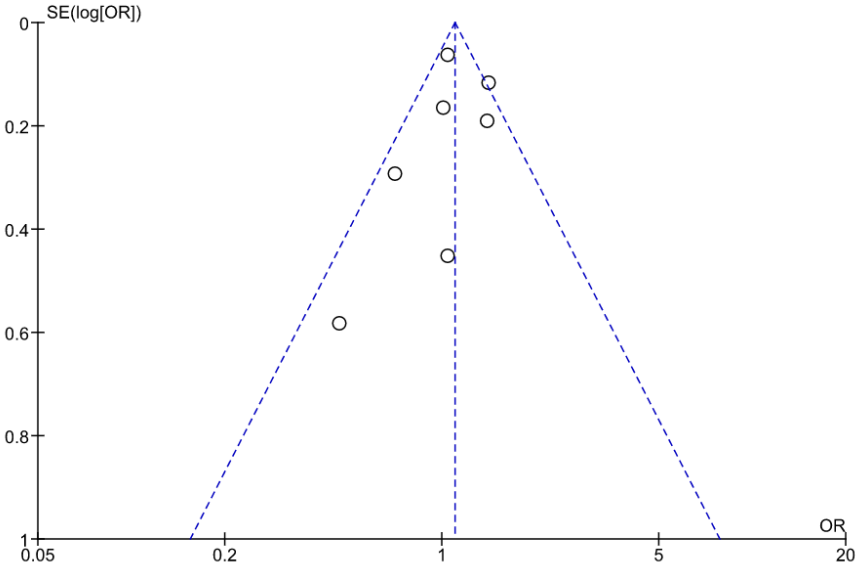

Figure 3. Funnel Plot of Association between Overweight and Mortality Risk in Hospitalized COVID-19 Patients

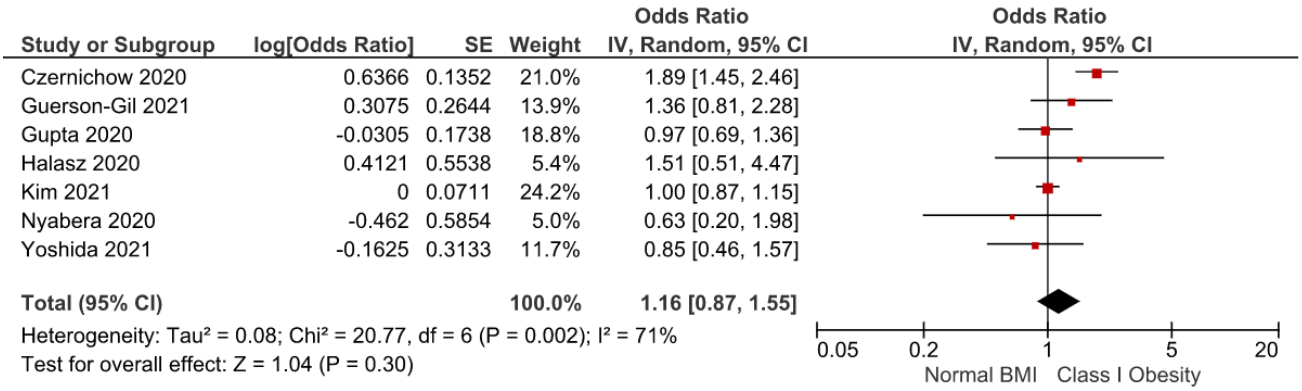

Figure 4. Forest Plot of Association between Class I Obesity and Mortality Risk in Hospitalized COVID-19 Patients

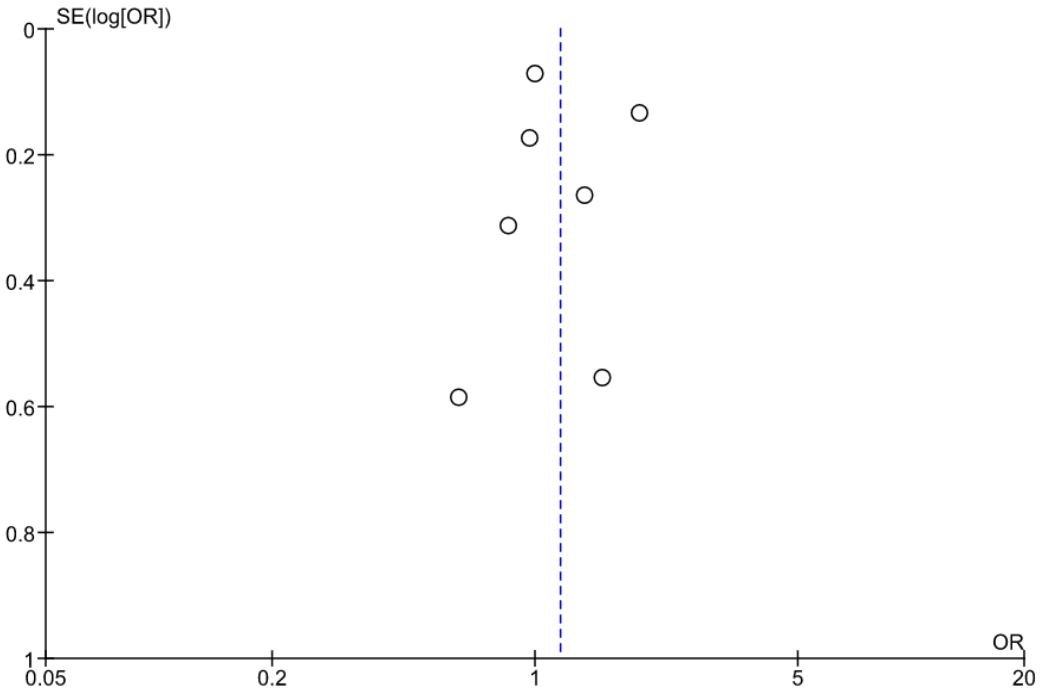

Figure 5. Funnel Plot of Association between Class I Obesity and Mortality Risk in Hospitalized COVID-19 Patients

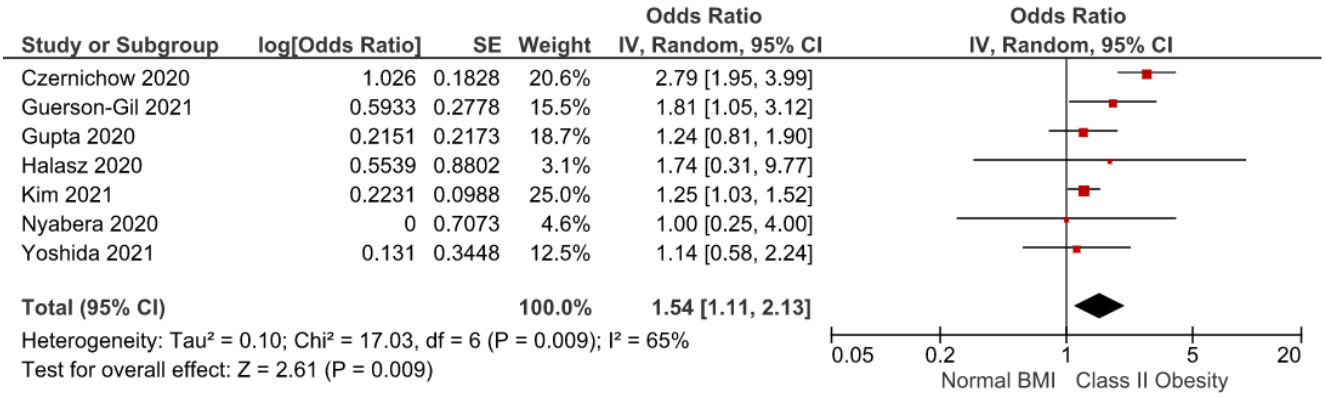

Figure 6. Forest Plot of Association between Class II Obesity and Mortality Risk in Hospitalized COVID-19 Patients

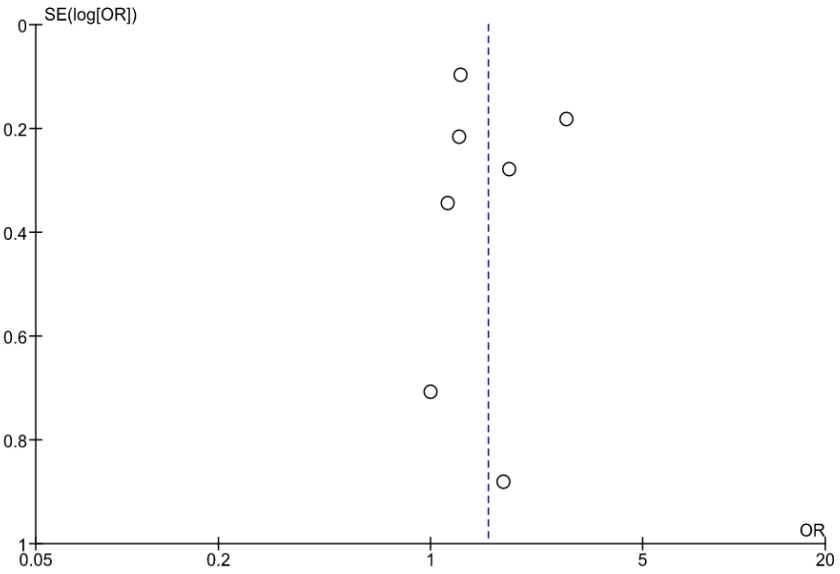

Figure 7. Funnel Plot of Association between Class II Obesity and Mortality Risk in Hospitalized COVID-19 Patients

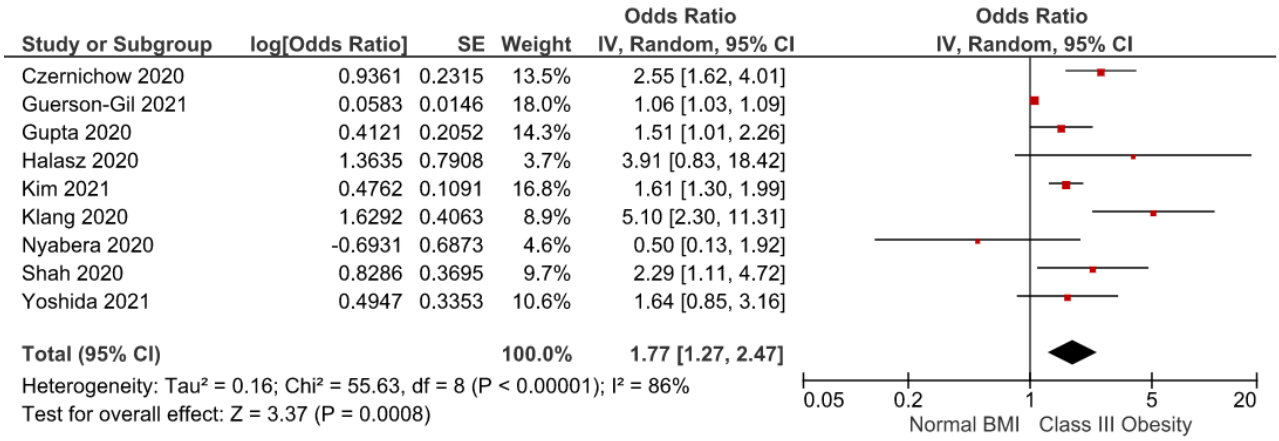

Figure 8. Forest Plot of Association between Class III Obesity and Mortality Risk in Hospitalized COVID-19 Patients

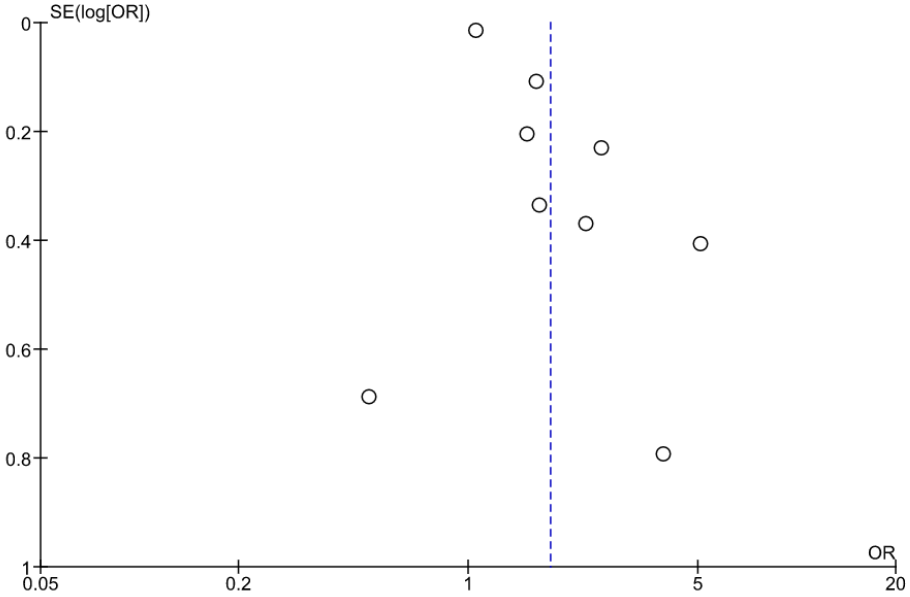

Figure 9. Funnel Plot of Association between Class III Obesity and Mortality Risk in Hospitalized COVID-19 Patients

DISCUSSION

This systematic review and Meta-Analysis investigated the association of high BMI and the risk of mortality in hospitalized COVID-19 patients based on four categories of high BMI range. All nine studies included in this review used an observational cohort design only to strengthen the validity of the results.

The findings of this study elucidated that a high BMI was associated with an increased risk of mortality in COVID-19 patients. Furthermore, this study discovered a possible dose-response relationship effect of higher BMI on mortality risk. There was a higher mortality risk of COVID-19 in class III obesity patients (aOR= 1.77; 95% CI= 1.27 to 2.47; p= 0.001) compared to overweight (aOR= 1.10; 95% CI= 1.00 to 1.21; p= 0.060), class I (aOR= 1.16; 95% CI= 0.87 to 1.55; p= 0.300), and class II obesity (aOR= 1.54; 95% CI= 1.11 to 2.13; p= 0.009).

The patients with BMI ranges of class II and III obesity demonstrated a moderate causal relationship, and it was statistically significant. In contrast, overweight and class I obesity demonstrated a weak causal relationship on the risk of COVID-19 mortality, and it was not statistically significant.

This study results aligned with the study conducted by Palaiodimos et al. (2020) with significant results of severe obesity (BMI= ≥35 kg/m²) increased the risk of in-hospital mortality (aOR= 3.78; 95% CI= 1.45 to 9.83) along with the need of oxygen requirements and intubation. A large cohort study from 88 US hospitals also revealed that obesity classes I, II, and III were associated with progressively higher risks of in-hospital death or mechanical ventilation compared to individuals of normal weight (Hendren et al., 2021). A J-shape association between BMI and risk of death was occurred, even after adjusting for obesity-related comorbidities, including metabolic and cardiovascular diseases (Tartof et al., 2020).

Besides COVID-19 pathogenesis, several mechanisms increase disease severity in obese patients. COVID-19 patients with obesity had significantly higher acute-phase reactants such as serum ferritin, erythrocyte sedimentation rate, C-reactive protein

(CRP), and D-dimer (Mehanna et al., 2021). They also have a higher rate of proinflammatory cytokine transcription, including tumor necrosis factor-α (TNF-α), interleukin-1 (IL-1), and interleukin-6 (IL-6). These inflammatory cytokines then upregulate the concentration and synthesis of CRP in the liver and develop feedback loops of acute phase reactants and chronic inflammation (Guglielmi et al., 2021; Chiappetta et al., 2020).

In addition, adipose tissue also expressed angiotensin II (ATII), which was recognized as a receptor for SARS-CoV-2 antigen, resulting in a more vulnerable COVID-19 infection target (Seidu et al., 2021). The risk of thromboembolism, reduced lung mechanism, and proinflammatory cytokine cascade due to excess fat accumulation may add to the severity of COVID-19 infection (Mafort et al., 2016; Mehanna et al., 2021).

There are limitations to this review. The majority of included studies were from America (mostly from the USA), which may restrict the generalized ability to non-America individuals, including Asia, the Mediterranean, and the Middle East. Due to data constraints, only class III obesity can be applied to all included nine studies. Lastly, the researcher only included articles written in English, which may have resulted in non-English articles omission.

In conclusion, severe obesity may be a strong risk factor for mortality in COVID-19 patients with the potential of dose-response relationship effect of higher BMI on mortality risk. Future studies should consider subgroup analysis accounting clinical and demographic characteristics and dose-response relationship Meta-Analysis to ensure the evidence of the relationship between high BMI and mortality risk of COVID-19 patients. Also, the policymakers should consider the COVID-19 vaccination priority for the obese population, especially with high-risk morbid obesity.

AUTHOR CONTRIBUTION

Study conception and design: Yuzana Maung, Bhisma Murti
Data collection: Yuzana Maung, Eti Poncorini Pamungkasari
Data analysis and interpretation: Yuzana Maung, Bhisma Murti
Drafting of the article: All authors
Critical revision of the article: Eti Poncorini Pamungkasari, Bhisma Murti

CONFLICT OF INTEREST

The authors declare there were no conflicts of interest.

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