Original Article

Association between Obesity and COVID-19 Outcomes in the Intensive Care Unit of RSUP Dr. M. Djamil Padang

Ilham, Fenty Anggrainy, Dessy Mizarti

Department of Pulmonology and Respiratory Medicine, Faculty of Medicine, Universitas Andalas/ RSUP Dr. M Djamil Padang, Indonesia

Abstract

Background: Obesity is one of the risk factors for severe clinical COVID-19. This is because these patients tend to have comorbidities such as metabolic disease and cardiovascular disease. Obesity may result in poor outcomes, such as prolonged hospital stays, higher incidence of ARDS and mortality. The purpose of this study was to determine the correlation between obesity and the outcome of confirmed COVID-19 patients.

Methods: This was an analytical study with retrospective cohort design on COVID-19 patients treated in the intensive care unit (ICU) of RSUP Dr. M. Djamil Padang. Data were taken from patients' medical records between November 2021 and February 2022. The correlation between obesity with length of stay and patient mortality was analyzed using Chi-square test. Odds ratio was also assessed.

Results: This study obtained that the characteristics of obese COVID-19 patients were mainly women (54.20%). The most dominant age group was 60-69 years (31.3%). About83.3% of obese patients were found to be clinically critical. Inflammatory markers such as procalcitonin, ferritin, IL-6 and d-dimer were not significantly associated with obesity. Diabetes mellitus was significantly related to the outcome of COVID-19 patients with obesity and without obesity (0.009%). Obesity was not correlated with hospital length of stay of COVID-19 patients but was significantly associated with length of stay in the ICU [OR=3.67 (95% CI=1.09-12.35)]. Obesity was significantly associated with mortality [OR=2.84 (95% CI=1.12-7.18)] and length of conversion for COVID-19 patients in the ICU [OR=30.00 (95% CI=2.85-31, 61)]. The expansion of adipose tissue both subcutaneously and viscerally which could be observed in obese patients can increase the proinflammatory, prothrombotic, and vasoconstrictive state that might affect the clinical deterioration of COVID-19 patients. This condition also manifests as insulin resistance, hypertension, atherosclerosis, cardiovascular disease and immunocompromised conditions which can generate high mortality rate.

Conclusion: Obesity was found to be significantly associated with mortality, conversion time and length of stay for COVID-19 patients in the ICU.

Keywords: COVID-19, obesity, length of stay, length of conversion, mortality

Corresponding Author:
Ilham | Department of Pulmonology and Respiratory Medicine, Faculty of Medicine, Universitas Andalas, RSUP Dr. M Djamil Padang, Indonesia | ilh_am200@hotmail.com

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INTRODUCTION

Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) is a new type of coronavirus, first discovered on December 8, 2019 in Wuhan, China where several cases of clinical symptoms could progress to acute respiratory distress syndrome and death. The COVID-19 pandemic has spread throughout the world and various studies are being conducted to identify groups that are vulnerable of developing severe and life-threatening symptoms.[1]

Several studies were conducted to identify the effects of obesity and poor outcomes of COVID-19 patients. Williamson, et al. reported that obesity was one of the risk factors for severe clinical COVID-19, this was due to comorbidities such as metabolic disease and cardiovascular disease.[2] Albashir, et al. reported that 85% of obese patients required mechanical ventilation.[3] Rao, et al. also reported that being overweight was an independent risk factor for the severity of COVID-19.[4]

ObeseCOVID-19 patients had higher mortality rate, longer duration of hospitalization, greater incidence of ARDS and more frequent intensive care needs compared to patients with normal weight.[5–9] The high risk of obeseCOVID-19 patients for experiencing severe and critical clinical conditions that requires intensive care and the occurrence of poor outcomes, makes it important to determine the relationship between obesity and the outcomes of COVID-19 patients.

METHODS

An analytic retrospective cohort study was conducted from November 2021 to February 2022 at RSUP Dr. M. Djamil Padang. The study population was all confirmed COVID-19 patients who were treated in the intensive care unit (ICU) of RSUP Dr. M. Djamil Padang between January and August 2021. The inclusion criteria were confirmed COVID-19 patients from the results of SARS-CoV-2RT-PCR taken from a nasal/nasopharyngeal swab, aged >18 years, complete data of recent weight and height in the medical records. Exclusion criteria were COVID-19 patients with pregnancy, ascites and/or edema, or patients who were discharged with at their own will (against medical advice).

The characteristic data were presented in the form of a frequency distribution table. The analysis was carried out using the SPSS version 21 program. The correlation between demographic characteristics, clinical degrees, inflammatory markers and comorbidities of COVID-19 patients were analyzed using the Chi-square test on categorical variables while the numerical variables were analyzed using the Independent Sample T test. The association between obesity, length of stay and mortality was analyzed using Chi-square test and the odds ratio was assessed in each category (OR>1, is risk factor, when OR<1, is protective factor, and OR=1, is not a risk factor & not a protective factor).

RESULTS

The number of samples that met the research requirements were 96 patients. Characteristics of COVID-19 patients in the ICU of RSUP Dr. M. Djamil Padang is described in Table 1. This study obtained that most obese patients were in the age group of 60–69 years (31.3%) with more than half of them were women (54.2%), while the non-obese patients were mostly male (66.7%) in the age group of 60-69 years (33.3%). Most critical clinical cases were observed in both group of obese (83.3%) and non-obese patients (89.6%). The results of inflammatory markers such as procalcitonin, IL-6, D-dimer and ferritin, had median values that were almost the same in both obese and non-obese groups. Diabetes mellitus was the most common comorbid disease in the obese group (45.8%), while in the non-obese group it was hypertension (35.4%). There were more obese patients who had >1 comorbidities than the non-obese group (27.1% vs 14.6%).

Table 1 points out that there were no differences related to age (*P*=0,76), gender (*P*=0.064), clinical severity (*P*=551) and inflammatory markers between groups of obese and non-obese COVID-19 patients. The results revealed that there was no difference in the number of patients with one comorbidity between the obese and non-obese groups. Patients who had >1 comorbidities were found to be more on obese than non-obese patients, but from the results were not statistically significant. The most common comorbidities obtained in obese COVID-19 patients were diabetes mellitus (45.8%), hypertension (33.33%), and chronic kidney disease (16.7%). The length of hospital stay was shorter in obese patients compared to non-obese. The difference between obese and non-obese COVID-19 patients with comorbidities was found to be significant in patients with diabetes mellitus (*P*=0.009).

This study reported a total of 96 patients were admitted to the ICU, 68 of whom died and no PCR swab examination was performed, so that only 28 survived patients underwent PCR swab conversion which was then assessed for its association with obesity. The relationship between obesity and PCR conversion time in the ICU can be seen in Table 2.

Table 2 indicates that patients with length of stay in the ICU <14 days were found more in obese group (75.0%) compared to non-obese group (25.0%). Based on analysis using the Chi-square test, it was known that there was a relationship between obesity and the length of stay for COVID-19 patients in the ICU (*P*<0.05), with OR=3.67 (95% CI=1.09–12.35).

Table 3 shows that COVID-19 patients who died in the ICU were found more in obese patients (57.4%) compared to non-obese patients (42.6%). Based on the analysis using Chi-square test, there was a relationship between obesity and mortality of COVID-19 patients in the ICU (*P*<0.05), with OR=2.84 (95% CI=1.12–7.18).

Table 1. Characteristics of confirmed COVID-19 patients with and without obesity in the ICU of RSUP Dr. M. Djamil Padang

Patient Characteristics	Obese (n=48)	Non-obese (n=48)	*P*
Age group, f (%)			
<50 years	11 (22.90%)	8 (16.70%)	0.706[a]
50–59 years	13 (27.10%)	11 (22.90%)	
60–69 years	15 (31.30%)	16 (33.30%)	
≥70 years	9 (18.80%)	13 (27.10%)	
Gender			
Men	22 (45.80%)	32 (66.70%)	0.064[a]
Women	26 (54.20%)	16 (33.30%)	
Clinical severity, f (%)			
Severe	8 (16.70%)	5 (10.40%)	0.551[a]
Critical	40 (83.33%)	43 (89.60%)	0.551[a]
Inflammation markers, median (min-max)			
Procalcitonin (ng/ml)	0.75 (0.05–171.00)	0.28 (0.05–171.42)	0.114[b]
IL-6 (pg/ml)	73.70 (1.70–1,482.00)	42.35 (1.50–902.80)	0.570[b]
Ferritin (µg/L)	1,107.58 (11.30–12,001.00)	1,201.00 (11.30–12,001.00)	0.235[b]
D-Dimer (ng/ml)	3,494.50 (587.00–71,901.00)	3,400.50 (216.00–10,001.00)	0.930[b]
Comorbidity, f (%)			
Hypertension	16 (33.33%)	17 (35.40%)	1.000[a]
Diabetes mellitus	22 (45.80%)	9 (18.80%)	0.009[a*]
Chronic liver disease	1 (2.10%)	0 (0.00%)	n/a
Malignancy	1 (2.10%)	1 (2.10%)	1.000[a]
Chronic lung disease	1 (2.10%)	2 (4.20%)	1.000[a]
Chronic kidney disease	8 (16.70%)	6 (12.50%)	0.772[a]
Immunodeficiency	0 (0.00%)	1 (2.10%)	n/a
Number of comorbidities, f (%)			
None	14 (29.20%)	20 (41.70%)	
1 comorbidity	21 (43.80%)	21 (43.80%)	0.239[a]
>1 comorbidities	13 (27.10%)	7 (14.60%)	
Length of stays in hospital (mean±SD)	10.58±6.99	12.35±9.62	0.305

Note=*P*<0,05 significant; n/a not account; [a]Chi-square test; [b]Mann-whitney test

Table 2. The correlation between obesity and length of stay for COVID-19 patients in the ICU of RSUP Dr. M. Djamil Padang (n=96)

Obesity	Length of stay		Total	*P*	OR (95% CI)
	≥14 days	<14 days			
Obese	12 (75.0%)	36 (45.0%)	48 (50.0%)	0.045	3.67 (1.09–12.35)
Non-obese	4 (25.0%)	44 (55.0%)	48 (50.0%)		

Table 3. The correlation between obesity and mortality of COVID-19 patients in the ICU of RSUP Dr. M. Djamil Padang (n=96)

Obesity	Mortality		Total	*P*	OR (95% CI)
	Died	Survive			
Obese	39 (57.4%)	9 (32.1%)	48 (50.0%)	0.043	2.84 (1.12–7.18)
Non-obese	29 (42.6%)	19 (67.9%)	48 (50.0%)		

Table 5. The correlation between obesity and PCR conversion time of COVID-19 patients in the ICU of RSUP Dr. M. Djamil Padang (n=96)

Obesity	Conversion length		Total	*P*	OR (95% CI)
	≥14 days	<14 days			
Obese	8 (88.9%)	1 (11.1%)	9 (42.9%)	0.001	30.00 (2.85–31.61)
Non-obese	4 (21.1%)	15 (78.9%)	16 (57.1%)		

Table 4 reveals that COVID-19 survivor with conversion time of ≥14 days were found more in obese patients (88.9%) than non-obese patients (11.1%). Based on the analysis using Chi-square test, there was a relationship between obesity and conversion time of COVID-19 patients in the ICU (*P*<0.05), with OR=30.00 (95% CI=2.85-31.61).

DISCUSSION

The characteristics of COVID-19 patients in the ICU who were obese were mostly in the 60–69 years age group, which was 31.3% of total obese patients, followed by the 50–59 years age group. Dana, et al. who conducted a study in France also observed that the age group in obese COVID-19 patients was mostly

60–75 years old.[10] A cohort study by Pettit, et al. in Chicago also reported that the median age of hospitalized overweight and obese COVID-19 patients ranged from 51.1 years to 63.4 years.[11]

Another study by Surendra in Jakarta on hospitalized COVID-19 patients revealed that the most common age groups were 50-59 years (22%) and 40–49 years (19%).[12] COVID-19 can develop at any age, but its incidence and severity increase with age. There are two factors which affect the severity of age-related COVID-19 cases, including the escalating number of comorbidities that elderly patients have and dysregulation of the immune system as people aged.[13]

Aging process is associated with a change in pathogen recognition and clearance due to a decrease in T-cells and accumulation of memory T-cells. The aging process increases the risk of inflammation and death due to an imbalance in immune system function. Patients aged 50 years and over have a higher expression of ACE2 which is encoded by the ACE2 gene with other factors such as decreased immunity, decreased organ function and comorbidities that can increase the risk of death. Older age also has an inefficient antiviral response due to imbalanced cytokine release.[14]

More than half of obese COVID-19 patients in this study were female (54.2%). Estrogen plays a role in increasing body fat mass with age, especially after adolescence. History of pregnancy and childbirth are also factors that increase the risk of women experiencing obesity.[15] This study also observed that there were more male patients in the non-obese group (66.7%). Surendra, et al. also reported that the prevalence of male patients hospitalized due to COVID-19 was higher than the female (92%).[12] Women are less susceptible to COVID-19 infection, this was related to innate immunity, steroid hormones and factors associated with sex chromosomes. Immune regulatory genes encoded by the X chromosome in women lead to lower viral load and decreased inflammation compared to men, in addition to higher CD4+ T-cells and a better immune response in women. TLR7 levels in women are also higher and biallelic expression indicates a better immune response and intensifies resistance to viral infections. Men are associated with poorer lifestyles such as smoking and higher alcohol consumption.[16]

Most of the obese COVID-19 patients had critical clinical degrees, which was 83.3% of all patients in the ICU, this is in line with study by Dana, et al. who reported that among 222 patients admitted to the COVID-19 ICU, only 15.3% had a BMI within normal limits, the remainder being patients with mild to severe obesity.[10] A meta-analysis by Zhang, et al. pointed out that obese patients had a higher risk of requiring hospitalization when infected with COVID-19 and experienced a more severe clinical course.[17]

Adipose tissue in obesity produces proinflammatory cytokines and hormones that can have direct effects on the lungs. These mediators are released from adipose and leukocytes that infiltrate adipose tissue. These inflammatory factors then enter the circulation, including leptin, TNF-α, IL-6 and IL-8,[10] C-reactive protein, and monocytes chemoattractant protein-1 (MCP-1). Chronic inflammation in obesity initially occurs in adipose tissue, but later this process progresses to systemic inflammation.[18]

There was a difference in the median values of inflammatory markers procalcitonin, IL-6 and D-dimer, which were higher in the obese group than non-obese, while the median value of ferritin was lower in the obese group than in the non-obese group, but the difference was not statistically significant. Ellulu, et al. in Malaysia stated that obesity predisposed to a pro-inflammatory state through the mechanism of increasing inflammatory mediators, namely IL-6 and TNF-α compared to non-obese populations. IL-6 levels are associated with obesity which can affect the liver to synthesize and secrete CRP.[19]

A study by Ferreira, et al. also observed increased CRP, ferritin and D-dimer values among obese patients. Obesity induces chronic inflammation, so that IL-6 and TNF-α values are consistently elevated in the circulation in both human and mouse models. This increase induces an inflammatory state through elevated infiltration of macrophages into adipose tissue, macrophage polarization and augmentation of cytokines and chemokines.[20]

About 43% of obese COVID-19 patients had one comorbidity and 27.1% of them had more than one comorbidity. COVID-19 patients with obesity are most often accompanied by diabetes mellitus, followed by hypertension and kidney disease. These results are similar to study by Ferreira, et al. who reported that the most common comorbidities accompanying obese patients were hypertension and diabetes mellitus.[20] Obesity is a risk factor for the occurrence of type 2 diabetes mellitus caused by impaired sensitivity of muscle and fat tissue to insulin resulting in insulin resistance.[21]

A study by Heialy, et al. in Dubai found that obese patients had more comorbidities such as cardiovascular disease, hypertension, diabetes mellitus, cancer, and chronic kidney disease (78%) compared to patients with normal BMI (40%).[22] COVID-19 patients with obesity and diabetes mellitus have immune dysregulation such as phagocytic cell dysfunction, impaired immune cell chemotaxis, impaired T cell response, and altered cytokine production, which leads to ineffective microbial clearance during viral infections and prolongs the duration of viral conversion. This situation escalates mortality by extending inflammatory state of the body. Obesity and diabetes separately increase poor outcomes in COVID 19 patients. This could be seen from the results of several studies which reported an increase in mortality, length of stay and the need for ICU as well as the duration of viral conversion. Therefore, the combination of these two conditions was expected to further worsening the outcome of COVID-19 patients.

The mean length of stay for obese COVID-19 patients in hospitals was shorter than the non-obese, although the results were not significant. There was no relationship between obesity and length of stay for COVID-19 patients. Pouwels, et al. in Netherlands stated similar results where there was no significant difference of the median duration of hospitalization on COVID-19 patients between the non-obese group and the obese group.[23] Dana, et al. also reported that there was no significant difference between the length of stay of patients with normal weight, overweight and obesity, both in recovered and deceased COVID-19 patients.[10] This might be due to the assessment of the length of stay in this study was not only for patients who were discharged as survivor but also for patients who were not survive during hospital stay. This study revealed that 70.8% of COVID-19 patients admitted to the COVID-19 ICU died, resulting in a high mortality rate that was biased towards the total length of stay in the hospital.

More obese COVID-19 patients died in the ICU (57.4%) than non-obese patients (42.6%). The results of statistical analysis showed that there was a relationship between obesity and mortality of COVID-19 patients in the ICU (P<0.05) with OR=2.84 (95% CI=1.12-7.18). Poly, et al. also stated that obesity was significantly associated with an increased risk of death among COVID-19 patients, especially in patients over 65 years of age.[24] The underlying mechanisms involve abnormalities in the balance of leptin and adiponectin, increased ACE-2 expression, altered pulmonary physiology and impaired lung function that may promote the development of respiratory viral infections in obese patients.[25]

Tartof, et al. also reported that there was an association between BMI and risk of death, even after adjustment for obesity-related comorbidities.[26] Obesity is associated with chronic hypertension through increased heart rate, cardiac output and renal tubular sodium reabsorption as well as impaired renal natriuresis pressure, which occurs as a direct result of α-adrenergic and β-adrenergic receptors stimulations and indirectly through activation of other systems such as RAAS and sympathetic nervous system.[27] Obesity has a substantial effect on the immune system, where adipocytes are able to produce mediators such as cytokines, chemokines and adipokines that lead to chronic inflammation, cell necrosis as well as cell dysfunction and at a systemic level alter the immune response. In addition, the leptin resistance observed in obesity also causes an immunosuppressive phenotype.[28]

Severe obesity, particularly among younger patients, and the risk of death posed by other obesity-related comorbidities, such as history of myocardial infarction, diabetes, hypertension, or hyperlipidemia,

suggest a significant pathophysiological relationship between excess adiposity and COVID-19 with a clinically significant degree of obesity. Obesity is not only an extension of subcutaneous adipose tissue but is also associated with an increase in ectopic fat, including visceral, perivascular, and epicardial adipose tissue. This fat distribution promotes chronic proinflammatory, prothrombotic, and vasoconstrictive states, which can manifest as insulin resistance, type 2 diabetes, hypertension, atherosclerosis, cardiovascular disease and immunocompromised states leading to high mortality rates. In addition to chronic disease, visceral adiposity also increases mortality among critically ill patients with ARDS.[29]

COVID-19 survivor who had a conversion time of ≥14 days were found to be more in obese patients (88.9%) than non-obese patients (11.1%). The difference was significant with *P*<0.05 and OR=30.00 (95%=CI 2.85-31.61). A cohort study by Bennasrallah, et al. in Tunisia obtained that the median conversion time for COVID-19 patients was 20 days (IQR=17-32 days). This study observed that the presence of symptoms and the use of masks were associated with conversion time, whereas increase in age, gender, comorbidities and smoking habits were not associated with an escalated conversion time.[30]

Mo, et al. in Wuhan stated that most of obese patients had mean conversion time of 18 days (IQR=11-25 days) starting from the first day of symptoms onset, with factors related to the prolongation of conversion time was cough, high levels of leukocytes, neutrophils and ESR as well as low values of CD3+ and CD4+ lymphocytes.[31] This difference might be associated to the heterogeneity of the patients and the severity of disease in this study. Study by Zhang, et al. in China comparing COVID-19 patients with obesity and non-obesity revealed that on day 14, about 94.9% of non-obese patients had converted.[32] This study suggested that obesity status was a positive risk factor for viral clearance at day 14. Another study by Moriconi, et al. also reported a longer conversion time in obese patients than non-obese patients (19±8 vs 13±7 days, *P*=0.002).[7]

Obesity is often accompanied by insulin and leptin resistance which interfere with viral clearance. ACE2 produced by adipocytes which provide viral enter the adipose tissue, therefore adipose tissue had their role as a reservoir place of virus. The expanded of adipose tissue could lead to the oxidative stress in cells, after which increase viral receptor expression in adipose tissue and other organs. Obese patients with diabetes experience dysregulation of immune deposition such as phagocytic cell dysfunction, impaired neutrophil movement, impaired T cell-mediated immune response, altered cytokine production, leading to interrupt and ineffective microbial clearance during viral infections.[33,34]

The length of stay for ≥14 days in the ICU was observed more in obese patients (75.0%) than in non-obese patients (25.0%) with the results showing that there was a correlation between obesity and the length of stay for COVID-19 patients in the ICU with *P*<0.05 and OR=3.67 (95% CI=1.09-12.35). A study by Sjogren, et al. in Sweden reported that obese individuals had longer duration of hospitalization and BMI was one of the determinants of prolonged hospitalization in COVID-19 patients. An increase of one standard deviation of BMI was associated with 1.35 days longer intensive care (95% CI=0.58-2.11) in linear regression after adjusting for age, sex and comorbidities. A longer length of stay reflects a more severe disease course and is associated with greater functional impairment in COVID-19 patients.[35]

Moriconi, et al. revealed that obese patients required mechanical ventilation and longer hospital stay (21±8 vs 13±8 days, *P*=0.0008).[7] Another study by Suresh, et al. and Plataki, et al. obtained different results in which obesity was found to be unrelated to the need for mechanical ventilation needs.[36,37] The mechanisms which influence the severity and the relationship to length of hospitalization may be multifactorial, ranging from decreased cardiorespiratory reserve and thrombogenesis, to hyperimmune reactivity. Expression of ACE2, the functional SARS-CoV-2 receptor and dysregulation of obesity in obese patients are some of the factors that can transform adipose tissue into a potential viral reservoir, as well as the effects of impaired cytokine balance. Regardless of the underlying mechanism,

there is a strong evidence that obese individuals are more likely to develop severe illness from COVID-19.[36]

LIMITATION

This study was conducted on patients with severe and critical clinical conditions in the ICU so that the patients already had poor outcomes from the time they were admitted to the hospital. As the only comorbidity that was statistically significant to the outcome of COVID-19 patients in this study, diabetes mellitus could be a confounding factor in determining the correlation between obesity status and length of hospitalization and mortality, therefore, further research is needed.

CONCLUSION

Characteristics of obese COVID-19 patients in the ICU of RSUP Dr. M. Djamil Padang were mostly woman aged 60-69 years. Diabetes mellitus was significantly associated with both obese and non-obese COVID-19 patients. Obesity was not associated with overall length of stay in the hospital. Obesity was found to be significantly correlated with mortality, conversion time and length of hospitalization for COVID-19 patients in the ICU.

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CONFLICT OF INTEREST

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