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Meta-Analysis

Meta-Analysis the Effects of Obesity and Type 2 Diabetes Mellitus on Covid-19 Mortality

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ABSTRACT

Background: COVID-19 is a disease caused by a new coronavirus called SARS-CoV-2. In more severe cases, COVID-19 can cause death. The most severe COVID-19 patient mortality is associated with underlying health conditions. The most common associated comorbidities are pulmonary disease, diabetes, obesity and old age. However, the effects of obesity and T2DM disease on the 2019 coronavirus disease (COVID-19) pandemic are controversial. This study aims to analyze the magnitude of the influence of obesity and T2DM on COVID-19 mortality.

Subjects and Method: This study uses a systematic review and meta-analysis research design. The time of the selected test results is between January 2020 to January 2021. The search for articles is carried out for 1 month. Research data was searched from databases: PubMed, Google Scholar, JAMA, Willey and Science Direct. Using search keywords: (Type 2 diabetes mellitus OR diabetic) AND (mortality OR death) AND (COVID-19 /OR Coronavirus OR SARS-CoV-2) AND ("adjusted odds ratio" OR "aOR"), (obesity OR obese) AND (mortality OR death) AND (COVID-19 OR Coronavirus OR SARS-CoV-2) AND ("adjusted odds ratio" OR "aOR"). The inclusion criteria in this study were full text articles in English, observational study designs were collected using PRISMA, and analyzed using the Review Manager application (RevMan 5.3).

Results: A total of 15 articles were reviewed in this study. A meta-analysis of 10 cohort studies showed that people with COVID19 who had comorbid obesity were 1.50 times more likely to die from COVID-19 compared to those without obesity (aOR = 1.50; 95% CI = 1.17 to 1.93; p = 0.001). A meta-analysis of 6 cohort studies showed people with COVID-1919 who had comorbid T2DM 1.93 times to die from COVID-19 compared with those without T2DM (aOR = 1.93; 95% CI = 1.28 to 2.90; p = 0.002).

Conclusion: Obesity and T2DM are predictors of COVID19 mortality.

Keywords: obesity, type 2 diabetes mellitus, mortality, COVID 19

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BACKGROUND

In early 2020, the world was shocked by the emergence of new infectious diseases (Huang et al., 2020). WHO named the disease caused by this Novel Coronavirus as COVID-19 (Binti Hamzah et al., 2020). Since the first case in Wuhan, there has been an increase in cases in China every day and peaked between late January to early February 2020. Data on February 3, 2021 shows that there are 1.09 million confirmed cases and 30,277 deaths. The

mortality rate for COVID-19 in Indonesia is 2.7%. While data for the world, there are 103 million cases with a total death of 2.24 million (WHO, 2021).

A retrospective study based on hospital data from the Jakarta Health Service, a sample of 4,265 adults and children with COVID-19 were treated at 55 referral hospitals, during the first five months of the epidemic. Overall mortality was 12% (497/4,265), and deaths occurred at all ages. The increased risk of death in hospital is associated with increasing age and with the presence of one or more chronic comorbidities, which was recorded in 31% of patients (Setiati & Azwar, 2020).

In a study in Wuhan, the mortality rate from COVID-19 pneumonia was concentrated in patients over the age of 65, especially those with comorbidities. The most severe COVID-19 patient mortality is associated with underlying health conditions. The most common associated comorbidities are lung disease, diabetes, and old age (Knowns, 2020).

Obese people have a higher risk of COVID-19 and a poorer prognosis than those who are not obese (Hajifa-thalian et al, 2020; Onder et al, 2020). In a study by Ranil et al, COVID-19 mortality was significantly correlated with prevalence obesity (Jayawardena et al., 2020). Deaths in people with type 1 and type 2 diabetes rose sharply during the start of the COVID-19 pandemic in the UK. The increase in COVID-19-related mortality is not only associated with cardiovascular and renal complications of diabetes, but also with glycemic control and BMI (Holman et al., 2020b).

The effects of obesity on the COVID-19 disease pandemic are controversial (Cornejo et al, 2020). In addition, patients with T2DM tend to develop severe and critically ill, but there is no clear difference in mortality between patients with COVID-19 with and without T2DM (Wang et al., 2020).

Various studies have been conducted to look at the effect of obesity and T2DM as predictors of COVID-19 mortality, but the results of these studies still do not show consistent results. Further analysis is needed to reach convincing conclusions about the influence of obesity and T2DM as predictors of COVID19 mortality.

SUBJECTS AND METHOD

1. Study Design

This study uses a systematic review and meta-analysis with PRISMA flow diagram guidelines. Search articles using databases: PubMed, Google Scholar, JAMA, Willey and Science Direct and were carried out within 1 month. Search keywords used: (Type 2 diabetes mellitus OR diabetic) AND (mortality OR death) AND (COVID-19 /OR Coronavirus OR SARS-CoV-2) AND ("adjusted odds ratio" OR "aOR"), (obesity OR obese) AND (mortality OR death) AND (COVID-19 OR Coronavirus OR SARS-CoV-2) AND ("adjusted odds ratio" OR "aOR").

2. Inclusion Criteria

The authors developed inclusion criteria, namely an observational study design published from January 2020 to January 2021. The selected articles discussed the influence of obesity and T2DM as predictors of mortality in COVID19 patients. The articles used are articles published in English. The study sample was people infected with COVID19. The research data are multivariate. The final results of this study are reported using an adjusted odds ratio (aOR).

3. Exclusion Criteria

The exclusion criteria in this study were non-observational studies, the articles were not full text and were not published in English.

4. Operational Definition of Variables

In formulating research problems, researchers use PICO. Population is people infected with COVID19. Intervention is having comorbid obesity and T2DM, with a comparison that is not having comorbid obesity and T2DM and the outcome is death from COVID19.

Obesity is the accumulation of excessive fat due to an imbalance in energy intake with energy used for a long time.

T2DM is a chronic disease that occurs either when the pancreas does not produce enough insulin or when the body cannot effectively use the insulin it produces.

Mortality is the permanent loss of all signs of life at any time after live birth, i.e. the loss of life functions after birth, without the possibility of resuscitation.

5. Study Instrument

The research was conducted using the PRISMA flow diagram guidelines and the assessment of the quality of research articles using the Critical Appraisal Checklist for Cohort Study tools (CEBMa, 2014).

6. Data Analysis

The data in this study were analyzed using the RevMan 5.3 application, to calculate the effect size and heterogeneity of the study. The results of data processing are presented in the form of forest plots and funnel plots.

RESULTS

The article review process was carried out using the PRISMA flow chart, which can be seen in Figure 1. The total articles obtained were 15 articles. The distribution of the article is on 5 continents with details 3 from Asia, 7 from North America, 1 from Africa, 1 from South America and 3 from Europe. Figure 2 shows the areas of the articles taken that match the inclusion criteria.

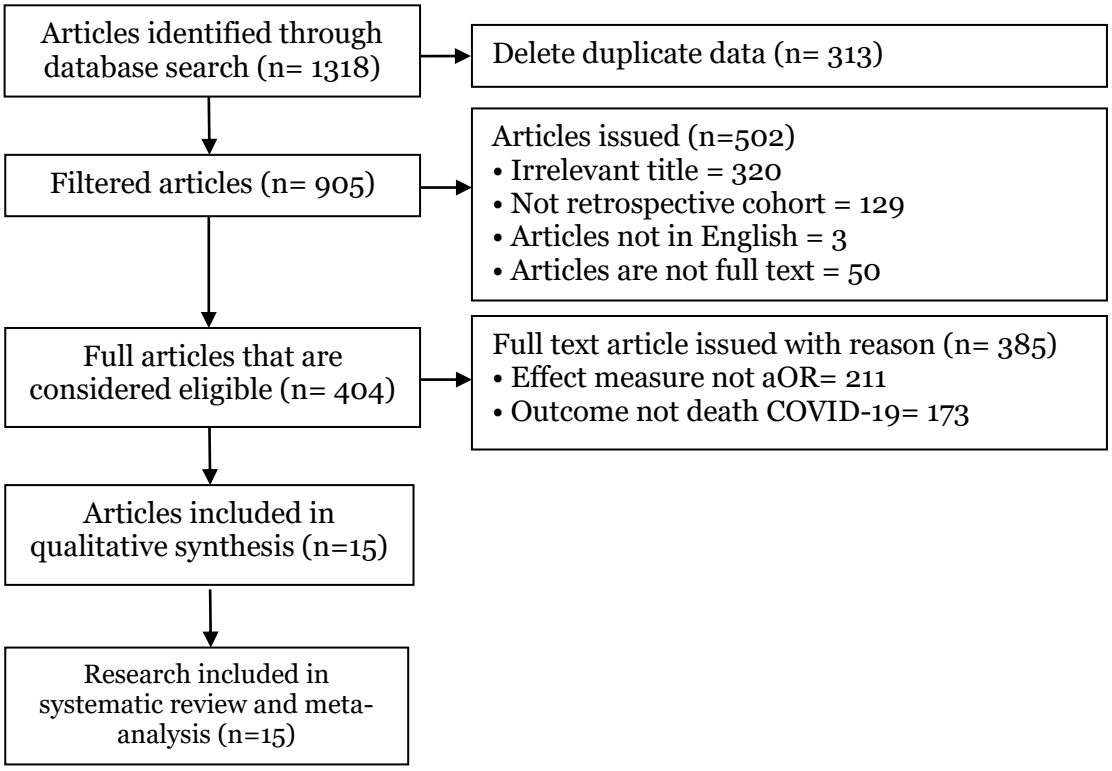

Figure 1. PRISMA flow diagram

Figure 2. Distribution of Primary Research by Continent

The assessment of the quality of the primary study was carried out quantitatively and qualitatively which can be seen in Table 1 below. This research was conducted using the Critical Appraisal Checklist for Cohort Study sourced from the Center for Evidence Based Management (CEBMa, 2014).

Table 1. Quality Assessment of Cohort Study Design Articles

Primary Study	Criteria												Total
	1	2	3	4	5	6	7	8	9	10	11	12	
Id et al. (2021)	1	1	1	1	1	0	1	0	1	1	1	1	1
Hoobs et al. (2021)	1	1	1	0	1	1	1	0	1	1	1	1	10
Satman et al. (2021)	1	1	1	0	1	1	1	1	1	1	1	1	11
Barron et al. (2020)	1	1	1	1	1	1	1	0	1	1	1	1	11
Czernichow et al. (2020)	1	1	1	1	1	1	1	0	1	1	1	1	11
Seiglie et al. (2020)	1	1	1	0	1	1	1	1	1	1	1	1	11
Ullah et al. (2021)	1	1	1	1	1	0	0	1	1	1	1	1	10
Palaiodimos et al. (2021)	1	1	1	1	1	1	1	0	1	1	1	1	11
Gerwen et al. (2020)	1	1	1	1	1	0	1	1	1	1	1	1	11
You et al. (2020)	1	1	1	1	1	0	1	1	1	1	1	1	11
Giacomelli et al. (2021)	1	1	1	0	1	0	1	1	1	1	1	1	10
Sun et al. (2020)	1	1	1	0	1	1	1	1	1	1	1	1	11
Pietre et al. (2020)	1	1	1	0	1	1	1	0	1	1	1	1	10
Salacup et al. (2020)	1	1	1	1	1	1	1	0	1	1	1	1	11
Pettit et al. (2020)	1	1	1	0	0	1	1	1	1	1	1	1	10

Note: Answer: 1 = Yes and 0 = No

Based on the assessment of the quality of the primary articles above, the value of article quality is 10 to 11. This indicates that the article has good quality for meta-analysis (CEBMa, 2014).

Table 2. Description of the primary study of the association of obesity with COVID-19 mortality

Author (year)	Country	Study Design	Sample	P (Population)	I (Intervention)	C (Comparison)	O (Outcome)
Giacomelli et al (2021)	Italy	Prospec-tive Cohort Study	520	Patients with confirmed COVID19, Median age = 61 (50, 72), Gender: L 161 (69.1%); P 72 (30.9%)	Have comorbidities Obesity (BMI > 30 kg/m2), CD, critical illness, fever, d-dimer > 500, LDH > 245	No comorbid obesity (BMI <30 kg/m^2), CD, critical illness, no fever, d-dimer <500, LDH<245	COVID-19 deaths
Ullah et al. (2021)	Pennsylvania	Retro-spective Cohort Study	132	Patients with confirmed COVID-19, Gender = L (BMI<35 = 88.4%; BMI>35 = 11.6%), P (BMI<35 = 67.8%; BMI>35 = 32.2%)	Have comorbid obesity (BMI >35 kg/m2)	No comorbid obesity (BMI <35 kg/m2)	COVID-19 deaths, IMV use
Hoobs et al (2021)	SEUS	Retro-spective Cohort Study	502	Patients with confirmed COVID-19, Median age = 62 (49-71), Gender = P (44.8%) L (53.2%), Ethnicity = African American, Caucasian, Hispanic.	Have comorbid obesity (BMI > 30 kg/m2), DM, CD, CKD, stroke, HT, smoking, liver disease	Does not have comorbid obesity (BMI <25 kg/m2), DM, CD, CKD, Stroke, HT, liver disease, does not smoke	Death, severity of COVID-19
Salacup et al. (2020)	Pennsylvania	Retro-spective Cohort Study	389	Patients with confirmed COVID19, Median age = 66 (58-76), Gender = L (49%) P (51%), BMI = 29.39 ± 9.22	BMI >30 kg/m2	BMI normal	IMV use, COVID-19 deaths
Palaiodimos et al. (2020)	New York	Retro-spective Cohort Study	200	Patients with confirmed COVID-19, Median age = 64 (50–73.5), Gender = L (49%) P (51%), median BMI= 30 (IQR, 26–35)	Have comorbidities Obesity (BMI >35 kg/m2), DM, CAD, CKD, COPD, HT, Asthma, smoking, alcohol consumption, intravenous drug use	Does not have comorbid obesity (BMI <25 kg/m2), DM, CAD, CKD, COPD, HT, Asthma, does not smoke, does not consume alcohol, intravenous drugs	Intubation, need for oxygenation, COVID-19 deaths
Seiglie et al (2020)	Massachuttes	Retro-spective	450	Patients with confirmed COVID-19, Gender (all BMI	Obesity (BMI>30 kg/m2), Age >50 years, Hispanic	Not obese (BMI <25 kg/m2), Age <50	ICU treatment, IMV use, COVID-

		Cohort Study		= L (3791) P (2004)	white	years, Nonhispanic white	19 deaths
Pietre et al (2020)	Brazil	Retro-spective Cohort Study	235,555	COVID19 confirmed patient, Age= 61 (IQR=28), Gender = L (43.7%) P (56.3%), Ethnicity = white, black, yellow, brown, red	Having comorbid obesity treated with symptoms of dyspnea, oxygen saturation <95%, distress	Has no comorbid obesity treated with symptoms of dyspnea, oxygen saturation <95%, distress	COVID-19 deaths
Gerwen et al. (2020)	New York	Retro-spective Cohort Study	3703	Patients with confirmed COVID-19, Median age = 56.8+-18.2, Gender = L (55.3%) P (44.7%)	Have comorbid obesity (BMI > 30 kg/m2)	Has no comorbid obesity (BMI <25 kg/m2)	IMV use, COVID-19 deaths
Pettit et al. (2020)	Chicago	Retro-spective Cohort Study	238	Patients with confirmed COVID-19, Age = median : 58.5 (17), Gender = L (47.5) P (52.5%)	Have comorbidities Obesity (BMI > 30 kg/m2), HT, DM, CD, CKD, Cancer, Stroke, hyperlipidemia	Does not have comorbid obesity (BMI <25 kg/m^2), HT, DM, CD, CKD, Cancer, Stroke, hyperlipidemia	COVID-19 death, hypoxemia
Czernicho w et al. (2020)	France	Prospec-tive Cohort Study	5,795	Patients with confirmed COVID-19, Gender = (P = 2,004; L = 3,791)	Have comorbidities Obesity (BMI > 30 kg/m2), diabetes, HT, dyslipidemia, sleep apnea, CKD, HF, Cancer, Smoker	No comorbidities Obesity (BMI > 30 kg/m2), diabetes, HT, dyslipidemia, sleep apnea, CKD, HF, Cancer, Smoker	COVID-19 deaths

1. Results of the relationship between obesity and covid-19 death

a. Forest Plot

Interpretation of the results of the meta-analysis process can be seen through the forest plot. Figure 3 show that obesity increases mortality in COVID-19 patients. Meta-analysis results show obesity increases the incidence of death in COVID-19 patients 1.50 times compared to non-obese (aOR= 1.50; 95% CI= 1.17 to 1.93; p= 0.001). The heterogeneity of the research data shows I^2= 83% so that the distribution of the data is declared heterogeneous (random effect model).

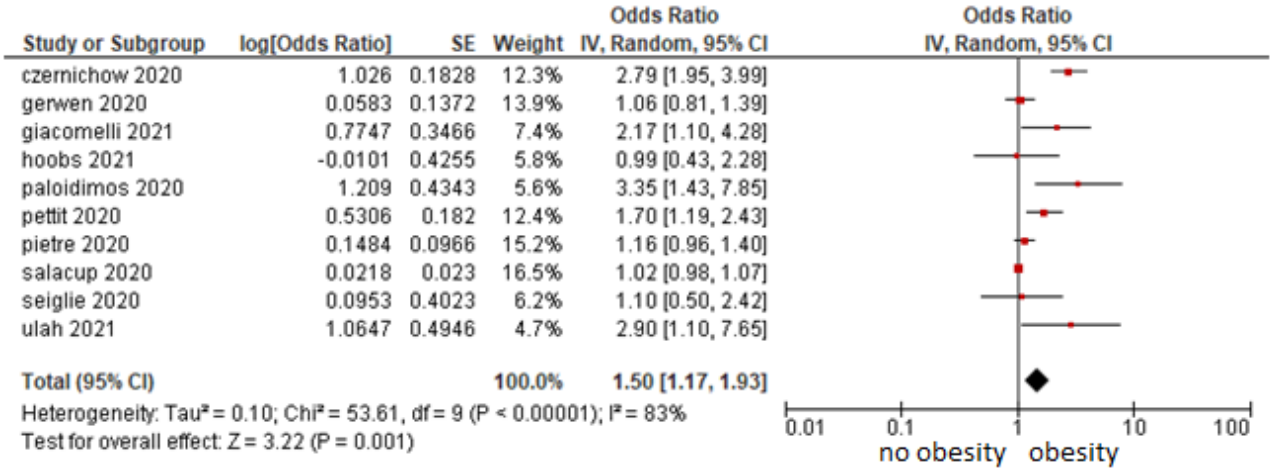

Figure 3. Forest plots the relationship between obesity and COVID-19 mortality

b. Funnel Plot

Based on Figure 4, the funnel plot of obesity with COVID-19 mortality, shows an asymmetric distribution of primary study estimates that are more to the right of the vertical line than to the left of the vertical line, which indicates that there is publication bias that overestimates the effect.

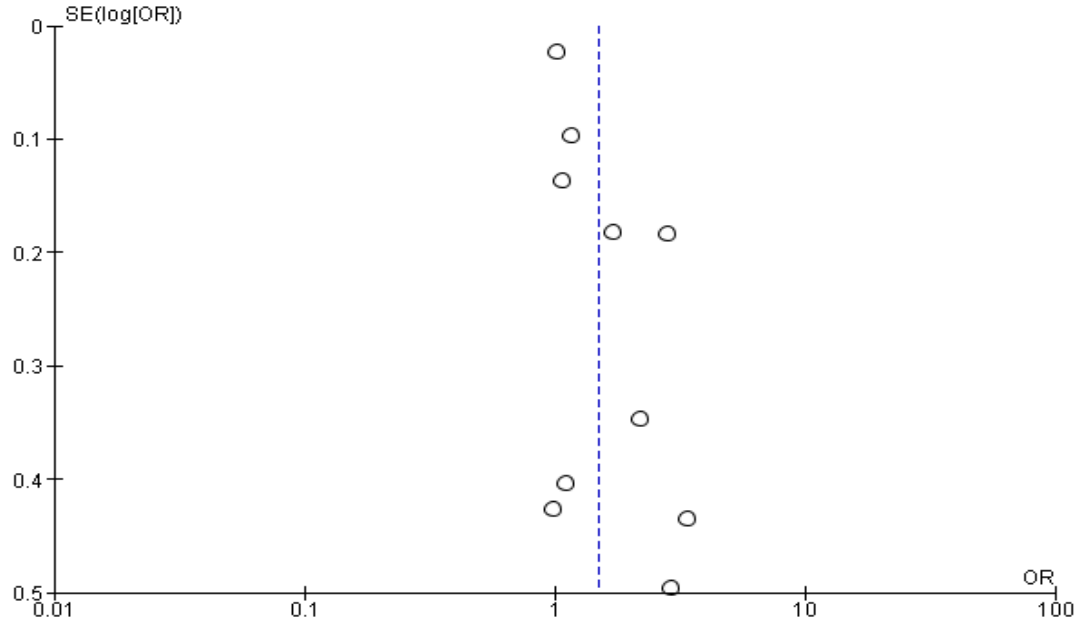

Figure 4. Funnel plot of obesity with COVID19 mortality

Table 3. Description of the primary study of the association of T2DM with COVID-19 mortality

Research	Country	Study Design	Sample	P (Population)	I (Intervention)	C (Comparison)	O (Outcome)
Id et al (2021)	Ethiopia	Retrospective Cohort Study	429	Patients with confirmed COVID-19 , Age <50 years (60.8%), male (64.1%), had comorbidities (43.8%) = T2DM (19.8%) HT (25.2%), Asthma (6.1%), CD (5.6%))	Having comorbid T2DM, n = 344 (80.2%)	No comorbid T2DM, n = 85 (19.8%)	Severity, death of COVID-19
Sun et al. (2020)	China	Retrospective Cohort Study	3400	COVID-19 confirmed patient, Age >65 years old	Have comorbidities of DMT2, HT, HT+DM	Does not have comorbidities of DMT2, HT, HT+DM	COVID-19 deaths
Seiglie et al (2020)	Massachut tes	Retrospective Cohort Study	450	Patients with confirmed COVID19, Age mean SD = T2DM 61.1 vs NT2DM 66.7, Gender = L (T2DM 54.8; NT2DM 61.8) vs P (T2DM 45.2; NT2DM 38.2, Race = White, Hispanic, African American	Have comorbid DMT2 (HbA1c 8.1%), BMI = overweight 25-29 kg/m2 (105), obese >30 kg/m2 (100)	No comorbidities with T2DM, (HbA1c -), BMI = overweight 25-29 kg/m2 (105), obese >30 kg/m2 (91)	ICU treatment, IMV use, COVID-19 deaths
Barron et al. (2020)	The UK	Retrospective Cohort Study	61,414,470	Patients with confirmed COVID19, Age = 0->80 years, Ethnicity = Asian, black, white	Have comorbidities of DMT1, T2DM, other types of DM	No comorbid DM	COVID-19 deaths
You et al. (2020)	Korea	Retrospective Cohort Study	5473	Patients with confirmed COVID19, Gender = P (55.4%) L (44.6%)	Have comorbid DMT2, n = 56, use antibiotics, oxygen therapy, ventilator, antiviral and antipyretic	Did not have comorbid DMT2, n = 28, did not use antibiotics, oxygen therapy, ventilator, antiviral and antipyretic	ICU care, COVID-19 death
Satman et al. (2021)	Turkey	Retrospective Cohort Study	93571	Age (IQR)=T2DM (20) non-DM (22), Gender = L T2DM (42.3%) non-DM (55%)	Have comorbid T2DM (HbA1c>7%)	No comorbid T2DM (HbA1c<7%)	Hospital admission, COVID-19 death

2. Results of the relationship between T2DM and Covid-19 deaths

a. Forest Plot

Interpretation of the results of the meta-analysis process can be seen through the forest plot. Figure 5 shows that T2DM increases mortality in COVID-19 patients. The results of the meta-analysis of cohort studies showed that T2DM increased the incidence of death in COVID-19 patients by 1.93 times compared to those without T2DM (aOR= 1.93; 95% CI= 1.28 to 2.90; p= 0.002). The heterogeneity of the research data shows I^2= 99% so that the distribution of the data is said to be heterogeneous (random effect model).

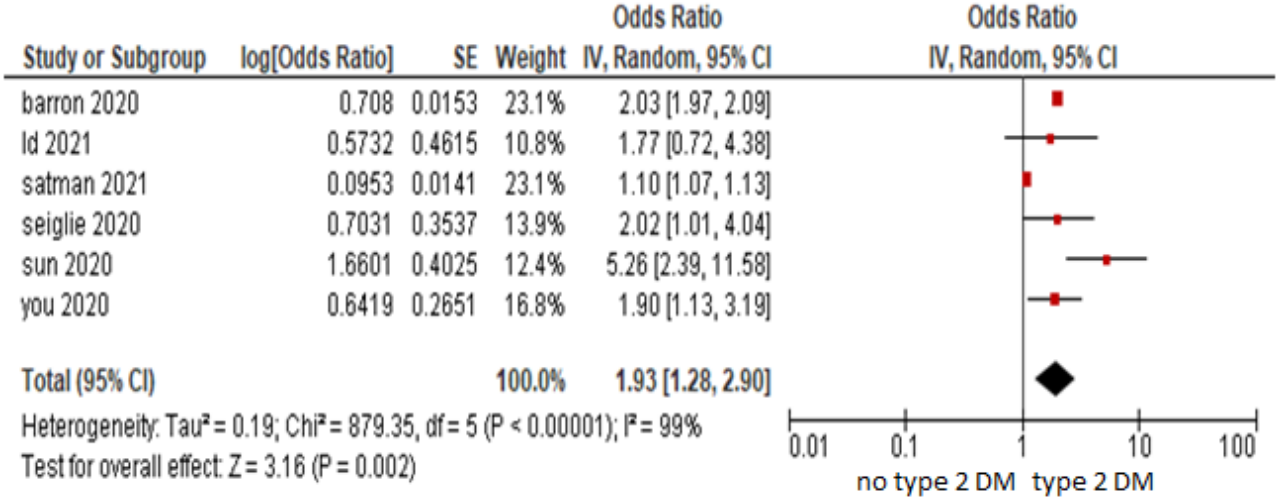

Figure 5. Forest plot of the relationship between DMT2 and COVID-19 mortality

b. Funnel Plot

Figure 6 funnel plot of DMT2 with COVID-19 mortality shows a fairly symmetrical distribution of primary study estimates to the left and right of the vertical line, not indicating publication bias.

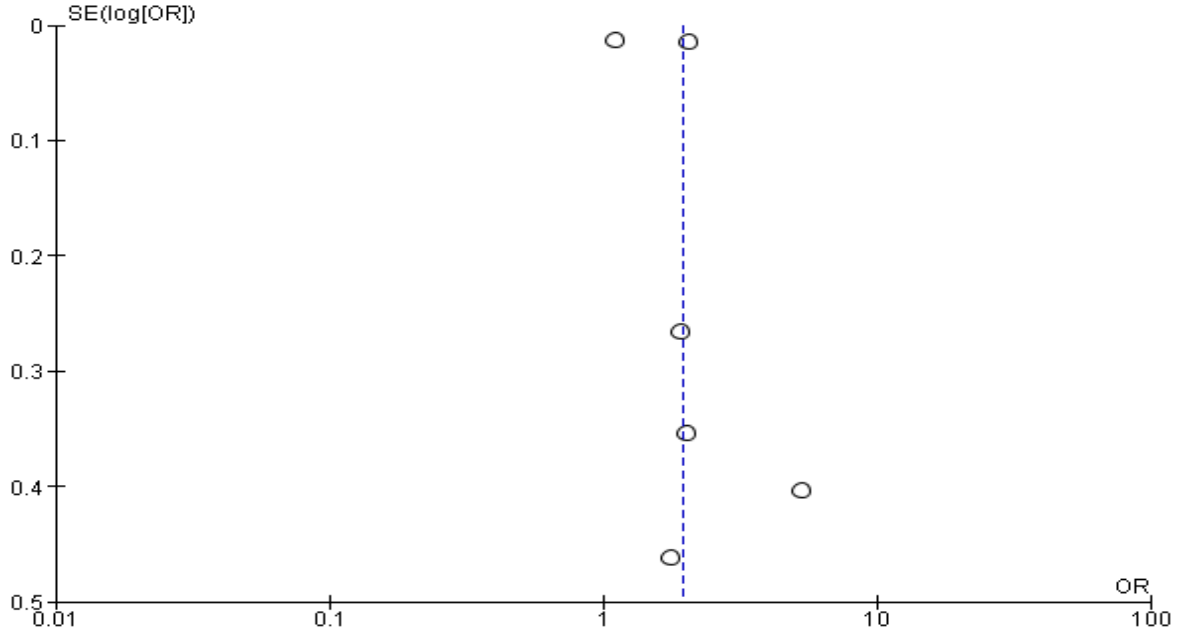

Figure 6. Funnel plot DMT2 with COVID-19 deaths

DISCUSSION

This systematic review and meta-analysis research raised the theme of the effect of comorbid obesity and T2DM on mortality from COVID19. The dependent variable analyzed was COVID19 mortality. This meta-analysis study uses research sources that control confounding factors or confounding factors that can be seen from the inclusion requirements of the study, namely multivariate analysis and the statistical results reported are adjusted odds ratio (aOR). The combined results of the relationship between obesity and T2DM with COVID-19 mortality were processed using the RevMan 5.3 application, while the results of a systematic study and meta-analysis were presented in the forest plots and funnel plots.

1. The relationship of obesity and COVID-19 mortality

The results of the forest plot of research articles with an observational cohort design showed that obesity was 1.50 times the risk of dying from COVID-19 compared to without obesity (aOR= 1.50; 95% CI= 1.17 to 1.93; p= 0.001).

Obesity plays an important role in the pathogenesis of COVID-19 infection. In fact, the immune system, which is a key player in the pathogenesis of COVID 19, also plays an important role in inflammation-induced adipose tissue. This inflamamation of adipose tissue results in metabolic dysfunction that has the potential to cause dyslipidemia, insulin resistance, type 2 diabetes mellitus, hypertension, and cardiovascular disease (Kassir, 2020).

This is supported by the study of Nakeshbandi et al. (2020), that overweight and obese patients who have COVID-19 are at increased risk for death and intubation compared to those with a normal BMI. After controlling for age, gender, diabetes, hypertension, and qSOFA scores, there was a significant increase in the risk of death in the overweight (RR= 1.4; 95% CI= 1.1 to 1.9) and obese (RR= 1.3; 95% CI= 1.1 to 1.7) compared with those with a normal BMI.

The Cunningham et al (2020) study revealed that comorbid obesity (aOR= 2.30; 95% CI; 1.77-2.98; vs no obesity; p < 0.001) was associated with a greater risk of death or mechanical ventilation. The odds of death or mechanical ventilation did not differ significantly by race and ethnicity. Comorbid obesity was present in 140 patients (41%) who died or required ventilation.

In addition, the study of Hendren et al (2020) revealed that obese patients were more likely to be hospitalized with COVID-19, and were at higher risk of dying in hospital or on mechanical ventilation, particularly if they were young (aged 50 years). Class III obesity was associated with a higher risk of in-hospital death (HR= 1.26; 95% CI= 1.00 to 1.58). Severe obesity (BMI 40 kg/m^2) was associated with an increased risk of in-hospital death only at 50 years (HR= 1.36; 95% CI= 1.01 to 1.84).

Yang et al (2020) in their study explained that compared to non-obese patients, obese patients had a significantly increased risk of infection (OR= 3.19; 95% CI= 1.45-7.03; I^2= 98%), hospitalization (OR= 1.77; CI 95%; 1.61 to 1.95; I^2= 43%), severe clinical disease (OR= 2.88; 95% CI: 1.99-4.16; I^2= 49.9%), mechanical ventilation (OR= 1.66; 95% CI= 1.42 to 1.94; I^2= 41.3%, intensive care unit (ICU) (OR=2.06; 95% CI= 1.49-2.85; I^2= 71.4%) and mortality (OR= 1.48; 95% CI= 1.18 to 1.85; I^2= 80.8%). Patients with obesity may have a 1.48 times greater risk of developing severe COVID-19 and dying.

2. The relationship between DMT2 and COVID-19 mortality

The results of the forest plot of research articles with an observational design

showed that T2DM had a 1.93 times risk of dying from COVID-19 compared to those without T2DM and the results were statistically significant (aOR=1.93; 95% CI= 1.28 to 2.90; p=0.002).

Patients with T2DM have a background of increased levels of inflammation associated with obesity and insulin resistance in addition to other comorbidities including hypertension, obesity, cardiovascular disease, dyslipidemia, and advanced age. T2DM with hyperglycemia is one of the factors leading to increased expression of angiotensin converting enzyme 2 (ACE2) in the lungs and other tissues; ACE2 is the cellular "receptor" and the entry site for viruses. Pre-existing chronic inflammation with an increased inflammatory response to infection and increased viral load causes an extreme systemic immune response (cytokine storm) that is strongly associated with increased severity of COVID-19 (Bloomgarden, 2020).

This is supported by Sonmez (2021), T2DM patients (n= 9213) were compared with a group without diabetes (n= 9213) which were matched using propensity scores for age and sex. Compared with the group without T2DM, 30-day mortality after hospitalization was higher in patients with T2DM (13.6% vs 8.7%; HR = 1.75; 95% CI: 1.58-1.93; p < 0.001). It was concluded that patients with T2DM who were hospitalized due to COVID-19 were at increased risk of death, length of hospital stay, and ICU admission.

The study (Holman et al., 2020a) conducted in the UK on 16 February and 11 May 2020, among 264,390 people with type 1 diabetes and 2,874,020 people with type diabetes 21,604 people with type 1 diabetes and 36,291 people with type 2 diabetes died from all causes. Compared with people with an HbA1c of 48–53 mmol/mol (6.5–7.0%), people with an HbA1c of 86 mmol/mol (10%) or higher had increased COVID-19-related deaths (HR=2.23; 95% CI= 1.50–3.30, p<0.001) in type 1 diabetes and (HR= 1.61; 95% CI= 1.47 to 1.77; p<0.001) in type 2 diabetes.

Rastad et al. (2020) in his study revealed that COVID19 patients with DM had a 1.69 times greater increase in mortality, besides that the lymphocyte count, creatinine and CRP concentration could be considered as significant predictors of COVID-19 mortality in these patients.

Huang et al. (2020) mention that DM is associated with mortality, severe COVID-19, ARDS, and disease progression in patients with COVID-19. Meta-analysis showed that DM was associated with a composite adverse outcome (RR= 2.38; 95% CI: 1.88-3.03; p < 0.001; I^2= 62%) and its subgroup consisting of death (RR= 2.38; 95% CI: 1.44 to 3.11; p <0.001; I^2= 72%), severe COVID-19 (RR= 2.45; 95% CI= 1.79 to 3.35; p < 0.001; I^2= 45%), ARDS (RR=4.64; 95% CI= 1.86 to 11.58; p<0.001; I^2= 9%), and disease progression (RR= 3.31; 95% CI= 1.08 to 10.14; p= 0.04; I^2= 0%).

The limitation of this study is that there is a publication bias that is shown in the funnel plot of the cohort study on the obesity variable. There is a language bias, because in this study the selected articles were only published in English, thus ignoring articles in other languages.

AUTHOR CONTRIBUTION

Oktaviana Kurniawati is the main researcher who chooses the topic, searches and collects research data. Hanung Prasetya and Bhisma Murti played a role in analyzing data and reviewing research documents.

FUNDING AND SPONSORSHIP

This study is self-funded.

CONFLICT OF INTEREST

There is no conflict of interest in this study.

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