Obesity as a predictor for a poor prognosis of COVID-19: A systematic review

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ABSTRACTS

Background and aims: COVID-19 is an emerging pandemic due to droplet infection of 2019-novel coronavirus (2019-nCoV). Due to its rapid transmission and high case-fatality rate, recognition of its risk and prognostic factor is important. Obesity has been associated with impaired immune system, increasing the susceptibility for 2019-nCoV infection. We aimed to study the impact of obesity to the prognosis and disease severity of COVID-19.
Methods: A systematic search and handsearching was conducted in four databases: Cochrane, MEDLINE, EMBASE, and PubMed. The identified articles were screened using the chosen eligibility criteria. We obtained three retrospective cohort studies (Wu J et al., Lighter J et al., and Simonnet A et al.) to be critically appraised using Newcastle Ottawa Scale.
Results: The findings of all included studies were consistent in stating the contribution of obesity as a risk factor to increase the requirement for advanced medical care. Study with the highest quality, Simonnet A et al., reported an increase need of invasive mechanical ventilation in COVID-19 patients with body mass index higher than 35 kg/m^2, OR: 7.36 (1.63–33.14; $p = 0.021$). This is associated with a higher mortality rate in obese population infected with COVID-19.
Conclusion: Obesity is an independent risk and prognostic factor for the disease severity and the requirement of advanced medical care in COVID-19. This systematic review highlights a particularly vulnerable group – obese, and emphasises on the importance of treatment aggression and disease prevention in this population group.

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1. Introductions

Coronavirus disease-2019/COVID-19 is a new emerging pandemic. Its rapid transmission, progressivity and high case fatality rate had affected global social welfare and economy [2]. Per 25 April 2020, the total confirmed coronavirus cases globally reached 2,902,708 along with 202,179 death [1].

The prognosis of COVID-19 has been consistently reported to worsen in advanced age [3,4] and with the presence of other comorbidities, such as hypertension, cardiovascular diseases, diabetes mellitus, and pulmonary diseases [3–6]. Nevertheless, the growing rate of hospitalization in younger population has been reported and associated with obesity [7,8], a condition of having excessive adipose tissue. The growing prevalence of obesity globally have risen the concern on its additional impact to worsen this pandemic [11].

Obesity has been associated with a condition of chronic inflammation and decreased immune system, increasing the susceptibility of an individual to infections [12,13]. Hence, this evidence suggests that obesity might act as an independent risk factor for a poor disease progression of COVID-19. Nevertheless, a meta-analysis by Ni Y (2017) reported the protective factor of obesity in Acute Respiratory Distress Syndrome (ARDS) patients [14]. Having ARDS as one of the devastating clinical manifestations of COVID-19 [4], this contradicting views raises doubts on the impact of obesity in the disease severity and prognosis of COVID-19.

Hence, we aim to investigate the impact of obesity to the requirement of advanced medical treatment in positively-identified

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COVID-19 patients, with the hypothesis of obesity being a poor prognostic factor for COVID-19.

2. Methods

2.1. Protocol and Registration

This systematic review was conducted based on the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) Statement [15]. The protocol of this systematic review has been registered in The International Prospective Register of Systematic Reviews (PROSPERO) database (CRD42020183068).

2.2. Eligibility criteria

We included longitudinal cohort studies or randomised controlled trials which observed the effect of BMI to the requirement of in-hospital critical care in patients infected with 2019-novel coronavirus (COVID-19). Exclusion criteria include infection of unspecific coronaviruses or other respiratory viruses.

2.3. Search strategy

A systematic literature search was performed on April 12–14th, 2020 using four different databases: Cochrane, MEDLINE, EMBASE, and PubMed; along with manual handsearching using keywords as listed in Table 1. Literature selection was performed without time limitation but restricted to only published English or Indonesian articles.

2.4. Data collection

Data from each study was extracted in a standardised form, compiling study citations, baseline characteristics of the included subjects, appropriate intervention, and the study findings. Study citations included the name of the first author, year of publication, and title of the study. Meanwhile, characteristics of each study refered to study design, location of the study, patients' characteristics (age, ethnicity, gender, sample size, BMI and presence of other comorbidities). We specified the extracted comorbidities to hypertension, respiratory system disease, cardiovascular disease, diabetes mellitus, and dyslipidaemia according to the acknowledged comorbidities for COVID-19 by other systematic reviews and meta-analysis [6,16]. The study findings extracted involved the hazard ratio/odds ratio analysed in each study.

2.5. Quality assessment and data synthesis

Two independent reviewers conducted the quality assessment of the studies (AT and DLT). The included studies were critically appraised using Newcastle Ottawa Quality Assessment Scale (NOS). Any discrepancies of NOS score between reviewers were discussed until it reached a conclusion. High-quality studies were defined as studies fulfilling NOS score of minimum 7.

Data was synthesised based on a minimum of three different and high-quality studies with consistent finding. The obtained data was analysed considering the method of variable analysis used, study size, odds/hazard ratio, along with its confidence interval.

3. Results

Literature searching performed using keywords as listed in Table 1 yielded several studies. Out of 573 articles identified, 18 articles were retrieved after title and abstract screening. After the exclusion of duplicates, five studies were assessed in full-text. Three studies remained after full-text screening using eligibility criteria, which were studies by Wu J et al. [17], Lighter J et al. [18], and Simonnet A et al. [19]. The exclusion of the remaining two studies was due to the usage of language other than English/Indonesian and investigation on other types of coronaviruses. The flow of our study selection is presented according to PRISMA Statement (Fig. 1).

The summary of baseline study characteristics is presented in Table 2. All studies had level 2 of evidence based on Oxford 2011 and were considered high-quality based on each NOS score. The results of the critical appraisal could be seen in Table 3. All studies used retrospective cohort design to explain the relationship between obesity (exposure) and COVID-19 severity. While studies by Simonnet et al. and Lighter J et al. used a body mass index (BMI) of more than 30 kg/m^2 to define obesity, study by Wu J et al. used 25 kg/m^2. These criteria were in accordance with the proposed criteria for obesity in Caucasian [9] and Asian population [10], respectively.

Using a multivariate analysis, study by Simonnet A et al. demonstrated that COVID-19 patients with obesity grade II had 7.36 (1.63–33.14; $p = 0.021$) times increased risk of having invasive mechanical ventilation during in-hospital care, compared to normoweight COVID-19 [19]. Meanwhile, study by Lighter J et al. stratified their study subjects by their age, dividing them into less than 60 years and over 60 years age-groups. Compared to normo- and over-weight groups, the rate of hospitalization increased 2.0 (1.6–2.6; $p < 0.0001$) and 2.2 (1.7–2.9; $p < 0.0001$) times in younger patient group with obesity grade I and II, respectively. Moreover,

Table 1
Search queries of this systematic review.

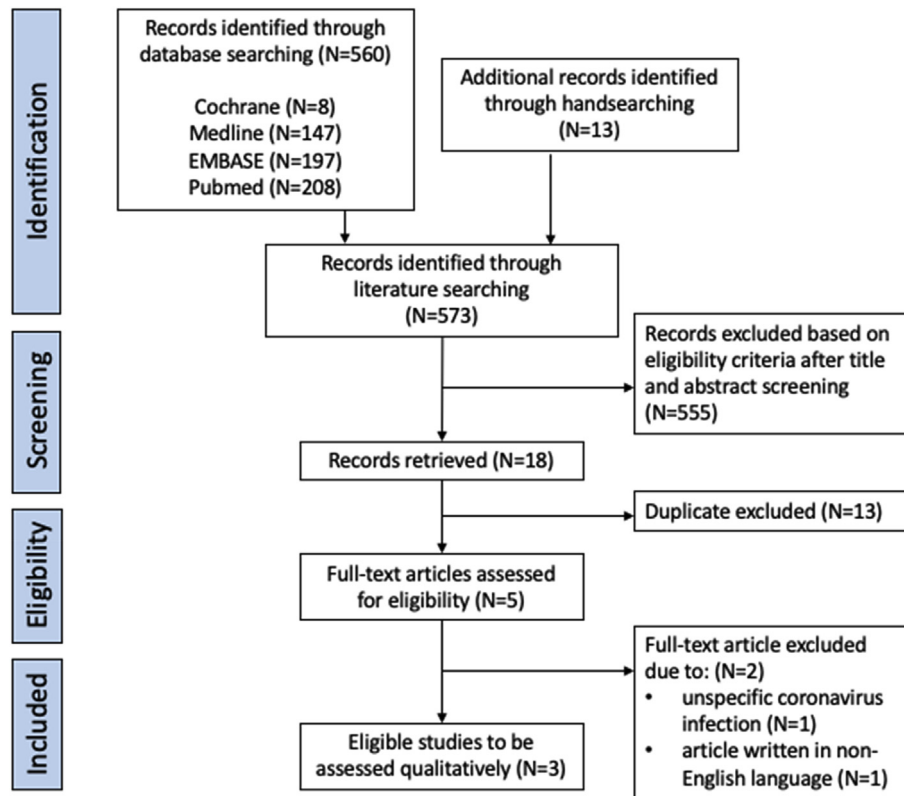| Databases	Search query	Hits
Cochrane	(covid-19 OR coronavirus OR sars-cov-2) AND (comorbid* OR obes* OR overweight OR high BMI OR unhealthy weight) AND (hospitali?ation OR admission OR hospital stay OR mortality OR morbidity)	8
EBSCO	(covid-19 or coronavirus or 2019-ncov or sars-cov-2 or cov-19) AND ((comorbidity or comorbidities or coocurence or comorbid) OR (obesity or overweight or fat or obese or unhealthy weight or high bmi)) AND ((hospitalization or hospitalization or admission or hospital stay or care episode) OR (mortality or mortality rate or death or death rate or morbidity))	147
EMBASE	((covid-19 or coronavirus or 2019-ncov or sars-cov-2 or cov-19).mp. [mp = title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]) AND ((comorbid* or obes* or overweight or high BMI or unhealthy weight).mp. [mp = title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]) AND ((hospitali?ation or admission or hospital stay or care episode or mortality or morbidity).mp. [mp = title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word])	197
PubMed	((covid-19 or coronavirus or 2019-ncov or sars-cov-2 or cov-19) and (comorbid* or obes* or overweight or high bmi or unhealthy weight)) and (hospital?action or admission or hospital stay or care episode or mortality or morbidity)	208
Handsearching	"obesity" AND "COVID-19"	13

Fig. 1. PRISMA flowchart of study selection.

Table 2
Summary of baseline characteristics and outcomes of the included studies.

Authors	Date (MM/DD)	Study location	Age (years)	Sample size		BMI (kg/m^2)		Comorbidities; N(%)					Findings (OR to develop severe COVID-19)
				Total	M/F	Mild-moderate	Severe	Hyper-tension	Respiratory diseases	CVD	DM	Dyslipi-daemia	
Wu J et al. [17]	03/27	China	43.12 ± 19.02	280	151/129	23.6 (20.4 −26.8)	25.8 (24.0 −27.6)	NA	6 (2.14)	57 (20.36)	34 (12.14)		Obesity grade I[a]: 1.30 (1.09 −1.54; p = 0.003)
Lighter J et al. [18]	04/09	USA	<60	402	NA	30−34	≥35	NA	NA	NA	NA	NA	Obesity grade I[a]: 1.8 (1.2−2.7; p < 0.006) Obesity grade II[a]: 3.6 (2.5−5.3; p < 0.0001)
Simonnet A et al. [19]	04/09	France	60 (51−70)	124	90/34	27 (25.3 −30.8)	31.1 (27.3 −37.5)	60 (49)	NA	NA	28 (23)	34 (28)	Obesity grade II[b]: 7.36 (1.63 −33.14; p = 0.021)

Notes.
CVD: Cardiovascular Disease.
DM: Diabetes Mellitus.
NA: not available/not known/not stated.
[a] Normo- and over-weight comparator group.
[b] Normoweight comparator group.

Table 3
Quality assessment of the included studies using Newcastle Ottawa Scale.

Studies	Selection	Comparability	Outcome	Total
Wu J et al. [17]	****	–	***	7
Lighter J et al. [18]	****	*-	***	8
Simonnet A et al. [19]	****	**	***	9

younger group patients with obesity grade I and II had an increased likelihood to receive critical care 1.8 (1.2−2.7; p < 0.006) and 3.6 (2.5−5.3; p < 0.0001) times respectively, compared to normo-weight and overweight groups [18]. Study by Wu J et al. also reported an increased risk of 1.30 (1.09−1.54; p = 0.003) times in COVID-19 patients with BMI higher than 25 kg/m^2 to develop severe COVID-19 compared to normo- and over-weight patients [17], however, it was attenuated in multivariate analysis.

4. Discussions

COVID-19 is a devastating infectious disease worldwide, commonly manifests in acute respiratory distress syndrome (ARDS) [4]. Its rapid transmission and considerably high case-fatality rate have called for the recognition of important risk factors and high-risk population for better prevention and treatment approach. Obesity has

been speculated to act independently in increasing the risk and worsening the prognosis of COVID-19 patients. In this systematic review, three included studies are consistent, despite a moderate degree of variability, in showing the deleterious effect of obesity in COVID-19 severity, inducing critical and advanced hospital care.

The findings from the included studies acknowledged the increased risk of COVID-19 severity in obesity. Nevertheless, those three studies reported a variable degree of association between obesity and severe COVID-19, which might be related to the differences in the definition of the reported outcome (invasive mechanical ventilation, ICU admission, severe infection), comparator group, sample size, and to a lesser extent, the use of different BMI cut off points for obesity.

In the aspect of sample size, study by Lighter J et al. was very precise with their findings statistically [18]. Meanwhile, study by Simonnet A, the highest quality study in overall aspects, had a lower sample size. This probably explains the need of a higher BMI to exceed statistical differences (35 kg/m^2) [19]. On the other hand, study by Lighter J only required 30 kg/m^2 to show a statistically significant impact of obesity to the necessity of advanced hospital care [18]. However, unlike Simonnet A study, the inclusion of other important comorbidities in multivariate analysis in Lighter J study was not known [19].

Furthermore, a careful interpretation of studies by Lighter J and Wu J should be made due to the use of different comparator group. Studies by Lighter J and Wu J compared the data of obese groups with both normo- and over-weight groups, whereas Simonnet A study compared the obese with normoweight patients. This might lead to an underestimated risk ratio measured by Lighter J and Wu J studies. Moreover, study by Wu J et al. reported the lowest relative risk, and even considered obesity not as an independent risk factor for COVID-19 disease severity [17] as the statistical significance was completely attenuated in the multivariate analysis.

Article with the highest quality was written by Simonnet et al. [19]. Although its sample size was the smallest among them, this research included multivariate analysis to omit the possibilities of other important comorbidities affecting the study outcome. Different to other prognostic studies, this study did not differentiate the mortality rate of obese and non-obese patients; hence, might not directly reflect a poorer prognosis of disease severity in obese COVID-19 patients. Nevertheless, a paper by Yang X et al. showed higher mortality rate of patients requiring mechanical ventilation [4]. Thus, choosing the necessity of mechanical ventilation in obese COVID-19 might be an appropriate outcome to assess prognosis and hospital cost.

Possible mechanisms related to disease severity in obesity are speculated to occur through higher ACE-2 concentration, chronic inflammation, and functional restrictive capacity of obese lung. ACE-2 receptor has been recognised as a coreceptor for 2019-nCoV entry and known to be expressed in many parts of human body: gastrointestinal tract, lung, heart and kidney [20]. A recent publication has reported the increased expression of ACE-2 receptor in adipose tissue [21]. This means having more adipocytes is equal to be having more ACE-2 receptors to catch 2019-nCoV. Moreover, chronic inflammation in obesity is apparent with the increased interleukin 6 (IL-6) level, adipokines, and pro-inflammatory cytokines (e.g., TNF-a, inferferon), inducing a chronic low-grade inflammatory state in obesity and impairing immune response [12,13,19]. The total lung capacity has also been reported to be reduced in obese patients, and improved by bariatric surgery [22,23]. Moreover, a study by Campos et al. also emphasised the impact of obesity to reduce lung function in sedentary subjects [23]. Hence, obese patients tend to be more susceptible to COVID-19 infection and rapid severe disease progression due to its lower baseline lung functional capacity than normoweight people.

On the other hand, a meta-analysis by Ni Y et al. (2017) reported the protective impact of obesity in ARDS patients. Study by Ni Y et al. correlated obesity to a higher rate of heparin prophylaxis and hypertension. Heparin helped to reduce coagulation and systematic inflammatory response whereas hypertension reduced fluid or vasopressor requirement in circulatory failure [14]. This condition was thought to contribute to a diminished potential of disease progression to ARDS. However, Ni Y study made no attempt to explain the direct effect of obesity and ARDS, in contrast to the previous explanation through molecular and lung functional capacity changes in obesity. Hence, our study also shed light on the contrasting view of ARDS and obesity. The severity of ARDS and overall COVID-19 clinical manifestations increased in obese patients infected with COVID-19 and this population even showed a higher need of invasive mechanical ventilation [19]. Findings from COVID-19 which were discussed in this study were also in line with previous coronaviruses studies: coronavirusHKU1 [24] and MERS-CoV virus [25]. These studies had previously stated the increased prevalence and risk of obese people to coronavirus infection.

The limitations of this study arise from the exclusion of articles written in languages other than English and Indonesian and unexplored grey literatures. We also failed to assess the baseline characteristics and variable analysis of Lighter J article. Moreover, this systematic review could not be proceeded to a quantitative analysis (meta-analysis) due to the heterogenous use of variable analysis. Thus, we recommended future studies to adjust comorbidities to their risk ratio presentation to clearly portray the effect of obesity to the disease severity of COVID-19.

Taken together, this is the first systematic review to proclaim obesity as an independent risk and prognostic factor for the requirement of advanced medical treatment due to COVID-19. Hence, the results from this study are important in the aspect of treatment aggression and disease prevention. Obese patients with COVID-19 should be treated as a higher risk population. In the aspect of prevention, while staying home has been campaigned globally to reduce COVID-19 rapid transmission, in long term, it may simultaneously increase the susceptibility of people to develop obesity, a risk factor to develop severe COVID-19.

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Author contribution

Idea and study design: DLT; Data collection and analysis: AT, DLT; Article draft writing: AT; Draft revision: DLT; Writing supervision: DLT. All authors have read the manuscript and have approved this submission.

Declaration of competing interest

The authors declare no conflict of interest.

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