Obesity and Severity Outcomes in COVID-19 Children A Systematic Review & Meta-Analysis

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Obesity and Severity Outcomes in COVID-19 Children: A Systematic Review & Meta-Analysis

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Abstract

Objective: This study has an aim to analyze the association between pediatric obesity with outcomes of COVID-19 in terms of hospital and ICU admission as well as mortality, considering the are limited studies available that discuss the issue. **Methods:** This is a meta-analysis whose investigation was conducted between June to July. Published papers were obtained from PubMed, Embase, Cochrane, and Google Scholar. This study utilized the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) checklist for protocol assurance. Keywords applied in the systematic search include [“COVID-19”] and [“Children"] and [“Obesity"] or [“Obese"]. **Results:** The analysis in this study shows that obese children are at higher risk for ICU admission (OR: 3.92 [95%CI: 3.49-4.40], p = <0.00001) and mortality (OR: 4.29 [95%CI: 3.76-4.89], p = <0.00001). The odds for obese children to be hospitalized for COVID-19 were found to be (OR: 1.72 [95%CI: 0.83-3.60], p = 0.15) but was not significantly correlated. **Conclusion:** Our data indicate that paediatric patients are more likely to be admitted for ICU and have a higher risk of mortality when they are obese.

Keywords: COVID-19, obesity, children, hospitalization, ICU

1. Introduction

Indonesia is a country with double burden malnutrition across all age groups. Meaning, the country faced problem of both underweight and obesity (**Maehara et al., 2019**). The prevalence of obesity in children under the age of five increased from 4.2% to 9.4% during 1993 to 2007 and remained level through 2014. During that span of 21 years, the prevalence of overweight in children aged 6-12 years old increased from 5.1% to 15.6% and in age group 13-18 years increased from 7.1% to 14.1%. These percentages are slightly lower when compared to overweight in adults which can be found in one-third of adults (**Oddo, Maehara, & Rah, 2019**). Obesity on itself has its own perils. However, with the entrance of novel SARS-CoV-2, obesity is a liability that may contribute to the downward slope in the battle against COVID-19. Children having comorbidities are at greater risk to suffer from severe form of COVID-19, obesity being one of them (**Tsankov et al., 2019**).

The severity and mortality of COVID-19 in adults are caused by several underlying mechanisms. Some of them are dysregulation of immune response (inflammation), involvement of angiotensin-converting enzyme-2 (ACE-2) for viral binding and entry, impaired lung function, and physiological lung alteration. Obesity increased the amount of adipose tissue (AT) in the body. Adipocytes secrete cytokines that create a chain reaction to increase substance that induce pro-inflammatory reaction and decrease substance that promotes anti-inflammatory reaction. AT is also known to increase ACE-2 expression level, hence increasing the gateway for viral entry. Obesity is also known to create changes in the structure and physiology of the lungs, such as reducing thoracic wall compliance that results in limited functional residual capacity (**Cai, Yang, & Zhang, 2020; Salvator et al., 2020; Fuster et al., 2016**).

Recently there have been many studies discussing the association between COVID-19 in adults with outcomes such as hospital admission, ICU admission, and mortality. However, there are limited studies available that discuss the issue of childhood obesity. Hence, the purpose of this study is to open a discussion regarding the topic.

2.Methods

2.1. Study Design

A meta-analysis was conducted from June to July 2021 to determine the association between obesity and COVID-19 in children. Published papers from PubMed, Embase, Cochrane, and Google Scholar were collected for the calculation of the pooled standard mean difference and 95% confidence interval (95% CI) using either random or fixed effect model. Our current study applied the checklist from Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) to ensure our protocols, including the papers selection, data extraction, quality assessment, and statistical analysis, conformed to the PRISMA guideline (**Moher et al., 2009**).

2.2. Search Strategy and Data Extraction

Several scientific websites (PubMed, Embase, Cochrane, and Google Scholar) were searched for papers assessing the association between obesity and COVID-19 in children as of July 31, 2021. We did not limit the language of publication. If articles with publication language neither in English nor Indonesia were found, we performed a consultation to the Language Center in our University. Furthermore, the following keywords were applied to carry out a systematic search: [“COVID-19”] and [“Children"] and [“Obesity"] or [“Obese"]. If we found papers with the same study data in our searching strategy, we only included papers with a larger sample size. Additionally, the following information of interest was extracted from each paper: (1) first author name, (2) year of publication, (3) sample size of case and control, (4) age of participants, (5) ethnicity, (6) main findings, (7) the number of hospitalization of case and control, (8) the number of ICU Admission of case and control, and (9) The number of death of case and control. To provide high-validity data, two independent authors performed data extraction to avoid human error (FF, VA). If a discrepancy was found, we performed a consensus and consultation with the senior researcher (MF, NR, YH).

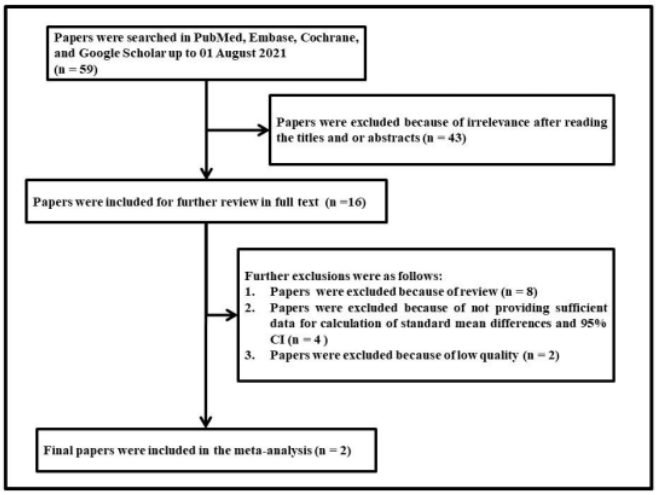


Figure.1. Paper selection pathway

2.3. Eligibility Criteria

The following criteria were used to include the papers in our study: (1) assessing the association between obesity and COVID-19; and (2) having required data for calculation of the total number or events and % of each case and control. Furthermore, the exclusion criteria were as follows: (1) unrelated titles and abstracts, (2) reviews and commentaries, (3) incomplete and or ungeneralized data, and (4) low-quality article.

2.4. Outcome Measures

The predictor covariate in our present study was the obesity. While the outcome measures were the hospitalization number, the number of ICU admission, and the number of death. They were determined after we performed initial searching for covariates screening to include in our meta-analysis calculation.

2.5. Assessment of the Methodological Quality

The quality of each paper was assessed using the New Castle-Ottawa scale (NOS) prior to included in the meta-analysis. The NOS score was ranging from 0 to 9, and it had three points: a selection of patients (4 points), comparability of the groups (2 points) and ascertainment of exposure (3 points). Paper was interpreted as having low quality (for scores ≤ 4), moderate quality (for scores 5-6), or high quality (for scores ≥ 7). Papers with low quality were excluded from our study. Two independent investigators (FF and YH) performed NOS assessment, and if the discrepancy was found, a consultation with a senior researcher (MF, NR) was conducted.

2.6. Statistical Analysis

The correlation and effect estimates between obesity in COVID-19 children with the hospitalization, ICU admission, and the number of death were assessed using a Z test. Prior to identification the significant factors, data were evaluated for heterogeneity and potential publication bias. The

heterogeneity among studies was assessed using the Q test. If heterogeneity existed ($p < 0.10$), a model of random effect was adopted, otherwise, a fixed effect model was applied. The test of Egger and funnel plot were used to determine reporting or publishing error ($p<0.05$ was considered having publication bias). The correlation and effect estimates were then presented using forest plot. The data were analyzed using Review Manager version 5.3 (Revman Cochrane, London, UK). In order to avoid methodological errors, two independent authors (FF and YH) conducted statistical analysis.

3. Results

3.1. Eligible Studies

Our searching strategy identified 59 potentially relevant papers. Among them, 98 papers were excluded because of irrelevant titles and abstracts. In total, 11 papers were included for review in full text. Of those, we excluded nine papers because of review (n = 5), incomplete data (n = 2), and low quality papers (n = 2). Finally, two papers were included in our analysis. Figure 1 summarizes the paper selection pathway in our study, and Table 1 outlines the baseline characteristics of papers included in our meta-analysis.

Table.1. Baseline characteristics of articles included in our study

Author & year	Sample size		Case setting	Age (months) (mean ± SD)	Ethnicity	NOS	Main findings
	Control	Obese					
Agarwal et al., 2021	1428	1371	Obese children with COVID-19	48.8 ±20,6	Caucasian	7	Obesity has only recently been identified as a risk factor for severe COVID-19 disease in children.
Garduno, 2020	10789	5089	Obese children with COVID-19	42±18.9	Caucasian	7	Obesity represents the strongest predictor for COVID-19 in children.

3.2. Data Synthesis

In data synthesis, we included two papers assessing the association between autoantibodies and duration of disease, two papers assessing the correlation between obese children with COVID-19 and the number of hospitalization, two papers assessing the association between obese children with COVID-19 and ICU admission, and two papers assessing the association between obese children with COVID-19 and the number of death (the number of autoantibodies detected). Our pooled

analysis found that obese children with COVID-19 and the number of hospitalization (OR: 1.72 [95%CI: 0.83-3.60], p = 0.15) was not significantly correlated. Meanwhile, the association between obese children with COVID-19 and the number of ICU admission (OR: 3.92 [95%CI: 3.49-4.40], p = <0.00001) was significantly correlated. Moreover, the association between obese children with COVID-19 and the number of death (OR: 4.29 [95%CI: 3.76-4.89], p = <0.00001) was significantly correlated. The summary of the association between obese children with COVID-19 and outcome parameters is outlined in Table 2.

Table.2. Summary of the association between obese children with COVID-19 and outcome.

Parameters	Outcome measure		Odds Ratio	95%CI	pE	pHet	P
	Control	Obese					
ICU admission	239.5 ± 200.11	480 ± 134.35	3.92	3.49-4.40	0.808	0.058	<0.00001
Hospitalization	1296.5 ± 1065.61	1229.5 ± 924.19	1.72	0.83-3.60	0.000	0.021	0.15
Mortality (The number of death)	176.5 ± 61.51	418 ± 8.49	4.29	3.76-4.89	0.050	0.400	<0.00001

Note, data were presented in mean ± SD; CI, confidence interval; pE, p Egger; pHet, p Heterogeneity.

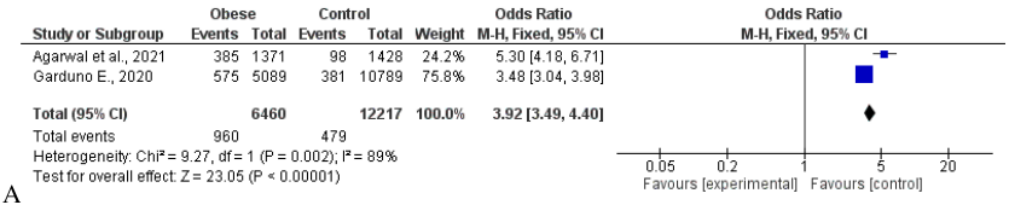
3.3. Heterogeneity among Studies

Our analysis found that the evidence for heterogeneity was observed in the following covariates: the number of hospitalization. Therefore, a random effect model was used to assess the association between obese children with COVID-19 and the number of hospitalization. Conversely, we found no evidence of heterogeneity in the number of ICU admission and the number of death covariate. Therefore, fixed-effect model was used to evaluate the correlation between obese children with COVID-19 and the number of ICU admission and the number of death covariate. The evidence of heterogeneity among studies in our present meta-analysis is described in Figure 2**.**

3.4. Potential Publication Bias

We used Egger's test to determine the potential publication bias among studies. Overall, there was no publication bias in our studies. The summary of publication bias is described in Figure 2.

Figure.2. Forest Plot of the association between obese in children with COVID-19 and outcome parameters. A). ICU admission, B). Mortality



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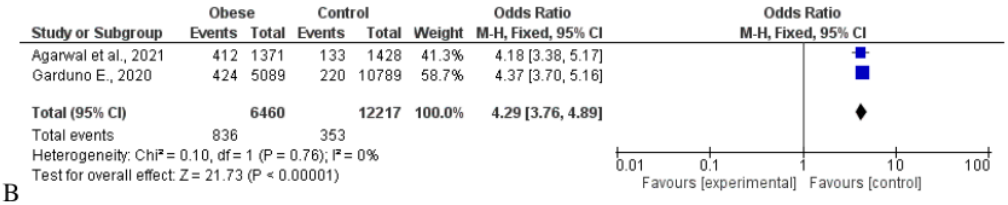

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4. Discussion

From the two studies included in this study, the analysis result shows a significantly correlated association between obesity in children with COVID-19 and the number ICU admission number with an odds ratio of3.92 [95%CI: 3.49-4.40]. This pattern was also observed in several other meta-analysis on association of obesity in adult COVID-19 patients with admission to intensive care unit. In which obese patient has greater odds of being admitted to the ICU with OR 2.25 [95% CI:1.55-3.27] in study by Cai et al. (2020), OR 1.51 [95% CI:1.16-1.97] in study by **Helvaci et al. (2021)**, and OR 1.48 [95% CI:1.24-1.77] in study by **Yang et al. (2021)**. In those studies, COVID-19 patients with obesity were also found to have higher odds at requiring invasive mechanical ventilation. There was a lack of considerable number of studies to obtain data on association between ICU admission and COVID-19 with obesity on children. This suggests the need for further exploration of paediatric obesity on COVID-19. Nevertheless, there are three main factors that has been suggested to link COVID-19 with obesity in adults. Those include chronic subclinical inflammation, impairment of adequate immune response, and underlying cardiorespiratory problems. Comorbidities that are found in adults may be observed in periods of childhood and adolescence. In addition to that, obese children were also found to lack adequate immune response to infections. It is a widely known phenomenon within current clinical setting that bacterial pneumonia is one of most common severe complications of COVID-19. This may explain the increased need for intensive care to manage the greater COVID-19 severity in at odds population of obese children, as depicted by the significancy of the correlation (**Nogueira-de-Almeida, 2017; Nogueira-de-Almeida et al., 2017**).

Another significant finding of this study is the association between obese children and the number of death due to COVID-19, with obese children having odds of 4.29 [95% CI:3.76-4.89]. This finding is in line with the associations observed in obese adults. This confirms previous study findings by **Cai et al. (2020)**, in which obese COVID-19 patients has a significantly increased mortality in addition to increased chance of infection, hospitalization, and use of mechanical ventilation when compared to nonobese patients. **Yang et al. (2021)** also provided similar results in which obese patients has a higher risk of in-hospital mortality, OR 1.14 [95% CI:1.04-1.26]. This study's result regarding mortality, however, are not in line with the study findings by **Helvaci et al. (2021)**, in which although having OR of 1.77, the statistical significance for increased risk of death were not reached due to unidentified factors and/or obesity survival paradox. Again, the comparative study results were obtained from adult obese COVID-19 patients since pediatric studies are limited. The mechanism for which obesity can increase COVID-19 mortality chances in children may involve various aspects on obesity itself, as well as its comorbidities including: insulin resistance and dyslipidemia, impaired respiratory physiology, cardiovascular architectural changes, subclinical inflammation, coagulopathy, renal dysfunction, intestinal dysbiosis, impaired immune system, and nutrient deficiencies (**Nogueira-de-Almeida et al., 2017**).

This study has provided a picture on the association of pediatric obesity with higher risk of ICU admission – implying greater severity of disease – and the subsequent significantly higher risk of mortality. Although meta-analysis of similar theme has been carried out in adults – whose results were discussed in this study – as per writing of this meta-analysis, there is yet to be found studies that addressed the issue on children. One of the urgencies to open discussion on children obesity was also driven by **Zhang et al. (2020)**, who claims that even in young patients, obesity has an inclination toward mortality when it comes to COVID-19. Hence, countries with a high prevalence amongst younger people might experience a shift in age curve for mortality. This study may be a call for precaution to manage the number of obese children in Indonesia, considering it is a country with double burden of malnutrition, both underweight and obese. Early preventive action may improve the already less-than-ideal struggle the country has with COVID-19.

This meta-analysis are not without its limitations. To begin with, heterogeneity was observed in this study regarding hospital admission. Aside from that, limited studies were available regarding the topic in children, creating a limited pool. Despite the limitations, this study was made with the sincerest hope to contribute to the current situation, and we encourage further studies with greater sample size to confirm the findings in this study.

5. Conclusion

Our study shows that obese children suffering from COVID-19 are at greater odds to be admitted into intensive care unit and have a higher odds for mortality. This study, however, does not find any significance between pediatric obesity and hospital admission for COVID-19. This study may serve as a call for precaution to the government to promote healthier lifestyle and supress the number of childhood obesity as one of preventive efforts to tackle COVID-19.

6. Acknowledgements

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7. Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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9. Disclosure

The authors declare that no conflicts of interest in this work.

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