

Liver function characteristics of COVID-19 patients with obesity at Dr. Soetomo Hospital: case series



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ABSTRACT

Background: Coronavirus disease 2019 (COVID-19) patients with obesity are more susceptible to liver injury. There is currently no published overview regarding COVID-19 patients with liver injury in Indonesia. Our study reported 7 cases of obese COVID-19 patients with an increase of serum glutamic oxaloacetic transaminase (SGOT) and serum glutamic pyruvic transaminase (SGPT), followed by 5 of them developing severe symptoms of COVID-19 in isolation room of Dr. Soetomo Hospital Surabaya within June-December 2020.

Case Presentation: A total of 7 COVID-19 patients, by the average age 46.2 ± 15.5 years, were obese. The mean body mass index (BMI) was 36.3 ± 3.4 kg/m². Five of them experienced serious symptoms. There were 3 patients (patient no. 2, 4, 7) who had normal SGOT level, while the rest had an increased SGOT level for $<2x$ upper limit of normal (ULN) at admission. During treatment, SGOT level increased in 5 patients for $1- <3x$ ULN and normal in the rest of them (patient no. 2, 4). Meanwhile, the normal SGPT levels were shown in 3 patients (patient no. 2, 4, 7) and increased in 4 others at admission for $1- <4x$ ULN. All of them tended to have an increased SGPT level during treatment for $1- <5x$ ULN. However, since the increase of SGOT and/or SGPT for $>3x$ ULN is defined as liver injury, it happened in 2 patients that occur since admission (patient no. 3) and during treatment (patient no. 5).

Conclusion: Obesity may impede the recovery of COVID-19 and manifest in the deterioration of liver function.

Keywords: COVID-19, liver, angiotensin converting enzyme 2, obesity, SARS-CoV-2.

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INTRODUCTION

Coronavirus disease 2019 (COVID-19) is one of the international health concerns that have caused long-term consequences and have disturbed multi-sectors.¹⁻⁵ Multiple diagnostic methods, prevention measures and treatments have been proposed; however COVID-19 waves are continuing. Obesity is one of factors that aggravate COVID-19, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2 infection).⁶⁻¹⁰ A study involving 382 COVID-19 patients, 32% of overweight and 10.7% of obese patients, showed that the obese patients were having more severe symptoms compared to the normal and overweight group.¹¹ In addition to respiratory symptoms, COVID-19 patients are also more susceptible to liver injury during the treatment.¹²

A study conducted in China revealed that 99 COVID-19 patients admitted to intensive care units experienced the

improved indicators of liver function such as serum glutamic oxaloacetic transaminase (SGOT) and serum glutamic pyruvic transaminase (SGPT).¹³ Another study confirmed that obese or overweight patients with COVID-19 might have liver injury following the lung manifestations.¹⁴ Based on these exposures, this case series is expected to provide an overview of liver function characteristics in COVID-19 patients with obesity at Dr. Soetomo Hospital Surabaya, Indonesia.

CASE PRESENTATION

A total of 7 patients (5 women, 2 men) included in this study were admitted to isolation room of Dr. Soetomo Hospital Surabaya within June-December 2020. Their laboratory examinations were carried out in the clinical pathology laboratory. The general profiles, symptoms, laboratory results, treatments and outcomes of these patients were recorded as shown in [Table 1](#).

The average age of all patients was 46.2 ± 15.5 years. The COVID-19 diagnosis was confirmed by real-time reverse transcription-polymerase chain reaction (RT-PCR) with nasopharyngeal swab specimen. The degree of obesity was assessed by measuring body mass index (BMI) with an average BMI was 36.3 ± 3.4 kg/m². All patients had fever and cough symptoms. Short breath was experienced by 5 patients (71.4%). One (14.2%) complained other symptoms such as nausea, vomiting, anosmia and diarrhea. None of them had chronic liver disease. There were 5 patients (62.5%) identified as severe COVID-19 cases. In terms of preventing the likelihood of chronic hepatitis virus infection, all patients underwent hepatitis B surface antigen (HbsAg) screening.

After admission, all patients received antiviral treatment, such as lopinavir-ritonavir 400mg twice a day in 6 patients (85.7%) and oseltamivir 75mg twice a day in 1 patient (14.3%). All patients received

Table 1. Characteristics of the obese COVID-19 patients.

Category	Overall (n=7)	Obesity Class 1 (n=2)	Obesity Class 2 (n=3)	Obesity Class 3 (n=2)
BMI (kg/m ²). mean±SD	36.4±3.4	32.1±1.4	36.8±1.5	40.1±0.1
Age (years). mean±SD	46.2±15.5	37.5±10.6	53±18.1	45±19.7
Male. n (%)	2 (28.5)	2 (100)	0 (0)	0 (0)
Female. n (%)	5 (62.5)	0 (0)	3 (100)	2 (100)
Symptoms. n (%)				
Fever	7 (100)	2 (100)	3 (100)	2 (100)
Anosmia	1 (14.2)	1 (50)	0 (0)	0 (0)
Cough	7 (100)	2 (100)	3 (100)	2 (100)
Shortness of breath	5 (62.5)	1 (50)	2 (66.6)	2 (100)
Nausea & vomiting	1 (14.2)	0 (0)	0 (0)	1 (50)
Diarrhea	1 (14.2)	0 (0)	0 (0)	1 (50)
Malaise	1 (14.2)	0 (0)	0 (0)	1 (50)
Laboratory				
HbsAg (-). n (%)	7 (100)	2 (100)	3 (100)	2 (100)
SARS-CoV-2 rapid test (+). n (%)	3 (42.8)	1 (50)	2 (66.6)	1 (50)
SGOT (u/L). mean±SD	39.8±17.4	42.5±19.9	42±26.1	34±2.8
SGPT (u/L). mean±SD	62±45.5	86±73.5	64.3±45.3	34.5±14.8
Leucocyte (μ/L). mean±SD	14141.4±10926.1	14675±13654.2	9573.3±3686.1	20460±18964.6
Neutrophil (%). mean±SD	76.4±16.3	79.3±21.4	69.6±20.6	83.5±5.8
Lymphocyte (%). mean±SD	15.3±13.0	11.8±13.1	21.7±17.5	9.2±2.6
NLR (%). mean±SD	9.8±13.0	20.5±24.7	5±3.6	6.5±7.7
CRP (mg/dL). mean±SD	8±6.3	5.85±6.5	10±9	7.2±4.1
RBG (mg/dL). mean±SD	213.4±109.3	157±5.6	267.3±149.5	189±103.2
Chest x-ray of pneumonia. n (%)	7 (100)	2 (100)	3 (100)	2 (100)
Treatment				
Antivirus. n (%)	7 (100)	2 (100)	3 (100)	2 (100)
Oseltamivir	1 (14.2)	0 (0)	1 (33.3)	0 (0)
Lopinavir-Ritonavir	6 (85.8)	2 (100)	2 (66.6)	2 (100)
Other Treatment. n (%)				
Paracetamol	7 (100)	2 (100)	3 (100)	2 (100)
Outcome				
Length of stay (days). mean±SD	11.4±4.9	16.5±6.3	9.3±2.0	9.5±5
Death. n (%)	4 (57.1)	0 (0)	2 (66.6)	2 (100)

BMI - body mass index, HbsAg - hepatitis B surface antigen, SARS-CoV-2 - severe acute respiratory syndrome coronavirus 2, SGOT - serum glutamic oxaloacetic transaminase, SGPT - serum glutamic pyruvic transaminase, NLR - neutrophil-to-lymphocyte ratio, PTT - partial prothrombin time, APTT - activated partial thromboplastin time, CRP - c-reactive protein RBG - random blood glucose.

symptomatic treatment, like paracetamol 500mg three times a day. The average length of treatment was 11.4 ± 4.9 days and 4 patients died during treatment.

Bilirubin level was only measured in 2 patients during treatment. One patient had 0.53 mg/dL of total bilirubin and 0.34 mg/dL of direct bilirubin. Meanwhile, another patient had 0.46 mg/dL of total bilirubin and 0.22 mg/dL of direct bilirubin.

The SGOT and SGPT levels were examined every 3 days during treatment, as shown in Figure 1. The overall mean of SGOT was 39.8±17.4 U/L and SGPT was 62±45.5 U/L. The mean SGOT in obesity class 1 (Group a), 2 (Group b) and

3 (Group c) groups were 42.5±19.9 U/L, 42±26.1U/L and 34±2.8 U/L, respectively. The mean SGPT in obesity class 1, 2 and 3 were 86±73.5 U/L, 64.3±45.3 U/L, and 34.5±14.8 U/L, respectively. At admission, 3 patients (patient no. 2, 4, 7) had normal SGOT level, while the rest (patient no. 1, 3, 5, 6) had an increased SGOT level for <2x upper limit of normal (ULN). During treatment, SGOT level increased in 5 patients; 2 (patient no. 1, 3) for <2x ULN and 3 (patient no. 5, 6, 7) for <3x ULN. The rest (patient no. 2, 4) showed normal SGOT levels. Meanwhile, SGPT levels also varied in each patient. The normal results were shown in 3 patients (patient no. 2, 4,

7) and increased in 4 others at admission; 2 (patient no. 5, 6) for <2x ULN, 1 (patient no. 1) for <3x ULN and another 1 (patient no. 3) had <4x ULN. All of them tended to have an increased SGPT level during treatment; <2x ULN in 4 patients (patient no. 2, 4, 6, 7), <3x ULN in 1 patient (patient no. 1) and <5x ULN in 2 patients (patient no. 3, 5).

DISCUSSION

The 7 cases presented here highlight a number of noteworthy insights. First, the rise in SGOT and SGPT levels upon admission and during therapy suggests that

obesity in COVID-19 patients may make liver injury more likely. Second, obesity may cause COVID-19's recovery more difficult by exhibiting severe symptoms. Third, the use of paracetamol and

lopinavir/ritonavir may also contribute in the occurrence of liver injury.

People who are obese have a higher risk of contracting infections like COVID-19 and experience more severe symptoms

than patients who are not obese.¹⁵ A study explained that overweight patients were 1.84 times more likely to have a severe COVID-19 condition than obese patients, who had a 3.4-fold increased risk.¹¹ Severe COVID-19 is defined when a patient meets one of the following criteria: (1) respiratory rate ≥ 30 /minute; (2) blood oxygen saturation $\leq 93\%$ at rest; (3) the partial pressure of arterial oxygen (PaO₂) to the fraction of inspired oxygen (FiO₂) ≤ 300 mmHg (1 mmHg = 0.133kPa); (4) and pulmonary infiltration $> 50\%$ in 48-72 hours.¹⁶ These criteria indicated that there were 5 out of 7 patients were categorized as severe COVID-19 sufferers in this case series.

Obese people have continuous low-grade inflammation, which affects their innate and adaptive immune responses to be dysregulated. Moreover, angiotensin-converting enzyme 2 (ACE-2) receptor is abundantly expressed in obese patients, encouraging viral internalization into adipocytes and boost TNF- α and IL-6 production. Given their reduced mobility, increased insulin resistance, and gut dysbiosis, obese people may have greater inflammatory reactions to SARS-CoV-2.¹⁷⁻¹⁹ Such aberration can lead to cytokine storm, characterized by an increase in inflammatory markers such as CRP and neutrophil-lymphocyte ratio (NLR), which were revealed high in the three study groups. The cytokine storm also becomes a plausible reason for the process of liver injury.^{20,21} Additionally, obesity causes compensatory changes in respiratory system that include weakened diaphragm and lungs, higher airway resistance, and poorer airflow.^{22,23}

Most of COVID-19 patients were associated with abnormal liver function especially during treatment.²⁴ Liver injury is characterized by an increase in SGPT and/or SGOT $> 3 \times$ ULN (both ULN values are 0-50 U/L for men and 0-35 U/L for women), or alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT), and/or total bilirubin (TBIL) $> 2 \times$ ULN, with each ULN is 49 U/L, 135 U/L and 17.1 $\mu\text{mol/L}$.²⁵ There were only 2 patients examined for bilirubin, but none of them having it increasing. However, the increase for $> 3 \times$ ULN of SGPT and/or SGOT were found in two patients that occur since

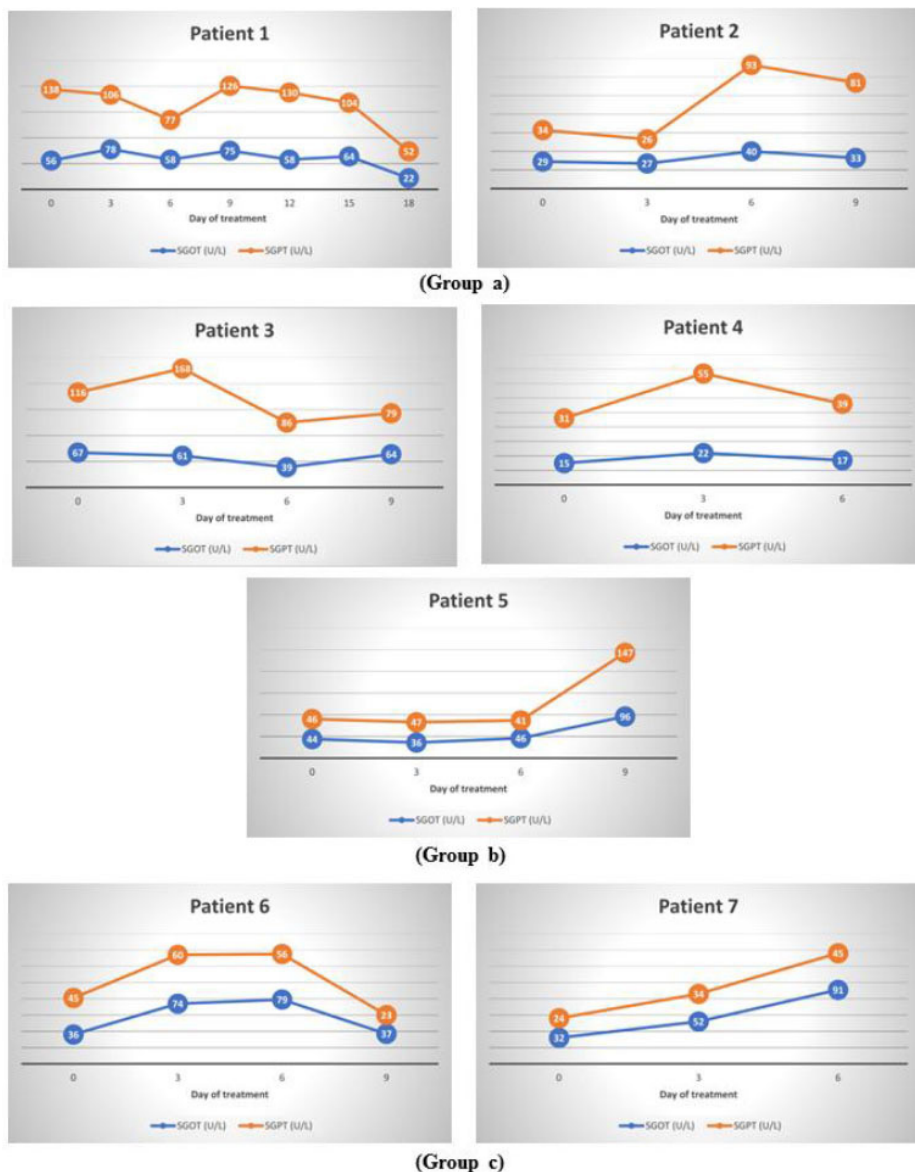


Figure 1. The SGOT and SGPT levels during hospitalization of the 7 patients in the isolation room of Dr. Soetomo Hospital, (Group a) 2 male patients obesity class 1 group, (Group b) 3 female patients of obesity class 2 group and (Group c) 2 female patients of obesity class 3 group. Three patients (patients no.2, 4, 7) had normal SGOT levels at admission, while 4 patients had SGOT levels that were 2x upper limit of normal (ULN). Five patients (patient no. 1, 3, 5, 6, 7) had SGOT levels that rose during treatment. On the other hand, 3 patients (patient no.2, 4, 7) had normal SGPT results, while 4 others had increased results at admission. During treatment, they all tended to have elevated SGPT levels. The normal reference for SGOT and SGPT level is 0-50 U/L for men and 0-35 U/L for women. All examinations were carried out in the clinical pathology laboratory of Dr. Soetomo General Hospital Surabaya. Liver injury is defined by the level of SGPT and/or SGOT $> 3 \times$ ULN or ALP, GGT, and/or TBIL $> 2 \times$ ULN.

admission (patient no. 3) and during treatment (patient no. 5).

Numerous investigations found a connection between obesity in COVID-19 patients and decreased liver function.^{26,27} Innate immune cells such as macrophages, NK cells and T cells, are abundant in the liver. Adipose cells and Kupffer cells have been shown to produce more pro-inflammatory cytokines in obesity. Adipose tissue and free fatty acids flow to the liver and activate hepatic macrophages which are categorized as M1 and M2 that respond in two different ways. M1 macrophages start the inflammatory process, providing the opposite effect of M2 macrophage response. M2 macrophage has anti-inflammatory properties and reparative functions with different chemokine expressions. The patient's clinical condition is determined by how well the two inflammatory reactions above balance one another. The dysregulation of the hepatic innate immune system contributes to the pathogenesis.^{28,29}

In this case series, all patients who had fever received 500 mg of paracetamol three times a day, and 6 of 7 patients received antiviral therapy with lopinavir-ritonavir 400 mg every 12 hours. Although it has not been sufficiently proven for lopinavir-ritonavir, the aforementioned drugs can also cause liver damage in COVID-19 patients, especially when administered at high doses as >4000 mg per day for paracetamol.^{30,31} One of the mechanisms underlying the occurrence of drug-induced liver injury (DILI) is the interaction of drugs with cytochrome P-450 (CYP) in the liver. For instance, CYP3A inhibition by lopinavir-ritonavir hampers the drug metabolism and clearance while CYP2E1 and CYP2A6 induction by paracetamol produces N-acetyl-p-benzo-quinone imine (NAPQI) that later becomes hepatotoxic.^{32,33}

This study has several limitations. First, this study is a case series with 7 patients. Second, coronavirus is known to enter bile duct epithelial cells via the ACE2 receptor, which in turn causes liver damage, but data regarding ALP and GGT were not available in this study. Third, there are no data related to abdominal ultrasound examination, so the influence of chronic liver disease and fatty liver on

liver function abnormalities cannot be completely ruled out.

CONCLUSION

We presented 7 obese patients with COVID-19, 6 of them developed severe symptoms. At admission, normal SGOT values were found in 3 patients and increased in 4 patients, while normal SGPT values were found in 3 patients and increased in 4 patients. Increased SGOT values were found during treatment in 5 patients, while SGPT values increased in all patients. All patients had elevated markers of inflammation. Obesity may hamper the recovery process of COVID-19 and manifest in the deterioration of liver function.

PATIENT CONSENT

All patients signed informed consent forms and agreed to be published in scientific journals.

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DISCLOSURE OF CONFLICTS OF INTEREST

There is no conflict of interest.

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AUTHOR CONTRIBUTION

Authors contributed significantly to the study.

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