SYSTEMATIC REVIEW WITH META-ANALYSIS OF OBESITY AS RISK FACTOR OF COVID-19 RELATED MORTALITY

by Lilik Djuari .

SYSTEMATIC REVIEW WITH META-ANALYSIS OF OBESITY AS RISK FACTOR OF COVID-19 RELATED MORTALITY

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ABSTRACT

A person with obesity has a high risk of getting a severe complication of COVID-19. This is related to the increasing of chronic illness cases caused by obesity. Obesity itself has been known to take part in the disruption of the human immune system. A person with obesity will be more susceptible to the infection and is suspected to be one of the risk factors that cause death in COVID-19. This study used observational analysis with a systematic review method and continued with Meta-Analysis. This study has been held at the Public Health Department of Faculty of Medicine, Universitas Airlangga, Surabaya, in July 2020. The data sources of this study come from online literature, such as published journals that match our inclusion criteria. The inclusion criteria for this study were journals that study the relation of obesity and mortality in COVID-19 cases, journals with a cross-sectional design, journals that used samples age >18 y.o., and journals that used BMI as the obesity classification. Five journals matched our criteria and were analyzed in this study. Four of 5 journals show that there is a relationship between obesity and mortality of COVID-19. There are 2133 subjects with COVID-19, and 361 of them have obesity. There are 1861 subjects with COVID-19 who are not dead; 1567 of them don't have obesity. An analytic study with a random effect model shows that obesity is the risk factor of mortality in COVID-19 cases (OR = 2.041; 95% CI 1.027-4.058). It also shows that there is a significant relationship between obesity and mortality in COVID-19 cases (p=0.042). Most journals analyzed with a systematic review and meta-analysis in this study show that obesity is the risk factor of mortality in COVID-19 cases.

INTRODUCTION

Coronavirus Disease 2019 (COVID-19) is a disease caused by novel Coronavirus. It first happens in Wuhan, China, as pneumonia with unknown etiology.[1] Later, the etiology of COVID-19 has been identified as Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2). WHO reports that the global COVID-19 cases until 19 July 2020 have reached 14.043.176 confirmed cases, and 597.583 have been reported dead. The global Case Fatality Rate (CFR) of COVID-19 is 4.3%. Meanwhile, in Southeast Asia, the confirmed COVID-19 cases reach 1.391.047 with a CFR of 2.4%.[2]

The Ministry of Health of the Republic of Indonesia reports that COVID-19 cases in Indonesia until 20 June 2020 have reached 88.214 confirmed cases with a CFR of 4.8%.[3]

Obesity increases the risk of chronic illnesses, such as type-2 diabetes mellitus, cardiovascular disease, cancer, disability, and depression.

A person with obesity has a high risk of getting severe complications in the COVID-19 cases. This is related to the increasing in chronic illness cases caused by obesity. In the intensive care unit, a person with severe obesity has quite a difficult level of patient management, and it is challenging for medical personnel.[4] A study in New York shows that most of the COVID-19 patients that need to be administered to the health service are those who have old age (>65 y.o.) and obesity.[5] Recent study in England also shows that patients with IMT <20 kg/m^2 (underweight) and IMT >28 kg/m^2 (obese) have high risk to get severe COVID-19 outcome.[6] Besides having the risk of increasing the severity of COVID-19 cases, obesity has also taken part in the disruption of the human immune system, leading patients to become more susceptible to infection and is suspected to be the risk factor of mortality COVID-19 cases.[7]

Based on the problems shown above, we are interested in studying obesity as one of the risk factors of COVID-19 related mortality. The method of this study uses systematic review and meta-analysis. We hope this study can be used as a reference to manage this COVID-19 pandemic.

MATERIALS AND METHODS

The journals used in this study were acquired from search engines such as Google, Google Scholar, and Pubmed. We search the journals in the search engine with this keyword: the relation between obesity and mortality in COVID-19 patients. We limit that only free international journals

with the English language published in 2020 can be used in this study.

The title and abstract of each journal were screened. Only journals relevant to this study were selected. The duplicate journals were excluded. The selected journals were then read entirely to determine their compliance with these study inclusion criteria. The literature research strategy diagram can be seen in Figure 1.

Data Selection Criteria

The inclusion criteria used in this study are journals contain data on obesity and COVID-19 mortality, journals with a cross-sectional design, journals that use subjects aged ≥18 years old, and journals that use BMI as their obesity classification.

Data Extraction

The data were extracted from the journals which match up with these study inclusion criteria. The data obtained consists of author names, research year, research location, research subjects, inclusion criteria, result, and conclusion of the research.

RESULTS

Study Characteristics

The result of the study of 5 journals obtained 2133 subjects with the least subjects are 107 subjects, and the highest is 928 subjects. Data collection in all studies regarding the relationship between obesity and mortality of COVID-19 used was carried out in the timeframe of 2020 and had a cross-sectional study design. Subjects used are males and females aged ≥18 years old.

Analysis

Four of the five journals used in this study conclude a significant relationship between obesity and mortality in COVID-19. Those 4 journals data were obtained from a random population group in specific

healthcare facilities or places, so it can plenty describe the global situation nowadays.
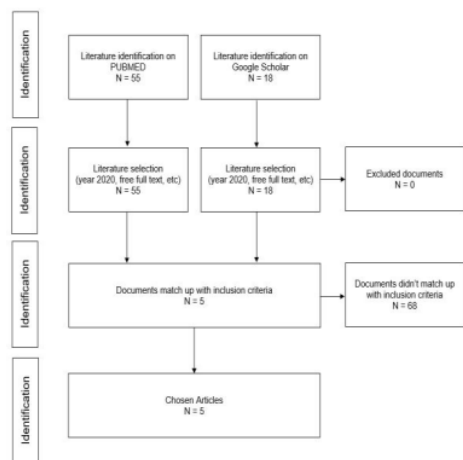

Figure 1. Literature research strategy.

Besides, one journal states that obesity does not significantly relate to COVID-19 mortality in COVID-19 patients with malignancy. Many factors affect the mortality of COVID-19 patients with malignancy rather than obesity itself.

Meta-Analysis of those five journals shows that obesity is the risk factor of mortality in COVID-19 (OR = 2.041; 95% CI = 1.027 – 4.058). There is also a significant relationship between obesity and COVID-19 mortality, proven by the p-value = 0.042.

DISCUSSION

Obesity is a risk factor for various diseases, including COVID-19. The research results in the previous section found that obesity is a risk factor for the mortality of COVID-19 with OR = 2.041; 95% CI = 1.027-4.058. *The p-value* in this study was 0,042 (p<0.05); these results indicate that this study is significant. The odds ratio obtained in this study illustrates that obese COVID-19 patients have a risk of mortality two times higher than the non-obese group.

Research by Cai *et al*., found that obese men compared to non-obese were 5.66 times more likely to fall into severe COVID-19 infection (OR 5.66; 95% CI 1.80–17.75; p = 0.003). In the same study, one in three patients who died were obese patients.[8]

Where Escalera-Antezana, who has researched on the first 107 cases of COVID-19 in Bolivia, found that age 60, hypertension, chronic heart failure, diabetes, obesity, and the need for ICU are significant risk factors for COVID-19 mortality.[9]

Giacomelli *et al*. conducted a study of mortality in the first 30 days of treatment in cases of the first wave of COVID-19 in Italy and found that the elderly and obesity increased the risk of death.[10]

Rottoli *et al*. who conducted a study to determine the relationship between obesity and the severity of COVID-19 found that obesity is a risk factor that can increase the risk of 2,32 times greater incidence of respiratory failure (OR: 2.32; 95% CI: 1.31 – 4.09, p = 0.004), 4.96 times the need for ICU care (OR: 4.96; 95% CI: 2.53 – 9.74; p <0.001), and 12,1 times the risk of death (OR: 12.1; 95% CI: 3.25 – 45.1; p <0.001) in the case of COVID-19.[11]

In a study that focused more on cancer patients with COVID-19 by Kuederer *et al*., It was found that 12% of all cancer patients who died from COVID-19 were obese. However, from statistical tests on patients with cancer who died from COVID-19, obesity was not a significant factor causing mortality from Covid-19. There are still many other factors involved in cancer patients, such as the result of cancer itself and the treatment being carried out.[12]

The study we conducted is still in line with the five studies we used for further analysis. Nearly all studies support that obesity is a

factor in the severity of mortality of COVID-19 cases. Apart from obesity, it was mentioned above that there are other risk factors, including old age, diabetes, and hypertension.

The pathophysiology of obesity as a mortality factor from COVID-19 is not yet clear; however, several theories try to explain the course of COVID-19 in obese patients.

Obesity affects various body systems related to the pathogenesis of COVID-19. People with obesity have reduced lung capacity and are more prone to respiratory infections. The lungs of obese people tend to be more restrictive or have more difficulty expanding so that vital lung capacity is reduced.[13] This reduced vital lung capacity can be fatal when we are in a state of increased oxygen demand, for example, in pneumonia. Obesity can exacerbate the state of respiratory failure.

Proinflammatory cytokine will be triggered by the excess of adipose cells in an obese individual, which will cause the inflammation process to happen. Obesity itself is a condition with chronic inflammation as a result of this adipose cell stack.[14] Adipose tissue contains various immune cells such as Th2, M-2, Treg, CD8+, and M-1. Those immune cells in normal conditions always maintain their balanced state. However, in obesity, the immune cells in adipose tissue that role as an anti-inflammation (Th2, M-2, Treg) are reduced, and the pro-inflammation immune cells (CD8+, M-1) are increased. This will lead Adipose tissue to become an inflamed tissue that excessively secretes cytokines. Cytokine storm is suspected to be one of the pathophysiologies of the severity of COVID-19, which will worsen if there is a chronic inflammatory condition, for example, in the case of obesity.[15]

Obesity is often found with bad lipid profiles such as dyslipidemia. Dyslipidemia will increase vascular coagulability and makes blood to be more viscous. This viscous blood condition is causing vascular to become inflamed, including the vascular in lungs. Vascular inflammation caused by hypercoagulation blood is suspected to be one of the causes of severity in COVID-19 cases.[16]

In the lungs, SARS-CoV-2 attacks ACE-2 receptors and makes its amount in the lungs become depleted. The decreasing number of ACE-2 receptors in the lungs will disrupt its function to convert the angiotensin-II into angiotensin. The increasing amount of angiotensin-II in the lungs can causa various problems such as vasoconstriction, oxidation, fibrosis, and lung inflammation that leads to Acute Lung Injury and a respiratory failure. This condition will increase the risk of mortality in COVID-19 patients.[16]

SARS-CoV-2 binds with ACE-2 (Angiotensin-Converting Enzyme-2) receptor to enter the cells. ACE-2 receptors are found in various places inside the human body; one is in Adipose cells.[17] In obese patients, the number of Adipose cells is increased as well as the ACE-2 receptors. This condition will make more viruses enter the Adipose cells, leading Adipose cells to become the reservoir of SARS-CoV-2. This condition will increase the viral load in obese patients and eventually lead to higher morbidity and mortality in COVID-19 cases.[18]

In Pancreas, the expression of ACE-2 receptor and SARS-CoV-2 causes dysfunction of the Pancreatic ß-cells that cause increases in blood sugar levels and insulin resistance.[19] This uncontrol hyperglycemic condition will increase the severity of COVID-19, especially in diabetes and obese patients.[20]

Table 1. Study Characteristics

	Author Names (Year)	Location and Research Year	Study Design	Inclusion Criteria	Sample Size	Statistic Analysis Result	Conclusion
1.	Cai, Q., et al (2020)[9]	Shenzen Hospital, China in 2020	Cross-sectional	All of the COVID-19 patients confirmed with a nasal swab and quantitative PCR (qPCR) assay in Shenzhen Hospital, China from 11 February until 2 February 2020	383	p-value = 0.007 (p<0.05) OR = 3.40	There is a significant relationship between obesity and mortality of COVID-19
2.	Escalera-Antezana, et al. (2020)[10]	Bolivia in 2020	Cross-sectional	All of the COVID-19 patients confirmed with RT-PCR in Bolivia from 2 March until 29 March 2020	107	p-value=0.002 (p<0.05) OR = 12.125	There is a significant relationship between obesity and mortality of COVID-19
3.	Giacomelli et al. (2020)[11]	Milan, Italy in 2020	Cross-sectional	All of the adult COVID-19 patients confirmed with RT-PCR hospitalized in Luigi Sacco Hospital, Milan, Italy between 21 February and 19 March 2020	233	p-value = 0.0029 (p<0.05) OR = 2.37	There is a significant relationship between obesity and mortality of COVID-19
4.	Rottoli et al (2020)[12]	Bologna, Italy	Cross-sectional	All of the COVID-19 patients confirmed with RT-PCR hospitalized in Sant'Orsola Hospital, Bologna, Italy, between 1 March and 20 April 2020	482	p-value < 0.001 OR = 12.1	There is a significant relationship between obesity and mortality of COVID-19
5.	Kuderer et al (2020)[13]	USA, Canada, and Spain	Cross-sectional	All the patients who have the history of malignancy aged >18 y.o., confirmed with SARS-CoV-2 infection between 17 March and 16 April 2020	928	p-value = 0.543 (p>0.05) OR = 0.853	Ther is no significant relationship between obesity and mortality in COVID-19 patient with malignancy

Table 2. A meta-analysis of the relation between obesity and mortality in COVID-19

Study name	Statistics for each study					Odds ratio and 95% CI
	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value	
Cai Q, et al (2020)	4.250	0.377	47.925	1.171	0.242	
Escalera A, et al (2020)	12.125	1.691	86.948	2.483	0.013	
Giacomelli A, et al (2020)	2.377	1.108	5.101	2.223	0.026	
Kuderer N.M, et al (2020)	0.853	0.512	1.423	-0.608	0.543	
Rottoli (2020)	2.123	1.288	3.500	2.953	0.003	
Random	2.041	1.027	4.058	2.035	0.042	

Meta Analysis

CONCLUSION

Most of the studies used in this systematic review and meta-analysis show that obesity is associated with increased mortality risk among patients with COVID-19.

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